



## Development of dietary small molecules as multi-targeting treatment strategies for Alzheimer's disease

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### ABSTRACT

Cognitive dysfunction can occur both in normal aging and age-related neurological disorders, such as mild cognitive impairment and Alzheimer's disease (AD). These disorders have few treatment options due to side effects and limited efficacy. New approaches to slow cognitive decline are urgently needed. Dietary interventions (nutraceuticals) have received considerable attention because they exhibit strong neuroprotective properties and may help prevent or minimize AD symptoms. Biological aging is driven by a series of interrelated mechanisms, including oxidative stress, neuroinflammation, neuronal apoptosis, and autophagy, which function through various signaling pathways. Recent clinical and preclinical studies have shown that dietary small molecules derived from natural sources, including flavonoids, carotenoids, and polyphenolic acids, can modulate oxidative damage, cognitive impairments, mitochondrial dysfunction, neuroinflammation, neuronal apoptosis, autophagy dysregulation, and gut microbiota dysbiosis. This paper reviews research on different dietary small molecules and their bioactive constituents in the treatment of AD. Additionally, the chemical structure, effective dose, and specific molecular mechanisms of action are comprehensively explored. This paper also discusses the advantages of using nanotechnology-based drug delivery, which significantly enhances oral bioavailability, safety, and therapeutic effect, and lowers the risk of adverse effects. These agents have considerable potential as novel and safe therapeutic agents that can prevent and combat age-related AD.

### 1. Introduction

Alzheimer's disease (AD) is a multifactorial neurodegenerative disease (NDD). It is the most common cause of dementia and one of the most serious problems facing the world's older adult population [1]. The World Health Organization (WHO) estimates that approximately 50 million people have AD or AD-related dementia, potentially accounting for 60–70% of all dementia cases [2]. This number is expected to reach 82 million by 2030 and 152 million by 2050. In the US, approximately 6.2 million people have AD, while in South Korea more than 1 million people are affected [3,4]. AD has a major impact on quality of life in affected individuals and imposes a significant economic burden on their families and society [5]. As a result, increasing attention is being paid to the pathogenesis and treatment of AD.

Formation of extracellular insoluble amyloid-beta (A $\beta$ ) plaques and intracellular aggregation of hyperphosphorylated tau protein in neurofibrillary tangles in the brain are typical pathological features of AD [6].

Tau proteins are a group of structural proteins that function predominantly in microtubules; when hyperphosphorylated, they become toxic and insoluble, forming aggregates that contribute to the pathophysiology of AD [7]. Tau hyperphosphorylation can lead to abnormal folding, fragmentation, aggregation, and/or the development of deposits known as neurofibrillary tangles. Extracellular A $\beta$  plaques and intracellular tangles in brain hippocampal and cortical areas are hallmarks of AD [8]. These changes lead to AD symptoms, such as progressive memory loss, difficulty remembering new information, cognitive decline, behavioral and emotional changes, loss of motor coordination, confusion, speech problems, and mood swings [9,10]. Although the underlying mechanisms leading to AD development have not been clearly defined, many risk factors have been identified, including age, genetic predisposition, environmental factors such as exposure to metals, lifestyle, malnutrition, traumatic brain injury, immune system dysfunction, infectious agents, vascular disease, and psychological impairment [11,12]. Recent research has demonstrated that

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sustained oxidative stress, altered lipid metabolism, cholinergic dysfunction, protein homeostasis, mitochondrial energy depletion, synaptic dysfunction, and subsequent neuronal loss also have prominent roles in AD progression [13,14]. Moreover, previous studies have demonstrated that elevated pro-inflammatory mediators like cytokines, chemokines, and interleukins (ILs) make major contributions to neuroinflammation-induced AD progression [15,16].

Cholinergic neurons synthesize acetylcholine (ACh), which plays a crucial role in learning and memory [17]. AD has been characterized by the loss of cholinergic neurons in both the cortical and hippocampal regions [18,19]. Serotonin (5-HT) is an important neuromodulator involved in various physiological functions including cognition, emotion, sexual function, and sleep [20,21]. In addition, 5-HT reductions in the hippocampus and frontal cortex are responsible for short- and long-term memory impairment [21]. Along with 5-HT, the gamma-aminobutyric acid (GABA [A]) receptor is altered in AD. The greater the expression of the GABA (A) receptor, the more neuropathological changes are apparent in people with AD [22]. Glutamatergic neurotransmission is another important mechanism involved in learning and memory. In AD, A $\beta$  induces oxidative stress, which interferes with glutamatergic neurotransmission, ultimately leading to its failure and attendant impairments of cognition, learning, and memory in patients [23].

The limited number of effective treatment options for AD has encouraged researchers to explore both potent pharmacological agents and a broad range of other biological activities as ways to prevent NDDs. Consequently, dietary small molecules from natural sources were investigated and shown to have potential therapeutic benefits in various NDDs, including AD. These molecules (e.g., flavonoids, phenolic acids, and carotenoids) have been widely reported as anti-AD agents both *in vivo* and *in vitro*, with only minor side effects. In this paper, we summarize recent advances in dietary small molecules and their bioactive

compounds as potential alternative therapies for the prevention and treatment of AD. We highlight the chemical structure, mechanism, and effective dose of each phytochemical. In addition, current challenges and prospects are discussed. The systematic literature search was conducted using Google Scholar, SciFinder, Science Direct, PubMed, Web of Science, EBSCO, Scopus, JSTOR and other web sources. The scientific literature preferably on natural dietary small molecules and their bioactive constituents in context to their neuroprotective properties and their mechanism of action were selected. Literature with scientific rigor published up to 2023 was included.

## 2. Molecular pathogenesis of AD

The molecular pathogenesis of AD remains under active investigation. The sporadic and familial forms of the disease, which are histopathologically indistinguishable, are characterized by neurodegeneration in the hippocampus and cerebral cortex that is associated with numerous aggregated A $\beta$  plaques and tau hyperphosphorylation (Fig. 1). Moreover, neuroinflammation mediated by activated microglia has increasingly received attention as a key pathogenic mechanism in AD [24].

Oxidative stress plays an important role in the initiation and progression of aging and age-associated AD. It is caused by redox imbalance, antioxidant dysregulation, and the production of reactive oxygen species (ROS) [25]. A large body of research suggests that oxidative stress changes vital cellular elements within the brain, such as proteins, lipids, and DNA [26]. These changes lead to deleterious alterations in brain neurotransmitter levels, modulation of intracellular signaling pathways, and ultimately attacks on neurons and glial cells, leading to increased neuronal apoptosis [27,28]. Moreover, the extensive oxidative damage observed in mild cognitive impairment (MCI) suggests that oxidative stress may be an early event in the progression from normal

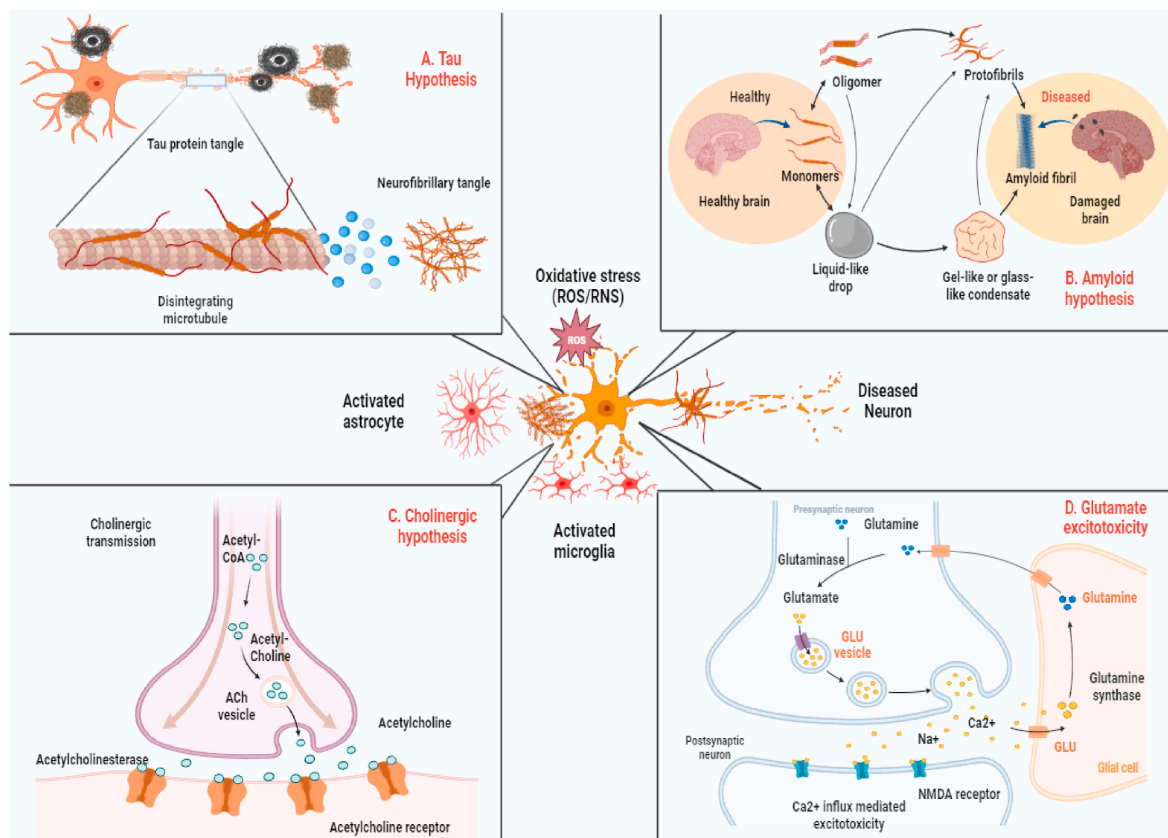


Fig. 1. The current knowledge of the factors contributing to AD pathogenesis. ACh: acetylcholine; ROS: reactive oxygen species; RNS: reactive nitrogen species.

aging to AD pathology [29]. Several preclinical studies have demonstrated that oxidative stress plays a key role in the initiation and progression of cognitive deficits and contributes to AD pathogenesis [30, 31]. Other studies have demonstrated that increased ROS production induces synaptic loss and promotes the accumulation and aggregation of A $\beta$  plaques in AD brains [32,33]. In addition, postmortem studies have revealed that age-dependent increases in oxidative damage and mitochondrial dysfunction may contribute to increased oxidative stress in AD [34–36]. Moreover, increased ROS levels are strongly associated with tau aggregates, tau phosphorylation, and neuronal cell death [37].

Senile plaques are mainly composed of A $\beta$  peptides, which are produced by amyloidogenic proteolytic processing of amyloid precursor protein (APP), a transmembrane protein with a large luminal domain and a short cytoplasmic domain [38]. A $\beta$  is generated from APP by consecutive cleavage by  $\beta$ -secretase and  $\gamma$ -secretase, while non-amyloidogenic processing is initiated by  $\alpha$ -secretase cleavage of APP within the A $\beta$  domain, followed by  $\gamma$ -secretase cleavage. Aberrant APP processing may result in an imbalance between the aggregation and clearance of A $\beta$  peptides, leading to the formation of toxic oligomers, fibrils, and senile plaques associated with neurotoxicity. However, previous studies have indicated that cognitive dysfunction in AD is linked to the accumulation of extracellular soluble oligomeric A $\beta$  species rather than amyloid plaque deposition in the brain [38–40]. It has been reported that oligomeric A $\beta$  can disrupt synaptic plasticity, induce synaptic degeneration, and reduce long-term potentiation (LTP), all of which contribute to AD progression [41]. Neurofibrillary tangles (NFTs) are fibrillar aggregates composed of paired helical filaments (PHFs) of abnormally hyperphosphorylated tau protein. Tau is a highly soluble, microtubule-associated phosphoprotein that regulates microtubule stabilization and polymerization and plays an important physiological role in microtubule dynamics and axonal transport [7,42]. In AD, aberrantly phosphorylated tau redistributes from the axon to the soma, inducing microtubule network breakdown and axonal transport deficits, resulting in neuronal atrophy and cell death. Moreover, when detached from microtubules, hyperphosphorylated tau is highly likely to self-aggregate into neurotoxic PHFs [43]. There is a strong relationship between the tau aggregation associated with NFT formation and neuronal loss in the brain, and this contributes to disease progression in AD [44].

Among the neurotoxic factors involved in AD progression, neuroinflammation has a crucial role. Microglia and astrocytes are the main components of the immune system within the central nervous system (CNS), and they play a vital role in the development and progression of neuroinflammation. While microglial cells typically protect and maintain homeostasis in the brain, their effects can be beneficial or detrimental to neurons in the CNS. Normally, microglia clear abnormal A $\beta$  protein aggregates by phagocytosis and degradation [45,46]. It has been reported that the loss of phagocytic efficiency by activated microglia is a key contributing factor to A $\beta$  accumulation [47]. In the presence of neuroinflammation caused by aging, AD, and other neuropathological conditions, chronic abnormal activation of microglia disrupts the CNS microenvironment, leading to the release of various pathogenic proinflammatory mediators including IL-1 $\beta$ , inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) [48–50]. Activated microglia also induce IL-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), two important proinflammatory cytokines that are directly involved in AD pathogenesis [51]. In patients with AD, changes have been observed in IL-6 and TNF- $\alpha$  levels in the brain and serum, which are associated with increasing A $\beta$  accumulation and APP expression. These in turn lead to AD pathology with clinical symptoms presenting later in life, suggesting a direct relationship between the expression of inflammatory markers and cognitive ability [52,53]. Evidence suggests that A $\beta$  accumulation involves several intracellular signaling pathways, including phosphorylation cascades leading to mitogen-activated protein kinase (MAPK) and nuclear factor (NF)- $\kappa$ B activation. Moreover, previous studies have suggested that NF- $\kappa$ B activation is mediated by microglial activation and that it significantly increases the expression of the inhibitor of NF- $\kappa$ B

p-I $\kappa$ B $\alpha$ /I $\kappa$ B $\alpha$  and the NF- $\kappa$ B family protein p-p65/p65 [54,55]. Additionally, activation of NF- $\kappa$ B and MAPK signaling helps trigger tau protein aggregation and tau hyperphosphorylation, which are responsible for AD development [56].

It is well known that synaptic alteration and dysfunction are among the earliest events in the initiation and progression of AD and are closely related to spatial memory impairment, neuronal loss, and cognitive decline [57]. Histological studies of brain tissue from patients with AD as well as AD mouse models have demonstrated that synaptic alterations include changes in dendrite and spine structure, loss of dendritic spines, aberrant sprouting and curvature of dendritic processes, dystrophic dendrites, compromised synaptic transmission, and reduced synaptic plasticity [58,59]. Increased levels of soluble A $\beta$  and tau hyperphosphorylation in the brain are strongly correlated with synaptic degeneration and loss of dendritic spines in humans and animal models of AD [60–63]. Evidence suggests that neuronal loss and synaptic degeneration have the most robust correlation with cognitive decline in AD [64]. Accordingly, preventing synaptic degeneration and restoring synaptic function may be a novel, early therapeutic approach to slow AD progression and preserve memory function.

### 3. Challenges for AD therapy and alternative treatment strategies

Currently, two types of drugs are approved by the United States Food and Drug Administration (FDA) for treating AD symptoms: acetylcholinesterase (AChE) inhibitors including galantamine (RAZADYN, REMINYL), donepezil (ARICEPT, ARICEPT ODT), rivastigmine (EXELON), and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (NAMENDA) [65,66]. Recent clinical trials in AD have shown some efficacy for antibody therapies in removing neuritic plaques. For example, a phase II study by Eisai and Biogen showed that the humanized IgG1 antibody lecanemab (BAN2401) significantly reduced A $\beta$  plaques, as did donanemab (LY3002813), another humanized IgG1 antibody developed by Eli Lilly. Some evidence of cognitive stabilization was seen in patients treated with these drugs during the trials, but there was also an increased incidence of amyloid-related imaging abnormalities-cerebral edema (ARIA-E). A similar antibody developed by Biogen (aducanumab [BIIB037]) was submitted to the FDA but was rejected for its weak efficacy.

Synthetic drugs for AD have side effects and do not halt disease progression. The discovery of medications that slow the progression of the disease has advanced in recent years. There are now particular therapeutics that can prevent the production of A $\beta$ , discontinue the activation mechanism of brain inflammation, improve cognitive and learning abilities, and be tolerated over an extended period. The process of creating new, efficient medications is challenging, time-consuming, and has a relatively high failure rate. Drug repurposing has made it possible to find effective treatments for a variety of ailments. The fact that the candidate compound's safety has been established is a key benefit of this strategy because it eliminates the need for additional preclinical safety testing, chemical optimization, or toxicology studies, which significantly cuts down on the time and expense needed to advance potential treatment into clinical studies. A reasonable safety database developed from prior registrational procedures, post-marketing experience, and safety surveillance is likely to exist for medications that have been put on the market. It is urgently necessary to find novel treatments and targets for creating more potent medications to slow AD progression and recover cognitive function [67].

The need for more effective AD therapies has led to the extensive study of natural dietary products and their isolated compounds. In general, natural dietary phytochemicals can bind with numerous proteins in the body and modify transporters, enzymes, hormones, and DNA, as well as chelate heavy metals and scavenge free radicals; therefore, many of these agents have strong antioxidant, anti-inflammatory, and neuroprotective properties [68,69]. Dietary

interventions can be a greatly accepted, inexpensive, and efficacious option to preserve against age-related cognitive decline and neurodegeneration, leading to important personal and societal benefits (67). Synchronously, considering the transformation at the colonic level and absorption, the good bioavailability of some dietary small molecules owing to the ability to pass the blood–brain barrier (BBB), to a various extent, facilitated the interest in these molecules as fresh neuroprotective agents against NDDs (68,69). Recent studies have shown that regular use of nutraceuticals, including dietary supplements and herbal medicines, has the potential to enhance cognitive ability in humans and treat many diseases [70,71]. Possible mechanisms for these effects include inhibitory effects on neuroinflammation-induced neuronal apoptosis, oxidative stress, key enzymes involved in A $\beta$  plaque production, tau phosphorylation, and other pathological products [72]. Furthermore, dietary small molecules thus exert their neuroprotective effects by maintaining neuronal quality and number in key brain areas, thus preventing the onset or progression of diseases responsible for decreased cognitive function. In the following sections, we will discuss the effects of dietary small molecules and their main constituents on spatial learning and memory, tau phosphorylation, the A $\beta$  plaque pathway, brain oxidative damage, neuroinflammation, neurotoxicity, and AD treatment.

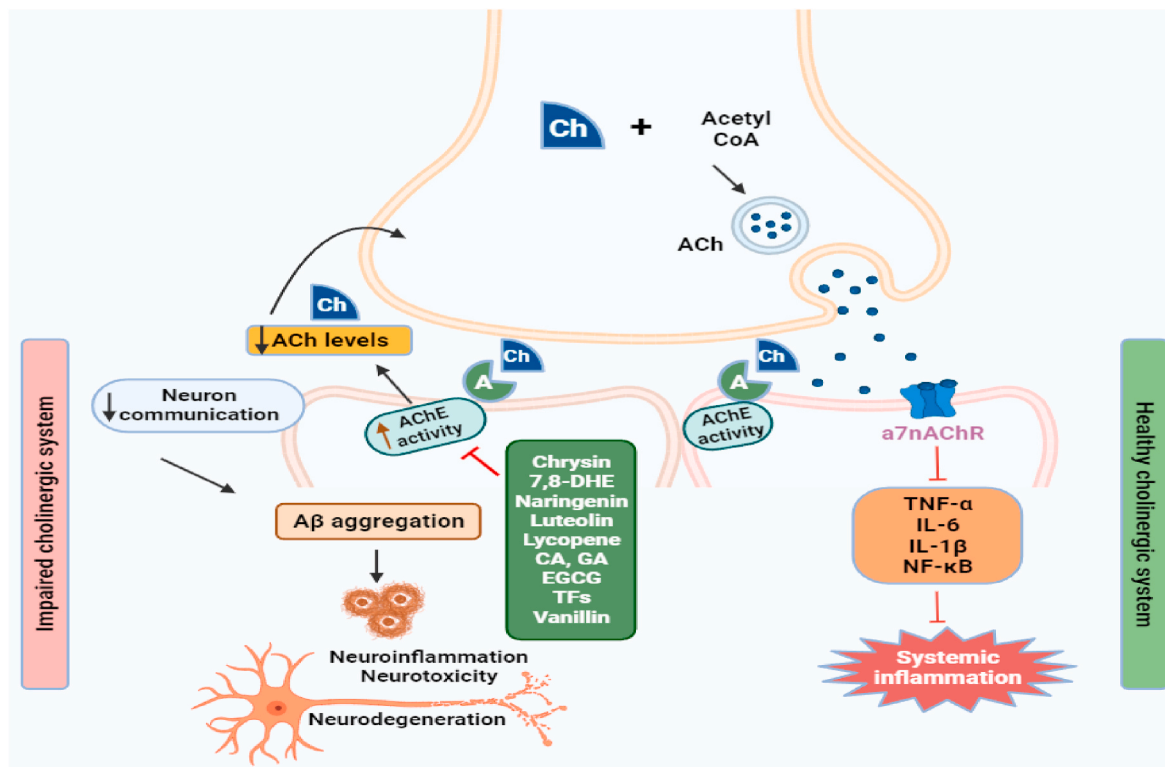
#### 4. Dietary small molecules and neuroprotection – a overview of potential molecular mechanisms

##### 4.1. Neuroprotective mechanisms of chrysin in AD

Chrysin is a promising, naturally occurring polyphenolic flavone with a 15-carbon backbone; it is well-studied and known to be beneficial to human health. Chrysin is abundant in medicinal herbs, honey, fruits,

flowers, dietary supplements, and many plant species. Structurally, chrysin has a lack of oxygenation in B and C rings, which is associated with its pharmacological activity and includes anti-inflammatory, antioxidant, anticancer, antiallergic, cardioprotective, hepatoprotective, and neuroprotective effects [73,74]. Chrysin's maximum plasma concentration and oral bioavailability have been estimated at 12–64 nM and 0.003–0.02%, respectively [75,76]. Opposing effects have not been reported with the usual daily oral dosage of 400–500 mg [77,78]. The recommended daily dose of chrysin is reported to be 0.5–3 g [79,80]. In a rat model, toxicological experiments showed that chrysin (1000 mg/kg) induced major changes in blood chemistry (albumin, bilirubin, alanine transaminase, aspartate aminotransferase, creatinine, and gamma-glutamyl transferase) and hematology parameters (red blood cells, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total leucocyte count, lymphocytes, and neutrophils). In addition, chrysin (1000 mg/kg) administration significantly increased oxido-nitrosative stress associated with the kidney and liver. The no observed adverse effect level (NOAEL) for chrysin was 500 mg/kg and the lowest observed adverse effect level was 1000 mg/kg following administration to both sexes [81].

Recent *in vitro* and *in vivo* studies have shown that chrysin has antioxidant and neuroprotective activity against AlCl<sub>3</sub>-induced neurotoxicity and related pathological changes in a Swiss mouse AD model. *In vitro*, chrysin (5  $\mu$ M) reduced early oxidative stress, significantly decreased proinflammatory mediator levels (iNOS, IL-1 $\beta$ , and TNF $\alpha$ ), and attenuated AlCl<sub>3</sub>-induced late necrotic cell death in neuronal SH-SY5Y cells. Oral administration of chrysin (10, 30, and 100 mg/kg body weight [bw]) for 90 days in mice with AlCl<sub>3</sub>-induced AD led to reduced cognitive impairment, decreased neuronal degeneration, and normalized AChE and butyrylcholinesterase (BChE) activity (Fig. 2). In addition, there was a reduction in oxidative damage that was shown by a

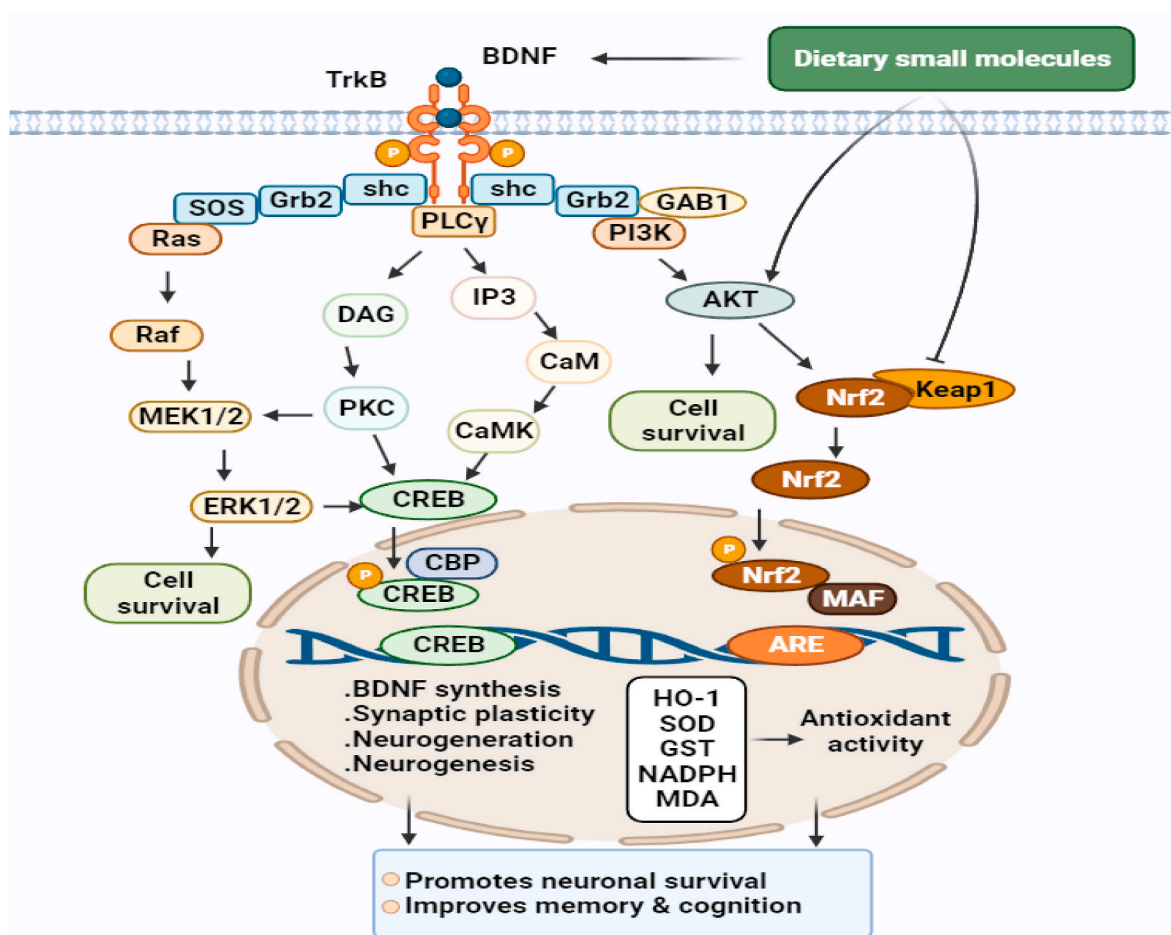


**Fig. 2.** Illustration of dietary small molecules inhibiting/reducing the AChE activity in cholinergic pathway involved in AD pathogenesis. Acetylcholine after being synthesized is released from the vesicles and supports memory formation. AChE causes the breakdown of acetylcholine. So, dietary small molecules like chrysin, 7,8-DHE, naringenin, luteolin, lycopene, CA, GA, EGCG, TFs, and vanillin are blocking AChE thus preventing acetylcholinesterase breakdown, A $\beta$  aggregation, neuroinflammation, and supporting memory formation. Ach: acetylcholine; A $\beta$ : amyloid beta; AChE: acetylcholinesterase; TNF- $\alpha$ : tumor necrosis factor-alpha; IL-1 $\beta$ : interleukin-1 $\beta$ ; IL-6: interleukin-6; NF- $\kappa$ B: nuclear factor kappa B.

decrease in lipid peroxidation and enhanced activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) in the cerebral cortex and hippocampus [82]. In a D-galactose-induced rat model of aging, chrysin treatment (20 mg/kg bw) for 8 weeks significantly raised the activity levels of enzymatic and non-enzymatic antioxidants such as CAT, SOD, glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST), GSH, glucose-6-phosphate dehydrogenase, and vitamins C and E; malondialdehyde (MDA) levels and protein carbonylation were diminished [83]. Similarly, oral administration of chrysin (10 or 30 mg/kg bw) for 28 days can attenuate spatial learning and recognition memory impairments in rats with D-galactose-induced aging. Chrysin also induces cell proliferation, supports cell survival, and regulates the depletion of hippocampal neurogenesis in these rats [84]. It has also been reported that oral administration of chrysin (125 or 250 mg/kg bw) for 8 weeks can regulate D-galactose-induced changes in behavior, brain biochemistry, neuroinflammation, and histopathology in aging mice. It was also demonstrated that chrysin elevated the percentage of spontaneous alternation, and increased locomotor activity and the

discrimination ratio in novel object recognition (NOR) memory in D-galactose-treated mice. In addition, brain levels of adenosine monophosphate-activated protein kinase (AMPK), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 $\alpha$ ), liver kinase B1 (LKB1), neurotrophin-3 (NT-3), NAD (P)H quinone oxidoreductase 1 (NQO1), heme oxygenase 1 (HO-1), and serotonin (5-HT) were increased and the proinflammatory mediators TNF- $\alpha$ , NF- $\kappa$ B, and glial fibrillary acidic protein (GFAP) were reduced. Chrysin also alleviated neuronal degeneration in the white matter and cerebral cortex [85].

A recent study has shown that chrysin treatment (25, 50, and 100 mg/kg bw) for 7 days inhibits sevoflurane-induced hippocampal oxidative stress and spatial navigation impairments in the elevated plus maze, NOR, and Morris water maze (MWM) tests in aged rats, suggesting that chrysin has potential as a memory-enhancing agent for AD [86]. Aged mice were investigated to identify the effects of chrysin on cognitive function. Oral administration of chrysin (1 or 10 mg/kg bw) for 60 days decreased ROS levels, restored SOD, CAT, and GPx activity, and increased levels of Na<sup>+</sup>, K<sup>+</sup>-ATPase activity, and brain-derived



**Fig. 3.** Molecular pathways are involved in the neuroprotective, antioxidant, and promoting neuronal cell survival of dietary small molecules. The PI3K/Akt pathway destabilizes Nrf2-Keap1 complex, which under basal conditions leads to the ubiquitination and degradation of Nrf2 by proteasomal system, and thus, promotes the nuclear translocation of Nrf2. This, in turn, activates the Nrf2-ARE antioxidant system and results in the expressions of multiple genes that encode antioxidant enzymes responsible for redox metabolism and GSH synthesis and metabolism. Activated Akt also regulates cell survival by maintaining a balance between pro-apoptotic and anti-apoptotic proteins. Furthermore, MAPK signaling pathways regulate neuronal survival and the transcriptions of CREB-dependent genes that encode BDNF, and other proteins required for synaptic plasticity and neurogenesis. Dietary small molecules may promote cell survival by activating TrkB signaling by functioning as BDNF mimetics or by promoting Akt phosphorylation or inhibiting Nrf2-Keap1 complex, and thus, activating the antioxidant defense system. TrkB signaling and the Nrf2-ARE antioxidant system are complementary to each other, and simultaneous activation of these pathways has been shown to confer neuroprotection against oxidative stress and to attenuate memory and cognition impairments in patients with AD or NDDs brain injury. BDNF: brain derived neurotrophic factor; CREB: cAMP response element-binding protein; TrkB: tropomyosin receptor kinase; Nrf2: nuclear factor erythroid 2-related factor 2; HO-1: heme oxygenase 1; (PI3K)/Akt: phosphoinositol 3-kinase; SOD: superoxide dismutase; GST: glutathione-S-transferase; MDA: malondialdehyde; ERK1/2: extracellular signal-regulated kinase 1/2; CaMK: Ca<sup>2+</sup>/calmodulin-dependent protein kinase; PKC: protein kinase-C.

neurotrophic factor (BDNF) expression in the hippocampus and cortex of aged mice [87]. Similarly, in C57BL/6 AD mice with methimazole-induced AD, treatment with chrysin (10 and 20 mg/kg bw) for 28 days improved spatial learning and cognitive function in the MWM and increased levels of the neurotrophins BDNF and nerve growth factor (NGF) in the hippocampus and prefrontal cortex. Additionally, molecular docking analysis demonstrated that chrysin effectively binds to the active site of tropomyosin receptor kinase (Trk) A and TrkB, and the p75 neurotrophin receptor [88]. Further experiments have demonstrated that chrysin treatment (10 and 20 mg/kg bw) for 28 days ameliorated long-term spatial learning and memory deficits, reduced glutamate levels, and decreased  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase activity in both the hippocampus and prefrontal cortex in C57BL/6 mice with euthyroid and methimazole-induced AD (Fig. 3) [89].

#### 4.2. Neuroprotective mechanisms of 7,8-dihydroxyflavone in AD

The flavone 7,8-dihydroxyflavone (7,8-DHF) is a natural flavonoid known to have neuroprotective activity. It is found in *Tridax procumbens*, *Godmania aesculifolia*, and various species of *Primula*. Preparations from these plants, such as decoctions, powdered leaves, teas, leaf juice, and oils, have been used as drugs or food supplements and are reported to have antifungal, antioxidant, anti-hepatotoxic, antimicrobial, immunomodulatory, analgesic, anti-inflammatory, and antidiabetic properties [90,91]. However, research into the relationships between structure and activity showed that a catechol group gives 7,8-DHF suboptimal oral bioavailability and brain exposure, suggesting that 7,8-DHF can cross the BBB and is orally bioactive [92,93]. Furthermore, a toxicity study found that following 7,8-DHF (3 mg/kg) treatment for 3 weeks and (2.4  $\mu\text{g}$ ) for 20 weeks, male and female C57BL/6 mice had normal blood cells counts and there were no adverse pathological effects in drug-treated liver, muscle, lung, kidney, heart, intestine, testis, spleen, hippocampus, or cortex [92].

Recent *in vivo* and *in vitro* pharmacological studies have shown that 7,8-DHF might be useful in treating AD. A study has shown the neuroprotective effect of 7,8-DHF (5  $\mu\text{M}$ ) in  $\Delta\text{K280 Tau}_{\text{RD}}$ -DsRed-induced neurotoxicity using SH-SY5Y cells as an *in vitro* model of AD. Treatment with 7,8-DHF reduced tau aggregation, oxidative stress, and caspase-1 activity, and also improved neurite outgrowth, restored the reduced heat shock protein beta-1 (HSPB1) and nuclear factor erythroid 2-related factor 2 (Nrf2) expression, and activated TrkB-mediated extracellular signal-regulated kinase (ERK) signaling to upregulate cAMP response element-binding protein (CREB) and its downstream anti-apoptotic B-cell lymphoma 2 (Bcl2) protein expression in SH-SY5Y cells expressing  $\Delta\text{K280 Tau}_{\text{RD}}$ -DsRed [94]. This neuroprotective effect of 7,8-DHF has also been detected in 6-OHDA-induced PC-12 cells. Interestingly, 7,8-DHF (1–100  $\mu\text{M}$ ) pretreatment protected PC12 cells against neuronal cell death by enhancing SOD activity and direct free radical scavenging, and inhibiting oxidative injury, mitochondrial dysfunction, and apoptosis [95]. In an intracerebroventricular (ICV)-streptozotocin (STZ)-induced AD mouse model, treatment with 7,8-DHF (5, 10, and 20 mg/kg bw) for 3 weeks attenuated cognitive deficits in MWM and NOR, increased activity of the antioxidant enzymes GSH, CAT, SOD, GPx, and decreased MDA, protein carbonyl (PCO), and nitrite levels. In addition, AChE activity was inhibited, NADPH and mitochondrial complex I, II, III, and IV were reduced, and p-tau protein expression was significantly lowered along with neuronal cell death in the cortex and hippocampus [96]. Chen et al. [97] observed that oral administration of 7,8-DHF (1 mg/kg bw) for 4 weeks improved spatial learning and cognitive function by blocking cholinergic signaling and reducing oxidative stress, synaptic degeneration, and A $\beta$  deposition in the hippocampus of rats with scopolamine-induced AD. Gao et al. [98] investigated the effects of 7,8-DHF in the Tg2576 AD mouse model and found that chronic administration of 7,8-DHF (5 mg/kg bw) for 4 weeks rescued spine density in CA1 pyramidal neurons and synaptoneurosomal fractions, and improved cognitive function. In addition, chronic 7,8-DHF treatment

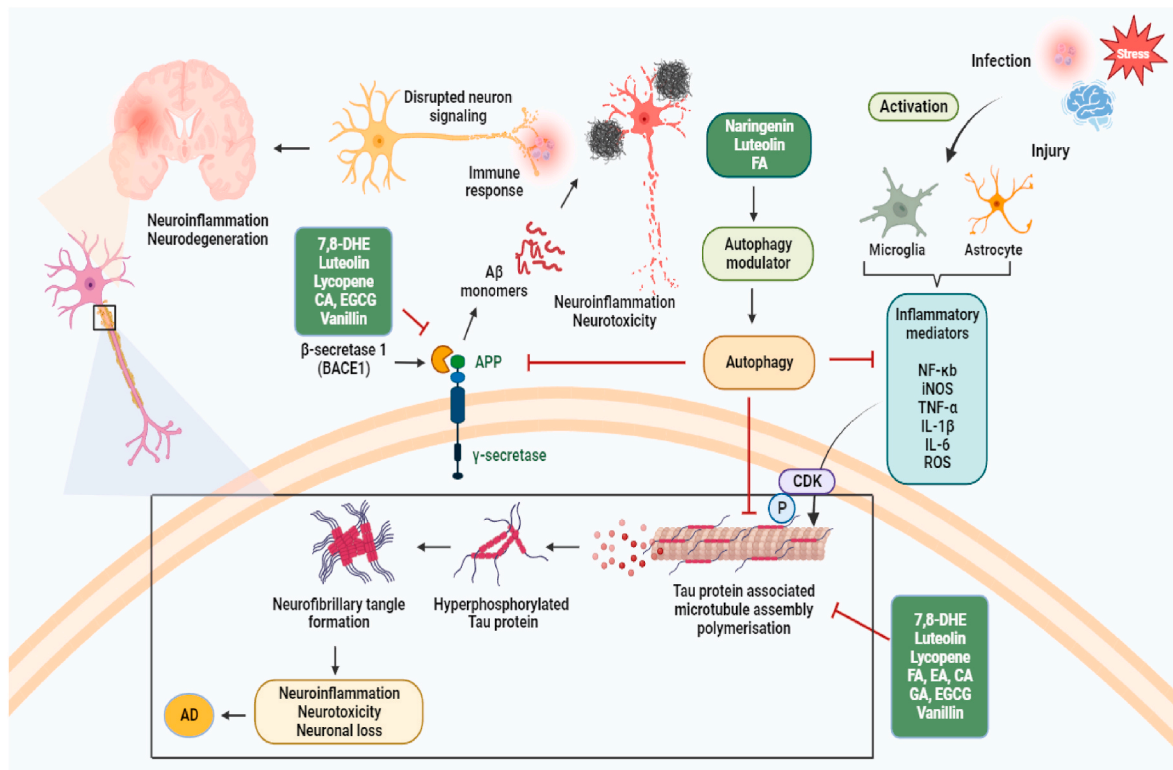
increased the levels of reduced proteins GluA1 and GluA2, two subunits of the glutamate AMPA receptor, and activation of TrkB (Y816) and its downstream phosphoinositol 3-kinase (PI3K)/AKT, Ras/ERK, and PLC $\gamma$  (phospholipase C- $\gamma$ )/Ca $^{2+}$ /calmodulin-dependent protein kinase-II (CaMKII) signaling pathways (Fig. 3).

Zhang et al. [99] found that 7,8-DHF treatment (1 mg/kg bw) activated TrkB signaling, restored synapse number and synaptic plasticity, and prevented A $\beta$  deposition, the loss of hippocampal synapses, and memory deficits in 5XFAD transgenic mice. Similarly, 7,8-DHF treatment (5 mg/kg bw) for 10 days rescued memory deficits, restored deficient TrkB signaling without affecting endogenous BDNF levels, blocked beta-secretase 1 (BACE1) elevations, and lowered levels of the  $\beta$ -secretase-cleaved C-terminal fragment of amyloid precursor protein (C99), A $\beta_{40}$ , and A $\beta_{42}$  in 5XFAD mice [100]. Another study reported that 7,8-DHF treatment (5 mg/kg bw) decreased cortical A $\beta$  plaque deposition and protected cortical neurons against reduced dendritic arbor complexity, hippocampal increases in choline-containing compounds, and glutamate loss, but had no significant impact on dendritic spine density or hippocampal neurogenesis in 5XFAD mice (Fig. 4) [101]. Furthermore, in a rat model of age-related memory loss, 7,8-DHF treatment (5 mg/kg bw) for 4 weeks prevented declines in the performance of fear conditioning tasks and cognition; significantly enhanced the activation of phosphorylated TrkB at the Y515 and Y816 sites; increased spine density and number in several brain regions that process fear memory, including the amygdala, hippocampus, and prefrontal cortex; and facilitated basolateral amygdalar synaptic plasticity [102]. Treatment with 7,8-DHF (5 mg/kg bw) for 28 days attenuated alcohol and high-fat diet (HFD)-induced memory loss, restored GSH levels, reduced nitrite and MDA levels and AChE activity, downregulated caspase-3, IL-1 $\beta$ , iNOS, and NF- $\kappa\text{B}$ , and upregulated Nrf2, HO-1, and BDNF mRNA levels in the rat hippocampus (Fig. 3) [103]. However, more recent studies concluded that 7,8-DHF administration significantly and selectively increased thin-spine density in the CA1 region, increased the number of newly formed oligodendrocytes in the corpus callosum, and significantly improved spatial learning and memory in MyRF $^{-/-}$  and CaM/Tet-DT $_A$  mice [104,105].

#### 4.3. Neuroprotective mechanisms of naringenin in AD

Naringenin is a flavanone that is highly lipophilic due to its chemical structure. It is found in oranges, grapefruits, tangerines, raw lemon peel, and cherries, as well as in vegetables, especially tomatoes [106]. Interestingly, grapefruits and oranges contain large amounts of naringenin, ranging from 14.17 to 53 mg/100g in grapefruits and from 1.47 to 11.15 mg/100 g in oranges [106]. Naringenin has strong antioxidant, immunomodulatory, antidepressant, anti-inflammatory, cardioprotective, neuroprotective, and antiaging properties [107]. It is also readily distributed in the stomach, small intestine, liver, brain, heart, kidney, and spleen through the intestinal epithelium via passive diffusion into enterocytes [108]. According to previous *in vitro* and animal studies, naringenin has high BBB permeability [109,110].

An *in vitro* study in PC12 cells revealed that naringenin performs an important function in reducing apoptosis and neurotoxicity in A $\beta$ -induced AD. The suppression of caspase-3, activation of PI3K/AKT, and regulation of glycogen synthase kinase-3 beta (GSK3 $\beta$ ) signaling pathways are among the intracellular processes responsible for naringenin's anti-apoptotic and neuroprotective actions [111]. It also abrogated the A $\beta$ -induced increase in ROS and decreased A $\beta$  toxicity in a concentration-dependent manner in PC12 cells [112]. A study using Neuro2a cells and primary mouse neurons revealed that naringenin treatment can induce autophagy-promoting proteins such as ULK1, beclin1, ATG5, and ATG7 and that naringenin restored transcript levels of AMPK after siRNA-AMPK knockdown, reduced A $\beta$  levels to a nontoxic concentration, maintained the mitochondrial membrane potential, and resisted ROS production in A $\beta_{1-40}$ -induced neuronal cells (Fig. 4) [113]. In lipopolysaccharide (LPS)-stimulated BV-2 microglial and N2a cells,



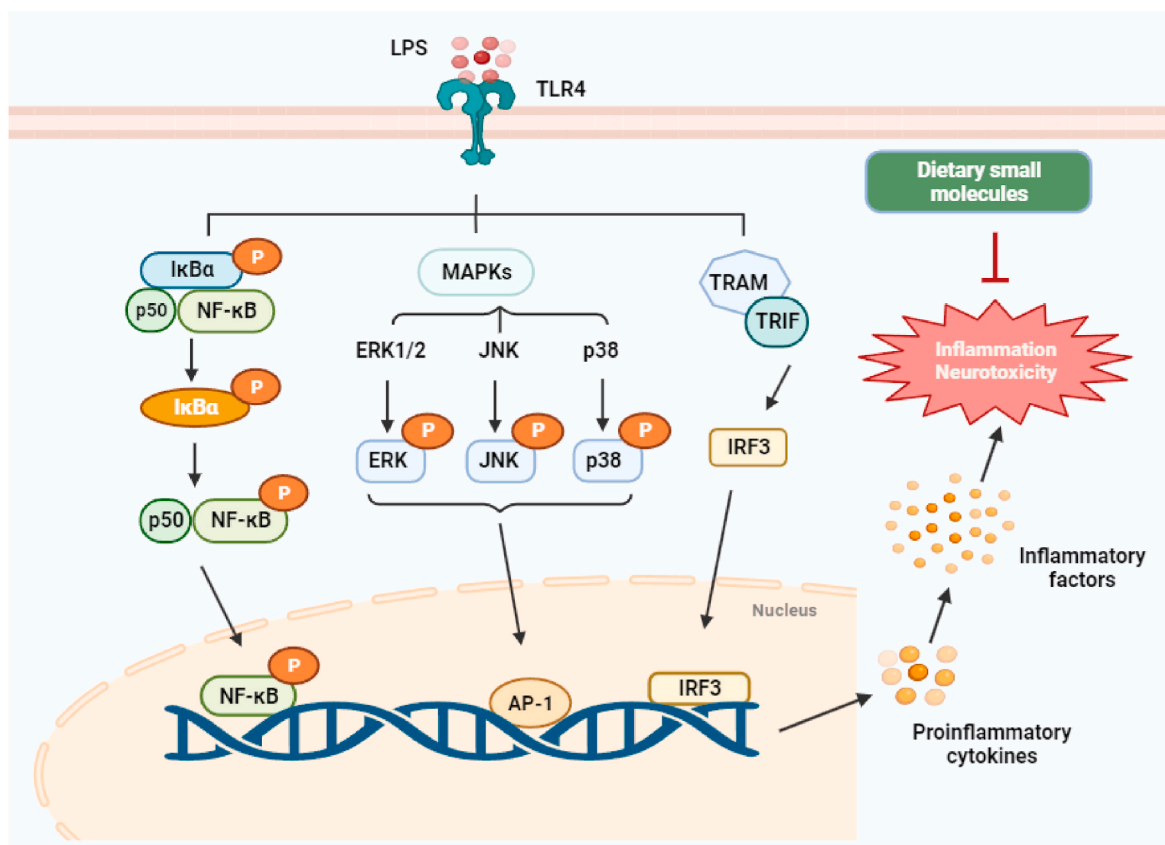
**Fig. 4.** Represents the potential role of dietary small molecules in promoting autophagy and inhibiting A $\beta$  plaques and NFT induced neurotoxicity and inflammatory responses in AD. A $\beta$  protein is generated through a series of proteolytic digestions of the single-pass transmembrane, APP. First  $\beta$  secretase (BACE) cleaves APP, releasing the soluble App $\beta$  fragment (sAPP $\beta$ ) into the extracellular space and leaves the C terminal fragment (CTF $\beta$ ) attached to the membrane. Subsequently, CTF $\beta$  is cleaved by an intramembrane-cleaving aspartyl protease complex,  $\gamma$  secretase to generate APP intracellular domain (AICD) and A $\beta$  isoforms (A $\beta$ <sub>40</sub> or A $\beta$ <sub>42</sub>). The major product is a 40 amino acid long A $\beta$ <sub>40</sub> while the 42 amino acid residues A $\beta$ <sub>42</sub> oligomerize faster and form A $\beta$  plaques in Alzheimer's brains. Mechanism of aberrant hyper-phosphorylation of tau protein that leads to microtubule depolymerization. Further, aggregation of oligomerized hyper-phosphorylated tau forms NFTs which accounts for neuronal death. Autophagy is suggested to involve in the clearance of A $\beta$  and hyper-phosphorylated tau aggregates, restraining generation of A $\beta$  plaques and NFTs, respectively. Autophagy inducers dietary small molecules can potentially enhance autophagic degradation of aggregated A $\beta$  and tau proteins and inhibit neuroinflammatory responses. ROS: reactive oxygen species; A $\beta$ : amyloid beta; TNF- $\alpha$ : tumor necrosis factor-alpha; IL-1 $\beta$ : interleukin-1 $\beta$ ; IL-6: interleukin-6; iNOS: inducible nitric oxide synthase; NF- $\kappa$ B: nuclear factor kappa B; BACE-1: beta-secretase 1; APP: amyloid precursor protein; NFTs: neurofibrillary tangles.

naringenin pretreatment inhibited NO release, the expression of iNOS and COX-2, as well as the expression of pro-inflammatory cytokines induced by the activation of suppressor of cytokine signaling-3 (SOCS-3) through the AMPK $\alpha$  and protein kinase C-delta (PKC $\delta$ ) signaling pathways (Fig. 5) [114].

A study in mice with LPS-induced AD demonstrated that naringenin treatment (10 and 20 mg/kg bw) had significant protective effects on microglial activation and improved motor coordination, as well as influencing anti-neuroinflammatory responses in the hippocampus and cerebral cortex [114]. In mice with A $\beta$ -induced AD, naringenin treatment (100 mg/kg bw) for 1 day improved spatial learning and memory function, lowering hippocampal MDA and NO levels and successfully restoring SOD levels and neuronal loss [115]. In ICR mice with scopolamine-induced amnesia, naringenin treatment (1, 3, and 4.5 mg/kg bw) for 3 weeks significantly ameliorated spatial learning and memory deficits as measured in both the passive avoidance and Y-maze tests, and inhibited AChE activity [116]. Similarly, in rats with ICV-STZ-induced AD, 2 weeks of naringenin treatment (50 mg/kg bw) significantly decreased non-enzymatic 4-hydroxynonenal (4-HNE), MDA, thiobarbituric acid reactive substances (TBARS), H<sub>2</sub>O<sub>2</sub>, and PCO levels, and increased GSH levels and GPx, GR, GST, SOD, CAT, and Na<sup>(+)</sup>/K<sup>(+)</sup>-ATPase activity; loss of choline acetyltransferase (ChAT)-positive neurons in the hippocampus was attenuated and there was significant improvement in spatial learning and memory (Figs. 2 and 3) [117]. Another study found that ICV-STZ-induced rats receiving naringenin supplements (25, 50 mg, 100 mg/kg bw) for 3 weeks had better learning and memory performance. This was accompanied by increased

mRNA expression of insulin and insulin receptors, and reduced tau hyperphosphorylation and A $\beta$  upregulation in both the hippocampus and cerebral cortex through downregulation of GSK3- $\beta$  activity. In addition, naringenin enhanced insulin signaling in the brain and the peroxisome proliferator-activated receptor gamma (PPAR- $\lambda$ ) in these rats [118].

However, in a study of iron-dextran-induced neurotoxicity in AD rats, administration of naringenin (50 mg/kg bw) for 28 days significantly improved antioxidant enzyme activity (SOD, CAT, and GPx) and attenuated oxidative damage by decreasing TBARS and PCO levels, and DNA apoptosis, as well as reducing AChE activity and reducing the density of degenerating and necrotic cells in the cerebral cortex [119]. In rats, oral administration of naringenin (50 mg/kg bw) for 2 weeks successfully improved spatial learning and recognition memory and significantly ameliorated MDA, AChE, and 5-hydroxyindoleacetic acid levels by modulating GSH, SOD, CAT, and GPx levels in the hippocampus and cortex while simultaneously increasing ACh, 5-HT, and dopamine levels as well as maintaining normal neuronal morphology in AlCl<sub>3</sub>-induced AD rats [120]. Oral administration of naringenin (25, 50, and 100 mg/kg bw) for 7 days can prevent LPS-induced spatial memory deficits, oxidative damage, and improve levels of antioxidant enzymes such as SOD, CAT, and GSH in the hippocampus. In addition, naringenin treatment at the same doses significantly increased Nrf2 and decreased NF- $\kappa$ B, TNF- $\alpha$ , toll-like receptor 4 (TLR4), GFAP, iNOS, and COX2 in the hippocampus in LPS-induced rats [121]. Furthermore, naringenin (200 mg/kg bw) for 12 weeks can prevent memory impairment and neuroinflammation; these effects were associated with the inhibition of A $\beta$



**Fig. 5.** Molecular pathways are involved in the anti-inflammatory effect of dietary small molecules. LPS is a potent activator of the NF- $\kappa$ B, MAPK, and IRF3 signaling pathways. Phosphorylation of I $\kappa$ B $\alpha$  by IKK results in the release of cytoplasmic NF- $\kappa$ B and subsequently its translocation into the nucleus. In the nucleus, NF- $\kappa$ B activates the expression of the pro-inflammatory gene. NF- $\kappa$ B can also be activated by MAPK and IRF3 signaling pathways. Dietary small molecules mainly inhibit the secretion and expression of related inflammatory factors through multiple molecular pathways. LPS: lipopolysaccharide; TLR4: toll-like receptor 4; ERK1/2: extracellular signal-regulated kinase 1/2; JNK: c-Jun N-terminal kinase; p38: NF- $\kappa$ B; MAPK: mitogen-activated protein kinase.

production, oxidative stress, and tau hyperphosphorylation in the brain in mice with HFD-induced AD [122]. Another study reported that naringenin (25, 50, or 100 mg/kg bw) for 3 weeks significantly improved learning capacity and memory retention, effectively ameliorated cognitive dysfunction, reduced isoflurane-induced apoptosis, and modulated the PI3/Akt/PTEEN and NF- $\kappa$ B signaling pathways in isoflurane-induced rats [123].

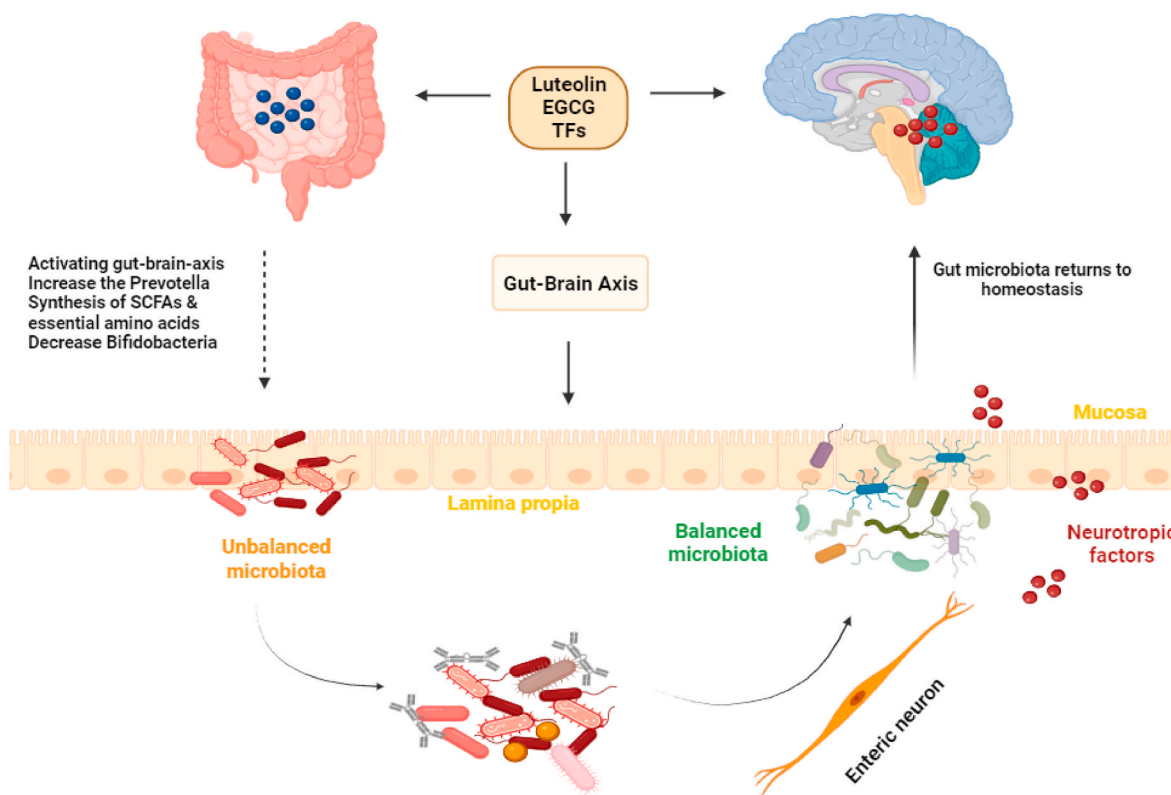
#### 4.4. Neuroprotective mechanisms of luteolin in AD

Luteolin is a flavonoid biophenol compound found in vegetables and fruits, including black and white pepper, broccoli, thyme, olive oil, pomegranate, cocoa, cucumber, buckwheat sprouts, and celery [124]. Evidence suggests that it has anticancer, cardioprotective, antioxidant, neuroprotective, and anti-inflammatory properties [124]. Luteolin has been commercially developed as a dietary supplement and can be found in food and cosmetic products because of its safety profile, with nontoxic side effects reported in mice at 2500 mg/kg and rats at 5000 mg/kg; this is equivalent to 219.8–793.7 mg/kg in humans [125]. In animals, glycosides of luteolin (10–70 mg/kg bw) can modulate systemic and brain insulin resistance, decrease A $\beta$  deposition by activating the gut-liver-brain axis, and prevent AD development (Fig. 6) [126]. A luteolin intake of about 2–125 mg per day is generally recommended as healthy [127].

In A $\beta$ <sub>25-35</sub>-induced PC-12 cells, luteolin treatment significantly prevented the A $\beta$ <sub>25-35</sub>-induced decrease in cell viability and inhibited apoptosis while significantly upregulating Bcl-2 expression and downregulating Bcl-2-associated X protein (Bax) and caspase-3. In addition, luteolin treatment significantly upregulated the expression of estrogen

receptor beta (Er $\beta$ ) and p-ERK1/2 in A $\beta$ <sub>25-35</sub>-induced PC-12 cells [128]. Zheng et al. [129] found that luteolin pretreatment suppressed the activation of the BACE1 promoter and inhibited NF- $\kappa$ B signaling by both directly and indirectly disrupting p65 complex formation, and inhibiting APP, C99 protein, and A $\beta$ <sub>1-42</sub> aggregation in lipofectamine 2000-transfected HEK293 and SH-SY5Y cells. Luteolin has also been used to investigate cellular toxicity, barrier function, cytokine production, and inflammation-related intracellular signaling pathways in A $\beta$ <sub>1-40</sub>-induced human brain microvascular endothelial cells (hBMECs) and human astrocytes (hAs). The results demonstrated that luteolin increased cell viability and protected barrier function by preserving transendothelial electrical resistance and relieving aggravated permeability in the human BBB. Luteolin also reduced the production of inflammatory mediators and cytokines, including COX-2, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-8 in hBMECs and hAs. In addition, luteolin treatment inhibited p-p38, p-ERK, and p-c-Jun N-terminal kinase (p-JNK) activation, downregulated p-I $\kappa$ B kinase (p-IKK), relieved inhibitory I $\kappa$ B $\alpha$  degradation, and blocked NF- $\kappa$ B p65 nuclear translocation in A $\beta$ <sub>1-40</sub>-induced hBMECs and hAs (Fig. 5) [130]. Similarly, in APP-overexpressed SH-SY5Y cells, luteolin treatment increased cell viability, reduced intracellular ROS generation, enhanced SOD activity, and reversed mitochondrial membrane potential dissipation. Furthermore, luteolin effectively inhibited caspase-mediated apoptosis, downregulated A $\beta$ PP expression, and lowered A $\beta$ <sub>1-42</sub> secretion in APP-overexpressed SH-SY5Y cells [131]. In another study, luteolin decreased zinc-induced tau hyperphosphorylation at the Ser262/356 epitope by regulating phosphorylation/dephosphorylation in SH-SY5Y cells [132]. In LPS-induced rat C6 glioma cells, pretreatment with luteolin (1 and 10  $\mu$ M) inhibited cell proliferation, reduced the release of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, and





**Fig. 6.** Regulative role of dietary small molecules in gut–brain axis. Dietary small molecules (luteolin, EGCG, and TFs) modulate gut microbiota diversity and subsequently involved in gut–brain axis; Dietary small molecules are related with the neurotrophic and neurotransmitter system and ultimately contributes to the regulation between gut homeostasis and brain function. SCFA: short-chain fatty acids; EGCG: epigallocatechin-3-gallate; TFs: theaflavins.

decreased the endoplasmic reticulum (ER) stress marker GRP78 (Fig. 5) [133].

In a mouse model of AD, luteolin administration (20 and 40 mg/kg bw) for 3 weeks improved spatial memory learning and cognitive function, and ameliorated A $\beta$ -plaque formation; this was accompanied by inhibition of both GFAP expression and neuroinflammation (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, NO, COX-2, iNOS, p-p38, and p-NF- $\kappa$ B) as well as decreased expression of GRP78 and inositol-requiring enzyme type 1 $\alpha$  (IRE1 $\alpha$ ) in brain tissue [133]. In an APP23 AD mouse model, treatment with luteolin (100 mg/kg bw) for 29 weeks ameliorated depression-like behavior and improved spatial learning, suppressed IL1- $\beta$  production by reducing endoplasmic reticulum (ER) stress, and reduced brain levels of activation factor 4 (ATF4), Iba-1, and CD68 [134]. Similarly, in rats with STZ-induced AD, luteolin treatment (10 and 20 mg/kg bw) for 1 week significantly ameliorated spatial learning and memory impairment and increased the thickness of the hippocampal CA1 pyramidal layer [135]. Another study revealed that luteolin treatment (50, 100, and 200 mg/kg bw) of A $\beta$ -induced AD rats for 17 days ameliorated A $\beta$ -induced learning and memory impairment; the ChAT, SOD and GPx activity was increased, there was a reversal of the increase in AChE and MDA activity, as well as increase the Bcl2/Bax ratio in the hippocampus [136].

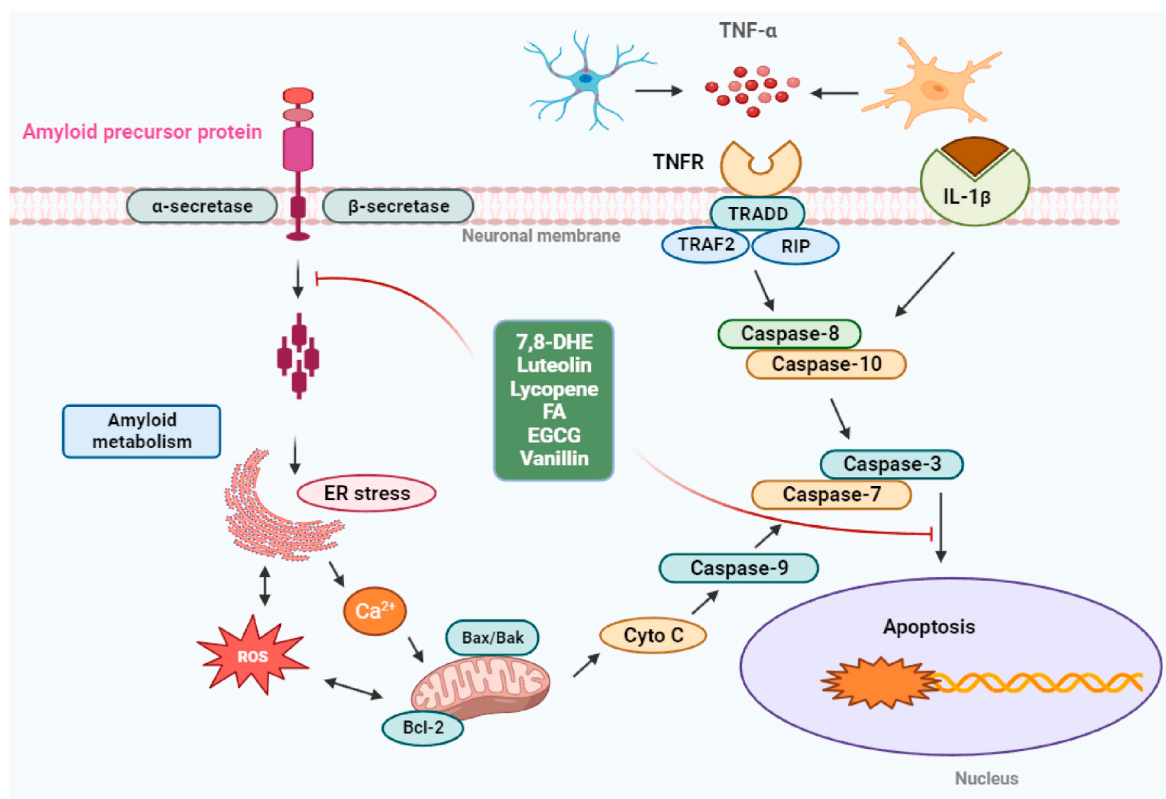
A very recent study demonstrated that oral administration of luteolin (20 or 40 mg/kg bw) for 8 weeks significantly ameliorated memory and cognitive impairment and provided neuroprotection by inhibiting A $\beta$  generation, restoring mitochondrial damage, reducing neuronal apoptosis and promoting PPAR $\gamma$  expression and function in 3  $\times$  Tg-AD mice [137]. In an A $\beta$ -induced AD mouse model, luteolin (80 mg/kg bw) for 2 weeks promoted A $\beta$  clearance by reducing levels of p-JNK, p-p38, GFAP, and Iba-1, and decreased the inflammatory markers p-NF- $\kappa$ B p65, TNF- $\alpha$ , IL-1 $\beta$  and COX-2 in the cortex and hippocampus. Luteolin exerted its anti-AD effects in A $\beta$ <sub>1-42</sub>-injected mice by enhancing synaptic proteins PSD-95 and SNAP-25 expression through reductions in BACE-1 and

A $\beta$ <sub>1-42</sub> expression and regulation of proapoptotic and antiapoptotic protein expression via decreased Bax and caspase-3 and increased Bcl2 in the cortex and hippocampus (Figs. 4 and 7) [138]. In a transgenic *Drosophila* AD model, luteolin treatment (5, 10, 15, and 20  $\mu$ M)—in a concentration-dependent manner—reduced A $\beta$  aggregation, LPO, protein carbonyl content (PCC), GST, AChE, caspase-9, and caspase-3 activity and increased SOD, CAT, and GSH expression while increasing the life span and climbing ability of the flies [139]. However, more recent studies found that administration of luteolin combined with palmitoylethanolamide (5 mg/kg bw) attenuated the activity of A $\beta$ -induced proinflammatory mediators (iNOS, COX-2, IL-1 $\beta$ , IL-6, IL-10, and TNF- $\alpha$ ), inhibited astrogliosis and microgliosis activation, and upregulated mRNA expression for neurotrophic markers such as BDNF and GDNF, as well as promoting neuronal survival [140,141].

#### 4.5. Neuroprotective mechanisms of lycopene in AD

Lycopene is a lipophilic aliphatic hydrocarbon carotenoid that can be obtained from many fruits and vegetables, including tomatoes, watermelons, pink guavas, papayas, pink grapefruits, and apricots. Tomato is a major source of lycopene and is also a considerable source of vitamins C, K, A, carbohydrates, and fiber, as well as potassium, iron, sulfur, and phosphorus [142]. Previous studies have shown that lycopene is an antioxidant that is cardioprotective, neuroprotective, anticancer, anti-inflammatory, and antihypertensive and that it improves memory [143]. Investigators recommend that a daily lycopene intake of about 5–10 mg is healthy [144]. No known adverse events were observed following rodent consumption of up to 3 g/kg per day of either dietary or formulated lycopene [145,146].

Recent pharmacological studies have shown that lycopene might be useful in treating AD. Fang et al. recently reported that lycopene may have neuroprotective activity in A $\beta$ -overexpressed M146L cells. Their



**Fig. 7.** Molecular pathways are involved in the anti-apoptotic effect of dietary small molecules. Apoptosis is conducted through intrinsic and extrinsic pathways in the pathogenesis of AD. Inflammatory cytokines, such as TNF $\alpha$  and IL-1 $\beta$ , can trigger the neuronal apoptosis through membrane receptor or extrinsic pathway (i.e., TNF $\alpha$ /caspase-8/caspase-3). The intrinsic pathway of neuronal apoptosis is activated by intracellular insults including tau aggregates, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, free radicals, etc. Mitochondrial cytochrome c (Cyt c) is released to initiate apoptosis signaling through the Cyto c/caspase-9/caspase-3 cascade. Dietary small molecules (7,8-DHE, luteolin, lycopene, FA, EGCG, and vanillin) can take an anti-apoptotic action by mediating different signaling targets. ROS: reactive oxygen species; TNF- $\alpha$ : tumor necrosis factor-alpha; IL-1 $\beta$ : interleukin-1 $\beta$ ; Bax: Bcl-2-associated X protein; Bcl2: B-cell lymphoma 2; ER: endoplasmic reticulum.

results showed that lycopene treatment alleviated oxidative stress and apoptosis, activated the PI3K/Akt/Nrf2 signaling pathway, upregulated antioxidant and antiapoptotic proteins, downregulated proapoptotic proteins, and inhibited APP and BACE activity in M146L cells [147]. Another *in vitro* study reported that lycopene improved cell viability, reduced intracellular and mitochondrial ROS levels, and inhibited apoptosis and NF- $\kappa$ B-target gene expression in A $\beta$ -treated SH-SY5Y cells [148]. Similarly, Lim et al. reported that lycopene treatment increased mitochondrial respiration, mitochondrial membrane potential, and glycolytic function by reducing intracellular and mitochondrial ROS levels, DNA fragmentation, caspase-3 activation, cytochrome *c* release, and inhibited cell death and NF- $\kappa$ B activation in RCAN1-overexpressing SH-SY5Y cells [149]. Lycopene protected cells from LPS-stimulated neurotoxicity and attenuated neuroinflammation by inhibiting the Iba-1, COX-2, p-p38, p-Erk, p-JNK, and p-Akt and p-I $\kappa$ B- $\alpha$  and p-NF- $\kappa$ B signaling pathways, and significantly elevated expression of Nrf2 in the nucleus and cytosol, HO-1, and NQO-1, and reduced intracellular ROS production in BV-2 microglial cells (Fig. 5) [150]. Huang et al. [151] reported that lycopene treatment promoted the secretion of neuroprotective NGF, BDNF, vascular endothelial growth factor (VEGF), and increased Bcl2 expression by inhibiting the expression of Bax, cleaved caspase-3, and cytochrome *c*. It has also been reported that lycopene increased expression of the synaptic proteins PSD-95 and synaptophysin (SYP) and activated the PI3K/Akt pathway in a *tert*-butyl hydroperoxide (t-BHP)-induced AD primary culture model. Qu et al. [152] observed that lycopene treatment efficiently attenuated A $\beta$ -induced neurotoxicity in a primary culture AD model as evidenced by improved cell viability, inhibited ROS generation and mitochondrial membrane potential

depolarization, restored levels of proapoptotic Bax and antiapoptotic Bcl-2, and inhibited caspase-3 activation (Fig. 7). Another study showed that lycopene attenuated A $\beta$ -induced oxidative stress by decreasing intracellular and mitochondrial ROS production and mitochondria-derived superoxide production, opening mitochondrial permeability transition pores leading to cytochrome *c* release and ameliorating mitochondrial morphological dysfunction. Lycopene also restored ATP levels, improved mitochondrial complex activities, prevented mitochondrial DNA damage, and increased levels of mitochondrial transcription factor A within mitochondria in an A $\beta$ -induced primary culture AD model [153].

In rats with A $\beta$ <sub>1-42</sub>-induced AD, lycopene treatment (2.5 and 5 mg/kg bw) improved memory retention in MWM and markedly attenuated oxidative stress as indicated by significant decreases in MDA, LPO, and NO activity, reduced mitochondrial damage, inhibition of caspase-3 activity, IL-6, and TNF- $\alpha$ , and restoration of BDNF levels [154]. Similarly, treatment with lycopene (1, 2, and 4 mg/kg bw) reduced mitochondrial dysfunction, inhibited caspase-3 activity associated with neuronal cell death, and improved spatial memory learning and memory by reducing levels of the proinflammatory cytokines TNF- $\alpha$ , TGF- $\beta$ , and IL-1 $\beta$  as well as NF- $\kappa$ B in the hippocampus and cerebral cortex in A $\beta$ <sub>1-42</sub>-induced AD rats [155]. Recently, Xu et al. observed that lycopene treatment (4 mg/kg bw) improved learning and memory function, induced liver X receptor (LXR) expression and activated LXR-PI3K-AKT signaling, and inhibited A $\beta$ -plaque formation and neuroinflammation in APP/PS1 mice [156]. Other research found that lycopene administration (4 mg/kg bw) effectively restored cognitive and memory impairment by diminishing A $\beta$  deposition, reducing inflammatory responses by

blocking inflammatory cytokine production and NF- $\kappa$ B p65 and TLR4 protein expression in the hippocampus of A $\beta$ -induced AD rats (Fig. 4) [157]. In mice with LPS-induced AD, 5 weeks of lycopene treatment (30 mg/kg) lowered APP levels, prevented accumulation of A $\beta$ , and suppressed neuronal BACE1 and elevated expression of the  $\alpha$ -secretase ADAM10. Furthermore, lycopene downregulated Iba-1 expression, reduced inflammatory mediator levels, and inhibited oxidative stress in the hippocampus (Fig. 4) [150].

Furthermore, in a fructose-induced mouse model of AD investigating lycopene treatment (4 mg/kg) for 10 weeks, spatial learning and memory were improved, oxidative stress was reduced, and AChE activity was reduced in both the hippocampus and cerebral cortex. In addition, lycopene also significantly reduced insulin resistance and the expression of insulin-like growth factor 1 receptor, PI3K, and p-AKT proteins, significantly reduced plasma insulin and Homeostatic Model Assessment for Insulin Resistance; it also reduced TNF- $\alpha$ , IL-1 $\beta$  and NF- $\kappa$ B and elevated PPAR $\gamma$  protein expression in both the hippocampus and cerebral cortex [158]. Xu et al. [159] showed that the administration of lycopene (5 mg/kg), human amniotic epithelial cell transplantation, and a combination of the two significantly improved cognitive function and spatial learning, decreased TNF- $\alpha$  and IL-1 $\beta$  levels, downregulated TLR4 and NF- $\kappa$ B p65 mRNA and protein expression, and increased levels of the anti-inflammatory markers IL-10 and TGF- $\beta$ 1 in the cerebrospinal fluid and hippocampal tissue in a rat model with A $\beta$ <sub>1-42</sub>-induced AD at the choroid plexus.

#### 4.6. Neuroprotective mechanisms of ferulic acid in AD

Ferulic acid (FA) is a natural phenolic compound found in oranges, wheat, peanuts, apples, rice, coffee, barley, vanilla beans, and many other foods [160]. FA has been confirmed to have anti-inflammatory, antiapoptotic, antidiabetic, anticancer, antioxidant, and neuroprotective properties [161]. In the United States, Japan, and most European countries, FA has been approved as a food additive and is also added to beverages and cosmetics [162]. Li et al. [163] reported that FA (300  $\mu$ g/mL) had no toxic effects on red blood cells, white blood cells, or platelets. Recommendations for a healthy daily intake of FA are lacking, but consumption from food sources can be estimated at approximately 200–1000 mg per day.

FA has been suggested as a possible neuroprotective strategy against AD due to its antioxidant and anti-inflammatory properties. Several studies have investigated FA using *in vitro* and *in vivo* AD models. Huang et al. [164] reported that FA treatment was neuroprotective by significantly reducing the production of TNF- $\alpha$  and IL-1 $\beta$  and upregulating CREB and p-CREB as well as phosphodiesterase 4 (PDE4) activity in LPS-stimulated PC12 cells (Fig. 3). Additionally, FA pretreatment of SH-SY5Y cells inhibited the transition of A $\beta$ <sub>42</sub> from monomers to oligomers by preventing A $\beta$ <sub>42</sub> from forming fibrils [165]. Similarly, another study in SH-SY5Y cells examined the effect of FA on A $\beta$ <sub>1-40</sub>-induced hallmarks of AD such as A $\beta$  aggregation, cell death, and ROS formation, and reported significant decreases in A $\beta$  aggregation and intracellular and mitochondrial ROS formation, as well as membrane damage repair [166]. A comparable study revealed that the anti-inflammatory effect of FA in LPS-stimulated BV-2 microglial cells was mediated via significant suppression of IL-1 $\beta$ , prostaglandin E2 (PGE2), and NO release, a reduction of COX-2 and iNOS expression, and the subsequent inhibition of TLR4 activity in a concentration-dependent manner [167]. The most recent study demonstrated that FA pretreatment inhibited TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 production and significantly decreased the expression of autophagy-related protein p62 by increasing beclin1, p-ULK1, p-AMPK, LC3, transcription factor EB, and lysosomal-associated membrane protein 2A in LPS-stimulated BV-2 microglial cells (Fig. 5) [168].

Kim et al. [169] highlighted that FA administration (20 or 50 mg/kg bw) for 28 days improved trimethyltin-induced cognitive deficits and increased ChAT activity. Most recently, FA improved behavioral and cognitive function and effectively attenuated A $\beta$ -induced upregulation

of intracellular Ca<sup>2+</sup>, inhibited PPI1, and activated dopamine and cAMP regulated phosphoprotein 32 kDa (DARPP-32) by increasing synapsin1 and synaptic protein PSD-95 and improving LTP, as well as preventing the loss of GluN2B phosphorylation and decreasing A $\beta$  accumulation in APP/PS1 mice [170]. Wang et al. [171] reported that FA (20 mg/kg bw) for 30 days reduced A $\beta$  plaque deposition and increased the diameter and density of hippocampal capillaries, thus facilitating the supply of oxygen and nutrients to the brain and the removal of metabolic waste; this led to improved spatial memory in the APP/PS1 AD mouse model. Mori et al. [172] also used transgenic APP/PS1 mice and found that FA (30 mg/kg bw) for 6 months decreased oxidative stress associated with A $\beta$  production and inhibited synaptotoxicity, amyloidogenic APP processing, microgliosis, astrogliosis, and neuroinflammation, leading to improvements in cognitive tasks. Yan et al. [173] showed that oral administration of FA (5.3 and 16 mg/kg bw) for 6 months significantly reduced neuroinflammation, which was associated with reduced A $\beta$ <sub>1-40</sub> and A $\beta$ <sub>1-42</sub> deposition and IL-1 $\beta$  levels in the hippocampus and frontal cortex as well as enhanced cognitive performance. Furthermore, Jin et al. [174] observed that treatment with FA (50, 100, and 250 mg/kg bw) for 3 weeks led to a strong IL-1 $\beta$  reduction, inhibition of GFAP, decreased phosphorylation of both ERK1/2 and p-p38 and inhibition of the apoptotic cascade, particularly caspase-3 and FasL protein expression in the hippocampus of rats induced with A $\beta$ <sub>1-40</sub>. A further study concluded that FA (1–100  $\mu$ M) inhibited AD-like symptoms induced by A $\beta$  neurotoxicity through clearance of A $\beta$  aggregation, reduction in lipid levels, and activation of autophagy pathways in a *C. elegans* AD model [175].

#### 4.7. Neuroprotective mechanisms of ellagic acid in AD

Ellagic acid (EA) is a natural polyphenol compound found in vegetables and fruits such as persimmons, black raspberries, wolfberries, strawberries, pomegranates, cranberries, walnuts, pecans, plums, and peaches, as well as in other plant foods [176]. It has shown anticancer, antioxidant, antidiabetic, antimutagenic, anti-inflammatory, antiaging, and neuroprotective properties [177]. A previous study observed that the no observable effect level was estimated at 3011 mg/kg bw per day for male rats and less than 778 mg/kg bw per day for females. Meanwhile, the lowest observed adverse effect level was estimated at 3254 mg/kg bw per day for male and female rats [178]. At present, standard dosing recommendations for EA are lacking, suggesting that the correct dose depends on several factors, including the age and health of the consumer.

Recent *in vitro* results showed that EA treatment improves cell viability and reduces cytotoxicity by reducing A $\beta$  fibril formation and oligomer loss in A $\beta$ <sub>42</sub>-induced SH-SY5Y cells [179]. Shen et al. [180] observed that EA treatment of H<sub>2</sub>O<sub>2</sub>-induced PC12 cells reduced cell damage and enhanced cell viability through two key mechanisms: inhibiting ROS production and reducing calcium ion influx. In another *in vitro* experiment using SH-SY5Y cells induced by D-galactose, EA exhibited antioxidant and anti-inflammatory effects by inhibiting ROS production and reducing MDA levels and neuroinflammation by targeting  $\beta$ -galactosidase, advanced glycation end products, and TNF- $\alpha$  activity, and by increasing GSH and improving cell viability [181]. A recent study demonstrated that the anti-inflammatory effect of EA in LPS-induced BV-2 microglial cells was associated with the downregulation of inflammatory mediators such as TNF- $\alpha$ , NO, and p-ERK1/2 (Fig. 5) [182].

Interestingly, Zhong et al. [183] reported that EA treatment (50 mg/kg bw) for 2 months ameliorated spatial learning and memory impairment, exhibited antiapoptotic effects by inhibiting caspase-3 activation and neuronal apoptosis, significantly inhibited A $\beta$  deposition and hyperphosphorylation of tau, and decreased GSK3- $\beta$  activity in the hippocampus of APP/PS1 mice. Jha et al. [184] previously investigated the anti-AD effect of a 5-week EA treatment (50 mg/kg bw) in STZ-induced AD rats. Their results showed that EA significantly

diminished oxidative stress, AChE levels, GFAP, and C-reactive protein expression, decreased the A $\beta$  plaque level, improved synaptic connectivity, and improved motor function and learning. Similarly, oral EA administration 50 mg/kg bw in AlCl<sub>3</sub>-induced AD rats significantly improved episodic memory and decreased APP and TBARS levels, increased CAT, SOD, and GSH activity, and reduced NFTs and neuritic plaques as well as downregulated caspase-3 and APP expression in entorhinal cortex sections (Figs. 3 and 4) [185]. Oral EA administration (10, 50, and 100 mg/kg bw) for 1 week provided neuroprotection, including remarkable decreases in levels of AChE, BChE, and oxidative stress markers, while increasing learning and memory and modulating the NF- $\kappa$ B/Nrf2/TLR4 signaling pathway in A $\beta$ -induced AD rats [186]. Assaran et al. subsequently reported that administration of EA (25, 50, and 100 mg/kg bw) for 3 weeks prevented learning and memory deficits and significantly reduced MDA activity but significantly increased SOD and CAT activity in the hippocampus and cortex in scopolamine-induced AD rats [187].

#### 4.8. Neuroprotective mechanisms of caffeic acid in AD

Caffeic acid (CA) is a phenolic compound widely distributed in vegetables and medicinal plants such as cabbage, turmeric, mushrooms, cauliflower, radishes, kale, and apples, and in plant-derived liquids and beverages like olive oil, wine, coffee, and tea [188,189]. It is reported to have antiviral, anticancer, anti-inflammatory, immunomodulatory, antioxidant, and neuroprotective properties [190,191]. Drinking a single cup of coffee provides as much as 70–350 mg of CA [192], and the daily intake of CA has been estimated at 500–1000 mg in humans through consumption of fruits, vegetables, and CA-containing beverages [161]. A reproductive and toxicity study in mice revealed that the NOAEL was 150 mg/kg bw per day [193].

Recent pharmacological animal and *in vitro* studies have shown that CA has beneficial effects on the brain, including protection from neuronal damage induced by a variety of neurotoxic agents, and may be useful in treating AD. Furthermore, pretreatment of A $\beta$ <sub>1–42</sub>-induced PC12 cells with CA significantly reversed A $\beta$ -induced neurotoxicity by increasing cell viability, efficiently scavenging free radicals, attenuating increases in intracellular calcium and tau phosphorylation, and significantly decreasing the phosphorylation of GSK-3 $\beta$  [194]. Another *in vitro* study reported that CA pretreatment improved cell viability and attenuated acrolein-induced neurotoxicity, ROS accumulation, GSH depletion, and mitochondrial membrane potential dysfunction; CA also modulated MAPKs and Akt/GSK3 $\beta$  signaling pathways, and subsequently restored the changes to BACE-1 and ADAM-10 induced by acrolein [195].

A recent study in HFD-induced AD rats showed that CA treatment (30 mg/kg bw) for 30 weeks enhanced SOD and CAT activity, increased the expression of p-GSK3 $\beta$  and synaptophysin proteins, and reduced phosphorylated-tau (p-tau [Ser 396], p-tau [Ser 404], and p-tau [Thr 181]) expression in the hippocampus and cortex; it also attenuated APP and BACE1 expression, which led to the lowering of A $\beta$ <sub>1–42</sub> and drebrin accumulation in the hippocampus and cortex (Fig. 4) [196]. Using A $\beta$ -induced AD rats, Wang et al. [197] found that oral administration of CA (100 mg/kg bw) for 2 weeks significantly rescued learning deficits and increased cognitive function by reducing oxidative stress, increasing NO and AChE activity, and suppressing inflammation. This was accompanied by the inhibition of NF- $\kappa$ B-p65, p53, and p-p38 MAPK as well as decreased expression of caspase-3 in the hippocampus. Deshmukh et al. [198] found that CA (10, 20, and 40 mg/kg bw) for 3 weeks attenuated STZ-induced behavioral changes and cognitive function. Their results showed that CA treatment abrogated STZ-induced increases in AChE, NO, and PCO levels, reduced MDA, and modulated oxidative stress indicators in the hippocampus and cortex in AD rats.

Khan et al. [199] demonstrated that CA (50 mg/kg bw) for 2 weeks exerted neuroprotective effects against A $\beta$ <sub>1–42</sub>-induced AD in mice via improvements in spatial learning, memory, and cognitive abilities,

markedly reduced levels of ROS and TBARS, and increased expression of Nrf2 and HO-1 in the hippocampus. CA also has anti-inflammatory properties and has been shown to downregulate Iba-1 and GFAP over-expression, and reduce the proinflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$  in the hippocampus of AD mice. It also activated NF- $\kappa$ B and increased expression of the synaptosomal-associated proteins SNAP-25 and SNAP-23, SYN, and postsynaptic density protein 95, and significantly increased p-PI3K/p-AKT and BDNF proteins in these mice (Figs. 3 and 4). In an ApoE<sup>−/−</sup> AD mouse model, treatment with CA (20 mg/kg bw) for 2 months alleviated spatial learning impairment and cognitive decline, reduced A $\beta$  accumulation, upregulated mRNA levels for ATP-binding cassette (ABC) transporters ABCA1 and ABCG1, and elevated serum HDL cholesterol concentration, as well as reducing levels of serum TNF- $\alpha$ , monocyte chemoattractant protein-1, and IL-6 and decreasing local inflammation in the hippocampus [200]. A recent *C. elegans* AD model showed that CA treatment significantly alleviated A $\beta$ -induced toxicity, increased life span, decreased body paralysis, and improved reproductive defects. In addition, the treatment increased resistance to heat and oxidative stress and reduced polyglutamine (polyQ40) aggregate formation in strains N2 and CL4176. These protective effects were exerted via activation of transcription factor DAF-16 and its downstream targets SOD-3 and GST-4, which subsequently upregulated mRNA expression for heat shock proteins HSP-1 and HSP-16.2 in CL4176 [201].

#### 4.9. Neuroprotective mechanisms of gallic acid in AD

Gallic acid (GA) is a phenolic small molecule found naturally in numerous medicinal plants and a wide range of fruits, such as blueberries, strawberries, blackberries, mangoes, grapes, and pomegranates. It is also found in walnuts, wine, tea, cashew nuts, hazelnuts, plums, and other foods [202]. The therapeutic potential of GA is due to its anti-oxidative, anti-proliferative, chemoprotective, antimicrobial, antidiabetic, anti-inflammatory, antidepressant, and neuroprotective properties [202,203].

Recent *in vitro* and *in vivo* studies have drawn attention to the neuroprotective effects of GA. In an *in vitro* AD model, pretreatment with GA suppressed A $\beta$ -induced neuronal cell death, efficiently suppressed the expression of proinflammatory cytokines (iNOS, COX-2, and IL-1 $\beta$ ), and greatly reduced the levels of nuclear p65 and p65 acetylation in BV-2 microglial cells and Neuro-2A cells (Fig. 5) [204].

Moreover, treatment with GA (10 and 20 mg/kg) for 28 days ameliorated spatial working memory and cognitive dysfunction, as well as significantly inhibiting the expression of IL-1 $\beta$ , TNF- $\alpha$ , iNOS, and COX-2 in the hippocampus and cortex of A $\beta$ -induced AD mice. GA was also shown to restore A $\beta$ -induced NF- $\kappa$ B acetylation, substantially inhibit nuclear NF- $\kappa$ B activation, and dramatically suppress A $\beta$ -mediated neuronal cell death in AD mice [204]. Yu et al. [205] studied the anti-AD effects of GA in APP/PS1 mouse models and found that oral administration of GA (30 mg/kg) improved spatial learning and reference memory in both 4-month-old and 9-month-old APP/PS1 mice. Furthermore, GA treatment significantly elevated hippocampal LTP, increased expression of synaptic protein PSD-95, and decreased Iba-1 and GFAP protein expression in 9-month-old APP/PS1 mice. Further, fluorescence microscopy showed that GA significantly reduced A $\beta$ <sub>1–42</sub> aggregation and A $\beta$ <sub>1–42</sub>-induced intracellular calcium influx in both the hippocampus and cortex (Fig. 4). Another study reported that GA supplementation (20 mg/kg) for 6 months in APP/PS1 mice mitigated cerebral amyloidosis, including brain parenchymal and cerebrovascular A $\beta$  deposits, and decreased cerebral A $\beta$  proteins; reduced amyloidogenic and elevated nonamyloidogenic APP processing simultaneously elevated  $\alpha$ - and reduced  $\beta$ -secretase activity, inhibited neuroinflammation, and stabilized brain oxidative stress [206].

Similarly, in an AlCl<sub>3</sub>-induced AD rat model, treatment with GA (100 mg/kg) for 2 months decreased spatial memory impairment and learning deficits, significantly increased antioxidant enzymes (CAT,

GSH, and SOD), serum electrolytes (except  $K^+$ ) and neurotransmitter levels (except norepinephrine) with a corresponding decrease in stress markers (MDA,  $H_2O_2$ , and NO) in the hippocampus. In addition, histological studies showed that GA administration protected NFTs and amyloid plaques in the external granular layer in these rats (Fig. 3) [207]. GA treatment (30 mg/kg) for 26 days enhanced spatial memory performance and significantly prevented cognitive deficits associated with increased enzymatic SOD, CAT, and GPx activity and decreased TBARS levels in the hippocampus and cerebral cortex of ICV-STZ-induced AD rats [208]. In a sodium arsenite-induced memory model, co-administration of GA (50 and 1000 mg/kg) for 4 weeks produced antioxidant effects by normalizing oxidative stress indicators (SOD, CAT, and GPx), reducing AChE and MDA activity, and improving spatial learning and memory [209]. Finally, a small study showed that administration of (50, 100, and 200 mg/kg) for 10 days reduced neural damage and brain amyloid neuropathology and improved cognitive function via free radical scavenging and inhibition of A $\beta$  oligomerization in the hippocampus of rats with A $\beta$ -induced AD [210].

#### 4.10. Neuroprotective mechanisms of epigallocatechin-3-gallate in AD

Epigallocatechin-3-gallate (EGCG) is a green tea polyphenol that exerts metal-chelating, anti-inflammatory, free-radical-scavenging, antioxidant, anticancer, anti-apoptotic, and neuroprotective activity by modulating neuroprotective proteins, transcription factors, and other important neurotrophic growth factors [211,212]. Notably, *in vitro* and animal studies suggest that EGCG is highly absorbed, has moderate oral bioavailability, and can easily cross the BBB [213,214]. Food supplements containing green tea catechins provide a daily EGCG dose in the range of 5–1000 mg/day for adults [161]. Furthermore, a toxicity study showed that the NOAEL was 500 mg/kg bw per day following a 290-day green tea (EGCG) intervention in rats and mice [215,216], while a few 4-week oral intervention studies reported a NOAEL of 2500 mg/kg bw per day [217].

There is evidence that EGCG can decrease AChE activity and inhibit the A $\beta$  aggregation and tau phosphorylation associated with AD. An *in vitro* study showed that EGCG pretreatment effectively ameliorated A $\beta$ -induced cytotoxicity, suppressed increases in iNOS expression and subsequent production of NO and peroxynitrite, enhanced antioxidant enzyme levels, and altered the expression of proapoptotic signals in BV-2 microglial cells [218]. A similar study reported that EGCG administration significantly inhibited IL-6, IL-8, VEGF, and PGE2 production, decreased COX-2 expression, and inhibited NF- $\kappa$ B activation, with subsequent inhibition of phosphorylation of p38, JNK, and ERK in IL-1 $\beta$ +A $\beta$ <sub>(25-35)</sub>-induced U373MG cells [219]. Furthermore, in microglial BV-2 cells stimulated with LPS, pretreatment with EGCG significantly inhibited the production of the proinflammatory mediator NO, decreased the release of proinflammatory cytokine IL-6 while increasing TNF- $\alpha$ , downregulated MIF, CCL-2, and CSF2 and upregulated IL-3, IL-11, and TNFS10, significantly downregulated mTOR, NF- $\kappa$ B2, STAT1, Akt3, CCL5, and SMAD3 while significantly upregulating the expression of mRNA of Ins2, Pld2, A20/TNFAIP3, and GAB1 [220]. Similarly, EGCG is associated with protection against A $\beta$  and LPS-induced neurotoxicity in SH-SY5Y and BV-2 microglial cells through the inhibition of proinflammatory cytokines (IL-1 $\beta$  and IL-18), the reduction in Iba-1 over-expression, and the suppression of the co-localization of caspase-1 and Iba-1 activation as shown by immunofluorescence staining. In addition, EGCG treatment reversed the increased expression of NLRP3 and significantly reduced the expression of TLR4, p-IKK/IKK, and p-NF- $\kappa$ B/NF- $\kappa$ B in LPS + A $\beta$ -induced BV-2 microglial cells [221].

Zhong et al. [221] observed that the administration of EGCG (2 mg/kg bw) for 28 days reduced microglial inflammation and neurotoxicity by suppressing the activation of the canonical NLRP3 and noncanonical caspase-11-dependent inflammasome via the TLR4/NF- $\kappa$ B pathway in LPS + A $\beta$ -induced rat primary microglia and in the

hippocampus of APP/PS1 mice. Furthermore, EGCG supplementation (50 mg/kg bw) for 2 months had anti-AD activity, with significant attenuation of cognitive deficits, improvement in dendritic integrity and expression of synaptic proteins, decreased pro-inflammatory cytokine IL-1 $\beta$  and increased anti-inflammatory cytokines IL-4, IL-10, and IL-13, and subsequent alleviation of microglial activation in the brains of APP/PS1 mice. In addition, EGCG treatment markedly reduced A $\beta$  plaque formation and tau phosphorylation in the hippocampus of APP/PS1 mice [222]. Similarly, Nan et al. [223] reported that EGCG (100, 250, and 625 mg/kg bw) for 9 weeks increased ACh levels by inhibiting AChE activity, decreasing tau hyperphosphorylation and BACE1 expression, and suppressing A $\beta$ <sub>1-42</sub> expression in the hippocampus. In addition, EGCG treatment decreased the escape latency period while increasing the time at the target quadrant among AD rats. Interestingly, Lee et al. [224] reported that EGCG treatment (1.5 and 3.0 mg/kg bw) for 4 weeks prevented LPS-induced memory impairment and apoptotic neuronal cell death, suppressed A $\beta$  accumulation and the expression of APP, BACE1, and its product C99, while reducing the proinflammatory cytokines IL-1 $\beta$ , TNF- $\alpha$ , IL-16, iNOS, COX-2, and activating astrocytes as well as reducing amyloidogenesis.

Similarly, Etcheto et al. [225] observed that EGCG administration (40 mg/kg bw) for 3 months improved peripheral parameters such as insulin sensitivity and liver insulin pathway signaling, as well as central memory deficits. It also markedly increased synaptic markers and CREB phosphorylation rates, because of a decrease in unfolded protein response activation through a reduction in ATF4 levels and subsequent downregulation of protein tyrosine phosphatase 1B. In addition, EGCG significantly reduced brain A $\beta$  production and plaque burden by increasing ADAM10 levels in C57BL/6 WT and APP/PS1 mice; neuroinflammation was subsequently reduced as suggested by the decrease in astrocyte reactivity and TLR4 levels. In mice with estrogen deficiency and HFD-induced AD, EGCG administration (45 mg/kg bw) for 2 months improved object recognition and spatial memory, restored the diversity and structure of the gut microbiome in HFOVX mice, with increased *Prevotella* and inhibition of *Bifidobacteriales* but no effect on the decreases in *Alloprevotella* and *Lactobacillaceae* or on the increase in *Enterorhabdus* (Fig. 6) [226]. Soto-Mercado et al. [227] subsequently showed that EGCG treatment significantly inhibited the aggregation of (i)sAPP $\beta$ , blocked p-tau, increased  $\Delta\Psi_m$ , decreased oxidation of DJ-1 at residue Cys106-SH, and inhibited the activation of transcription factor c-JUN and P53, PUMA, and caspase-3 in mutant cholinergic-like neurons (ChLNs) compared to wild type. In addition, it reversed the  $Ca^{2+}$  influx associated with dysregulation as a response to ACh stimuli in PSEN1 E280A ChLNs, inhibited NF- $\kappa$ B activation, and reduced the secretion of pro-inflammatory IL-6 in wild-type astrocyte-like cells when exposed to mutant ChLNs culture supernatant.

#### 4.11. Neuroprotective mechanisms of theaflavins in AD

Theaflavins (TFs) are major polyphenols found in black tea and include theaflavin-3, 3'-digallate, theaflavin-3-gallate, and theaflavin-3'-gallate [228]. TFs have anticancer, anti-obesity, antiviral, antioxidant, antidiabetic, anti-inflammatory, and neuroprotective properties [229]. A pharmacokinetic study in humans demonstrated that consumption of 700 mg of TFs once a day (corresponding to about 30 cups of black tea) resulted in maximum blood plasma concentration and improved oral bioavailability [230].

Cao et al. [231] reported that theaflavin-3,3'-digallate treatment (15, 30, and 60 mg/kg bw) improved learning and memory in the NOR and Y-maze tests, increased the brain/body mass ratio, decreased glutamate concentration and AChE activity and increased ACh concentration in the brain, and enhanced ChAT, glutaminase, and glutamine synthetase activity. It has also been reported that theaflavin-3,3'-digallate treatment of D-galactose-induced AD mice increased activity of the antioxidant enzymes GPx and SOD, while the concentration of MDA was reduced; the antioxidant genes Nrf2, Prx2, GSH-px1, and SOD1 were

subsequently upregulated in the brain. Another study reported that administration of TFs (10 and 50 mg/kg bw) for 3 days to C57BL/6J mice with LPS-induced AD significantly increased spontaneous alternations in the Y-maze test and reduced immobility in the tail suspension test, indicating improved spatial memory and cognitive function. The results also showed suppressed production of inflammatory cytokines and the prevention of dendritic atrophy and spine loss in the brain [232]. A very recent study demonstrated that TFs effectively upregulate brain neurotrophic factors, improving behavioral function by maintaining gut homeostasis, boosting the immune response and antioxidant activity, restructuring the gut microbiome, strengthening tight junction proteins, and altering core microbiota metabolites, i.e., short-chain fatty acids (SCFAs) and essential amino acids (Fig. 6) [233].

#### 4.12. Neuroprotective mechanisms of vanillin in AD

Vanillin is an important phenolic flavoring agent naturally found in plant species including *vanilla tahitensis*, *vanilla planifolia*, and *vanilla pompona*. It is widely used in the production of foods, pharmaceuticals, beverages, cosmetics, and perfumes [234]. Vanillin has anti-mutagenic, antioxidant, antidepressant, and anti-inflammatory properties [234], and has neuroprotective effects in several neuropathological conditions, including AD [235]. For a person weighing 70 kg, the recommended daily dose of vanillin is 10 mg/kg, which has been approved by the Food and Agriculture Organization of the United Nations/WHO and the European Union [161]. Moreover, toxicology studies in rodents receiving intraperitoneal and oral vanillin confirmed that it is safe at a high concentration of 300 mg/kg and produced no adverse effects on blood cells or the liver or kidneys [236].

An *in vitro* study examined the neuroprotective effects of ethyl vanillin on A $\beta$ <sub>1-42</sub>-induced oxidative injury in PC12 cells. The results revealed that vanillin treatment increased cell viability, markedly alleviated intracellular lipid peroxidation levels, and ROS production, induced the antioxidative enzymes SOD, CAT, and GPx, increased Bcl2 expression, and reduced Bax and caspase-3 expression in A $\beta$ <sub>1-42</sub>-induced PC12 cells [237]. NO release and protein and mRNA expression of the pro-inflammatory cytokines IL-1 $\beta$ , TNF- $\alpha$ , IL-6, COX-2, and iNOS were significantly reduced by vanillin in LPS-activated BV-2 microglial cells in a dose-dependent manner. In addition, vanillin treatment effectively inhibited the phosphorylation of MAPK and NF- $\kappa$ B signaling [238].

Anand et al. [239] demonstrated that vanillin administration (10 and 20 mg/kg bw) for 10 days significantly improved memory and behavioral functions, inhibited AChE activity and TBARS levels, enhanced activity of the antioxidant enzymes GSH and CAT, and significantly decreased the levels of IL-6 and TNF- $\alpha$  in the cortical and hippocampal regions of the brain in scopolamine-induced AD mice. Vanillin was also shown to prevent amyloidogenesis by inhibiting AChE activity, BACE1, and caspase-3, enhancing degradation of A $\beta$  and elevating BDNF levels in the hippocampus and cortex of AlCl<sub>3</sub>- and D-galactose-induced AD mice [240]. Moreover, two animal studies have shown that vanillin (40 mg/kg bw) administered for 28 days markedly attenuated cognitive deficits, increased ID-1 protein expression, and effectively restored the number of Ki-76, DCX, ID-1-immunoreactive cells as well as increasing the number of NeuN-immunoreactive neurons in the hippocampus of mice with scopolamine-induced AD [241,242]. Table 1 summarizes the latest preclinical research findings on the neuroprotective efficacy of dietary small molecules against AD.

### 5. Neuroprotective mechanisms of dietary small molecules analogs in AD

Recent *in vitro* and *in silico* studies reported the neuroprotective effects of the chrysin derivative 4-oxo-2-phenyl-4H-chromene-5,7-diyl bis(piperidine-1-carboxylate). The *in vitro* study demonstrated that the derivative had good anti-cholinesterase and antioxidant activity, appropriate BBB penetration, some inhibitory activity against A $\beta$

aggregation, as well as high selective inhibition of butyrylcholinesterase (BuChE) and AChE activity. In addition, *in silico* results showed that 4-oxo-2-phenyl-4H-chromene-5,7-diyl bis(piperidine-1-carboxylate) had high hydrophobicity and was predicted to have good BBB penetration and oral bioavailability [243]. Analogs of 7,8-DHF, including 7-O- $\beta$ -d-glucosyl-8-hydroxyflavone, 7-hydroxy-8-O- $\beta$ -d-glucosyl flavone, and 7,8-di-O- $\beta$ -d-glucosylflavone, showed anti-AD effects through interactions with amino acids of the human APP active site and suppressing the BACE1 enzyme in an *in silico* study [244]. Another *in vitro* study examined the naringenin derivatives compounds 3c and 5a in H<sub>2</sub>O<sub>2</sub>-induced HT22 cells. Interestingly, 3c and 5a could cross the BBB, considerably inhibited self-induced A $\beta$ <sub>1-42</sub> aggregation, activated the ubiquitin-proteasome system degradation pathway, and cleared the aggregated tau and APP proteins in HT22 cells. The same study also revealed that compound 3c showed good anti-neuroinflammatory effects by inhibiting the release of NO and suppressing TNF- $\alpha$  production in LPS-induced BV-2 microglial cells [245]. Table 2 summarizes the latest preclinical research findings on the neuroprotective efficacy of dietary small molecules bioactive compounds against AD.

Yang et al. investigated the neuroprotective and anti-inflammatory properties of naringenin derivatives in H<sub>2</sub>O<sub>2</sub>-induced PC12 and LPS-induced BV-2 microglial cells. They found that two bioactive compounds, 5f and 7k (naringenin-O-carbamate derivatives), were primarily responsible for naringenin's neuroprotective and anti-inflammatory activity by inhibiting NO release and suppressing TNF- $\alpha$  production in LPS-induced BV-2 microglial cells. Moreover, 5f and 7k could cross the BBB, significantly inhibited self-induced A $\beta$ <sub>1-42</sub> aggregation and huAChE-A $\beta$ <sub>1-40</sub> aggregation as well as selective metal chelators, and remarkably inhibited Cu<sup>2+</sup>-induced A $\beta$ <sub>1-42</sub> aggregation. In addition, the *in vivo* study reported that compound 5f significantly improved spatial learning and memory in scopolamine-induced AD mice [246]. Naringenin analog 5-hydroxy-2-(4-hydroxyphenyl)-4-oxochroman-7-yl piperidine-1-carboxylate, showed anti-AD effects by suppressing BuChE and AChE activity and scavenging OH and displayed better inhibitory potency on self-induced A $\beta$ <sub>1-42</sub> aggregation. In addition, a pharmacokinetics study demonstrated that 5-hydroxy-2-(4-hydroxyphenyl)-4-oxochroman-7-yl piperidine-1-carboxylate can cross the BBB and has improved oral bioavailability [247].

In previous studies, the FA derivative compounds 4g and 7f had neuroprotective effects on H<sub>2</sub>O<sub>2</sub>-induced and A $\beta$ -induced PC12 cell damage and could cross the BBB. It has also been demonstrated that they have considerable ability to inhibit hAChE and hBuChE, good A $\beta$  aggregation inhibition, and good antioxidant activity. Furthermore, compound 7f significantly reversed scopolamine-induced memory deficits in AD mice [248,249]. The FA analog TM-10 displayed neuroprotective and cognitive effects in A $\beta$ <sub>1-42</sub>-induced SH-SY5Y cells, AlCl<sub>3</sub>-induced zebrafish, and scopolamine-induced AD mice. *In vitro* results showed that TM-10 treatment had good penetration of the BBB, inhibited BuChE activity, and remarkably inhibited monoamine oxidases A and B, as well as inhibiting self-induced A $\beta$  aggregation; TM-10 subsequently exhibited potent antioxidant activity and had autophagic activator activity in A $\beta$ <sub>1-42</sub>-induced SH-SY5Y cells. In addition, TM-10 exhibited a favorable dyskinesia recovery rate and response efficiency in an AlCl<sub>3</sub>-induced zebrafish AD model. A further *in vivo* study demonstrated that TM-10 had low acute toxicity, and the step-down passive avoidance test indicated that this compound improved spatial learning and memory function in scopolamine-induced AD mice [250].

Recent *in vitro* and *in vivo* findings suggested that two bioactive FA analogs—methoxy-4-(2-(5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)vinyl)phenol (6j) and 2-methoxy-4-(2-(5-(4-(trifluoromethoxy)phenyl)-1,3,4-oxadiazol-2-yl)vinyl)phenol (6k)—have potent neuroprotective and memory-enhancing effects in A $\beta$ -induced SH-SY5Y cells and in a Wistar rat model. An *in vitro* study showed that compounds 6j and 6k had excellent BBB permeability and that they inhibited AChE, BChE, and BACE-1 activity and self-induced A $\beta$  aggregation in SH-SY5Y cells. Moreover, the *in vivo* study showed that compounds 6j and 6k

**Table 1**

Summarizes the latest preclinical research findings on the neuroprotective efficacy of dietary small molecules against AD.

Cell line/animal	Neurotoxin/duration	Drug concentration/duration	Behavioral parameters	Behavioral changes	Mechanism of action	Reference
<b>Chrysin – <i>in vitro</i> studies</b>						
SH-SY5Y cells	AlCl <sub>3</sub> (50 μM for 24 h)	50 μM for 24 h	–	–	Oxidative damage ↓ iNOS, IL-1β, and TNFα ↓ Cell death ↓	[82]
<b>Chrysin – <i>in vivo</i> studies</b>						
Swiss mice	AlCl <sub>3</sub> (100 mg/kg bw for 90 days)	10, 30, and 100 mg/kg bw for 90 days	Open-field test, chimney test, and step-down avoidance test	Amelioration of behavioral impairments	SOD, CAT, and GSH ↑ AChE, BChE, and lipid peroxidation ↓ Neuronal degeneration ↓	[82]
Albino Wistar rats	d-galactose (50 mg/kg bw for 8 weeks)	20 mg/kg bw for 8 weeks	–	–	SOD, CAT, GPx, GST, GR, G6PD, GSH, vitamins C and E ↑ MDA and protein carbonylation ↓	[83]
Sprague Dawley rats	d-galactose (50 mg/kg bw for 8 weeks)	10 and 30 mg/kg bw for 8 weeks	NOL and NOR	Improvement in spatial and recognition memory abilities	Cell proliferation, cell survival, and hippocampal neurogenesis ↑	[84]
C57BL/6 mice	d-galactose (200 mg/kg bw for 8 weeks)	125 and 250 mg/kg bw for 8 weeks	NOR and Y-maze	Elevation in the percentages of spontaneous alternation, locomotor activity, and spatial learning and memory abilities	AMPK, PGCl <sub>α</sub> , LKB1, NT-3, NQO1, HO-1, and 5-HT ↑ TNF-α, NF-κB, and GFAP ↓ Neuronal degeneration ↓	[85]
Albino Wistar rats	Sevoflurane anesthesia for 2 h	25, 50, and 100 mg/kg bw for 8 weeks	NOL, NOR, MWM, and elevated plus maze	Amelioration of anxiety and explorative behavior and improvements in spatial learning and memory function	Protein and mRNA expression of Nrf2, HO-1, and NQO1 ↑	[86]
Swiss Albino mice	–	1 or 10 mg/kg bw for 60 days	Open-field test and MWM	Improvements in spatial learning, cognitive function, and motor function	ROS level ↓ SOD, CAT, GPx, and Na <sup>+</sup> , K <sup>+</sup> -ATPase activity ↑ BDNF expression ↑	[87]
C57BL/6 mice	Methimazole (0.1% for 31 days)	10 or 20 mg/kg bw for 28 days	Open-field test and MWM	Prevention of cognitive dysfunction but no effects on locomotor activity	BDNF and NGF expression ↑	[88]
<b>7,8-DHF – <i>in vitro</i> studies</b>						
SH-SY5Y cells	ΔK280 Tau <sub>RD</sub> -DsRed for 7 days	5 μM for 7 days	–	–	Tau aggregation, oxidative stress, and caspase-1 activity ↓ Neurite outgrowth, HSPB1, Nrf2, CREB, and Bcl2 ↑	[94]
PC12 cells	6-OHDA (100 μM for 24 h)	1–100 μM for 24 h	–	–	Cell viability, MMP, and SOD ↑ Oxidative injury, MDA, caspase-3, and cell death ↓	[95]
<b>7,8-DHF – <i>in vivo</i> studies</b>						
Wistar rats	ICV-STZ (3 mg/kg for 3 weeks)	5, 10, and 20 mg/kg bw for 21 days	NOR and MWM	Recovery of spatial learning and memory function	GSH, SOD, CAT, and GPx ↑ NADPH activity and mitochondrial complexes I, II, III, and IV ↑ MDA, PCO, AChE, p-tau, and neuronal cell death ↓	[96]
Sprague-Dawley rats	Scopolamine (1 mg/kg for 2 weeks)	1 mg/kg bw for 4 weeks	MWM	Attenuation of learning and memory deficits	GSH and SOD activities ↑ p-TrkB, p-Akt, and p-Erk ↑ MDA, Aβ <sub>40</sub> , and Aβ <sub>42</sub> levels ↓	[97]
Tg2576 (Tg) mice and C57BL/6 N mice	–	5 mg/kg bw for 4 weeks	MWM, elevated plus maze, and open-field test	Improvement in learning and memory abilities	GluA1, GluA2, and AMPA receptor ↑ TrkB, PI3K/Akt, Ras/ERK, and PLCc/CaMKII signaling ↑	[98]
5XFAD mice and C57BL/6J mice	–	5 mg/kg bw for 8 weeks	MWM	Improvement in spatial learning and memory function	TrkB signaling, synapse number, and synaptic plasticity ↑ Aβ deposition and synapse loss ↓	[99]
5XFAD mice	–	5 mg/kg bw for 10 days	Y-maze	Improvement in spatial working memory function	p-TrkB signaling and BDNF ↑ BACE1, C99, and flAPP expression ↓	[100]
5XFAD mice	–	5 mg/kg bw 3 days a week for 8 weeks	–	–	Cortical neurons ↑ Aβ plaque deposition ↓	[101]
Sprague-Dawley rats	–	5 mg/kg bw for 28 days	Fear conditioning test	Improvement in memory function	p-TrkB signaling and BDNF ↑	[102]

(continued on next page)

Table 1 (continued)

Cell line/animal	Neurotoxin/duration	Drug concentration/duration	Behavioral parameters	Behavioral changes	Mechanism of action	Reference
Wistar rats	Alcohol/HFD (3–15% alcohol in 0.2% saccharin solution) for 12 weeks	5 mg/kg bw for 28 days	MWM	Attenuation of impaired spatial learning and memory retention	p-CaMKII, p-Erk1/2, p-CREB, and p-GluR1 ↑ Dendritic spines, synapse formation, and synaptic plasticity ↑ GSH content, Nrf2, and HO-1 ↑ BDNF expression ↑ MDA, nitrite level, and AChE ↓ Caspase-3, iNOS, IL-1β, and NF-κB expression ↓	[103]
<b>Naringenin – in vitro studies</b>						
PC12 cells	Aβ <sub>25-35</sub> (20 μM) for 24 h	0.4 μM for 24 h	–	–	Cell viability ↑ p-Akt and p-GSK3-β ↑ Cell apoptosis and caspase-3 ↓	[111]
PC12 cells	H <sub>2</sub> O <sub>2</sub> (100 μM) for 24 h	25–100 μM for 24 h	–	–	Cell viability ↑ ROS and LDH levels ↓	[112]
Neuro2a cells	Aβ <sub>25-35</sub> (10 μM) for 24 h	50 μM for 24 h	–	–	Cell viability ↑ p-AMPK, p-ULK1, and LC3II ↑ LDH, SQSTM1, Aβ accumulation ↓	[113]
BV-2 and N2a cells	LPS (100 ng/mL) for 24 h	5, 10, and 20 μM for 24 h	–	–	Cell viability ↑ SOCS-3 and PKCδ activation ↑ NO, iNOS, and COX-2 ↓	[114]
<b>Naringenin – in vivo studies</b>						
Swiss mice	LPS (20 mg/kg bw) for 1 day	10 or 20 mg/kg bw for 3 days	Rotarod	Amelioration of motor impairment	Microglial activation ↓	[114]
Wistar rats	Aβ (4 μL) for 1 day	100 mg/kg bw for 1 day	Y-maze, radial arm maze, and passive avoidance test	Improvement in spatial learning and memory function	SOD levels ↑ MDA, NO, and neuronal loss ↓	[115]
ICR mice	Scopolamine (1 mg/kg) for 30 min	100 mg/kg bw for 1 day	Y-maze and passive avoidance test	Amelioration of spatial learning and memory deficits	AChE levels ↓	[116]
Swiss Albino mice	ICV-STZ (3 mg/kg for 7 days)	50 mg/kg bw for 14 days	MWM and passive avoidance test	Prevention of spatial learning and cognitive function deficits	4-HNE, MDA, TBARS, H <sub>2</sub> O <sub>2</sub> , and protein carbonyl ↓ GSH, GPx, GR, GST, SOD, and CAT ↑ Na <sup>(+)</sup> /K <sup>(+)</sup> -ATPase activity and ChAT-positive neuron ↑	[117]
Sprague-Dawley rats	ICV-STZ (3 mg/kg bw for 21 days)	25, 50, and 100 mg/kg bw for 21 days	MWM	Improvement in learning and memory abilities	INS and INSR ↑ p-Tua and p-GSK3-β ↓	[118]
	Iron (Fe-dextran) (50 mg/kg) 5 days a week for 4 weeks	50 mg/kg bw for 28 days	–	–	SOD, CAT, and GPx TBARS, protein carbonyl, and DNA apoptosis ↓ AChE and neuron density loss ↓	[119]
Albino Wistar rats	AlCl <sub>3</sub> + D-gal (150 mg/kg + 300 mg/kg bw)	50 mg/kg bw for 14 days	MWM and NOR	Improvement in spatial learning and recognition memory	GSH, SOD, CAT, and GPx ↑ ACh, 5-HT, and DA ↑ Protected neurons ↑	[120]
Albino Wistar rats	LPS (167 μg/kg bw) for 7 days	25, 50, and 100 mg/kg bw for 7 days	Y-maze, novel object discrimination, passive avoidance test	Amelioration of memory dysfunction	MDA, AChE, and 5-HIAA ↓ SOD, CAT, GSH, and Nrf2 ↑ NF-κB, TNF-α, TLR4, GFAP, iNOS, and COX2 ↓	[121]
SAMP8 mice	HFD for 12 weeks	200 mg/kg bw for 12 weeks	Barnes maze and MWM test	Dramatic improvement in cognitive performance	GSH, SOD, and IL-10 ↑ MDA, NO, TNF-α, and IL-1β ↓ Aβ, APP, BACE1, GFAP ↓ Aβ <sub>40</sub> , and Aβ <sub>42</sub> ↓ p-tau and p-GSK ↓	[122]
Sprague-Dawley rats	Isoflurane (0.75% for 1 week)	25, 50 or 100 mg/kg bw for 3 weeks	Y-maze, elevated plus maze, open-field test, and fear conditioning test	Improvement in learning capacity and memory retention and amelioration of cognitive dysfunction	Bcl-xL, Bcl-2, and PI3K/Akt ↑ NF-κB, TNF-α, IL-6, and IL-1β ↓ Caspase-3, Bad, and Bax ↓	[123]
<b>Luteolin – in vitro studies</b>						
PC-12 cells	Aβ <sub>25-35</sub> (20 μM/L for 24 h)	10, 1, 10 <sup>-1</sup> , 10 <sup>-2</sup> , 10 <sup>-3</sup> , 10 <sup>-4</sup> , 10 <sup>-5</sup> , and 10 <sup>-6</sup> μM/L	–	–	Cell viability and Bcl2 ↑ Bax, caspase-3, p-ERK1/2 and cell death ↓	[128]
HEK293 and SH-SY5Y cells	Lipofectamine 2000	5, 15, and 30 μM for 24 h	–	–	BACE1 and p-NF-κB ↓ APP, C99, and Aβ <sub>1-42</sub> ↓	[129]

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Table 1 (continued)

Cell line/animal	Neurotoxin/duration	Drug concentration/duration	Behavioral parameters	Behavioral changes	Mechanism of action	Reference
hBMEC and hA cells	A $\beta$ <sub>1-42</sub> (20 $\mu$ M for 72 h)	3, 10, and 30 $\mu$ M for 72 h	–	–	Cell viability $\uparrow$ ROS levels $\downarrow$ TNF- $\alpha$ , IL-6, IL-8, and IL-1 $\beta$ $\downarrow$ p-p38, p-Erk1/2, and p-JNK $\downarrow$ p-I $\kappa$ B- $\alpha$ and p-NF- $\kappa$ B $\downarrow$	[130]
SH-SY5Y cells	A $\beta$ <sub>1-42</sub>	Neo and APP <sub>sw</sub> transfected cells	–	–	Cell viability $\uparrow$ ROS levels $\downarrow$ SOD and MMP $\uparrow$ Caspase 3 and caspase-9 $\downarrow$ CaMKII and p-CaMKII $\uparrow$ p-tau at Ser262/356 $\downarrow$	[131]
SH-SY5Y cells	Zinc (0, 100, 200, 300, or 400 $\mu$ M) for 1 h	5–100 $\mu$ M for 1 h	–	–	Caspase 3 and caspase-9 $\downarrow$ CaMKII and p-CaMKII $\uparrow$ p-tau at Ser262/356 $\downarrow$	[132]
<b>Luteolin – in vivo studies</b>						
3 $\times$ Tg-AD and WT, C57BL/6J mice	–	20 and 40 mg/kg bw for 3 weeks	MWM	Improvement in spatial learning and amelioration of memory deficits	GRP78, IRE1 $\alpha$ , and p-p38 $\downarrow$ TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and NO $\downarrow$ COX-2, iNOS, and p-NF- $\kappa$ B $\downarrow$ A $\beta$ -plaque formation $\downarrow$ eIF2 $\alpha$ , p-eIF2 $\alpha$ , and PS1C $\downarrow$ IL-1 $\beta$ , Iba-1, and ATF4 $\downarrow$	[133]
APP23 mice	Human APP <sub>751</sub>	100 mg/kg bw for 29 weeks	Y-maze, fear conditioning test, tail suspension test, and forced swimming test	Amelioration of depressive-like behaviors and improvement in spatial learning and memory function	eIF2 $\alpha$ , p-eIF2 $\alpha$ , and PS1C $\downarrow$ IL-1 $\beta$ , Iba-1, and ATF4 $\downarrow$	[134]
Sprague-Dawley rats	STZ (3 mg/kg on the fourth and sixth days)	10 and 20 mg/kg bw for 1 week	MWM	Amelioration of spatial learning and memory impairment	CA1 pyramidal layer $\uparrow$	[135]
Sprague-Dawley rats	A $\beta$ <sub>1-42</sub> (2 $\mu$ l for 1 day)	50, 100, and 200 mg/kg bw for 17 days	MWM and passive avoidance test	Improvement in spatial learning and spatial working memory	SOD level and GSH content $\uparrow$ ChAT and Ach content $\uparrow$ Bax and Bcl2 ratio $\uparrow$ MDA and AChE activity $\downarrow$ IDE and UCP2 $\uparrow$ SOD level and GSH content $\uparrow$ PGC- $\alpha$ , Nrf1, Nrf2, and TFAM $\uparrow$ PPAR $\gamma$ , Bcl2, and Mfn2 $\uparrow$ APP, BACE1, and A $\beta$ <sub>1-42</sub> $\downarrow$ ROS and MDA $\downarrow$ Drp1 and Fis1 $\downarrow$ Bax, caspase-3, caspase-9, and cyt-C $\downarrow$	[136]
3 $\times$ Tg-AD mice and WT mice	–	20 or 40 mg/kg bw for 8 weeks	NOR, open-field test, and step-down avoidance test	Recovery of cognitive deficits and amelioration of anxiety, locomotor, and exploration abilities	Bcl2, PSD95, and SNAP25 $\uparrow$ BACE1 and A $\beta$ <sub>1-42</sub> $\downarrow$ p-p38, p-JNK, Iba-1, and GFAP $\downarrow$ TNF- $\alpha$ , IL-1 $\beta$ , and p-NF- $\kappa$ B $\downarrow$ Bax, caspase-3, and COX-2 $\downarrow$	[137]
C57BL/6 N mice	A $\beta$ <sub>1-42</sub> (5 $\mu$ l for one day)	80 mg/kg bw for 2 weeks	–	–	Bcl2, PSD95, and SNAP25 $\uparrow$ BACE1 and A $\beta$ <sub>1-42</sub> $\downarrow$ p-p38, p-JNK, Iba-1, and GFAP $\downarrow$ TNF- $\alpha$ , IL-1 $\beta$ , and p-NF- $\kappa$ B $\downarrow$ Bax, caspase-3, and COX-2 $\downarrow$	[138]
<b>Lycopene – in vitro studies</b>						
M146L cells	A $\beta$ -overexpression	10 $\mu$ M for 24 h	–	–	Gclc and Gclm expression $\uparrow$ Nrf2, p-Akt, p-GSK-3 $\beta$ , and Bcl2 $\uparrow$ ROS and MDA levels $\downarrow$ APP, BACE1, and caspase-3 $\downarrow$	[147]
SH-SY5Y cells	A $\beta$ <sub>1-42</sub> (20 $\mu$ l for 24 h)	0.2 or 0.5 $\mu$ M for 24 h	–	–	Cell viability $\uparrow$ Bcl2 and MMP $\uparrow$ ROS, Bax, p53, and caspase-3 $\downarrow$ p-I $\kappa$ B $\alpha$ and p-NF- $\kappa$ B $\downarrow$	[148]
SH-SY5Y cells	RCAN1-overexpressing	1–2 $\mu$ M for 24 h	–	–	Cell viability $\uparrow$ RCAN1 and MMP $\uparrow$ ROS, caspase-3, and cyt-C $\downarrow$ p-I $\kappa$ B $\alpha$ and p-NF- $\kappa$ B $\downarrow$ Nrf2, HO-1, and NQO-1 $\uparrow$	[149]
BV-2 cells	LPS (1 $\mu$ g/mL 24 h)	12.5, 25, and 50 $\mu$ M for 24 h	–	–	ROS levels $\downarrow$ Iba-1 and COX-2 $\downarrow$ p-p38, p-Erk, p-JNK, and p-Akt $\downarrow$ p-I $\kappa$ B- $\alpha$ and p-NF- $\kappa$ B $\downarrow$	[150]
Primary culture	t-BHP (2 $\mu$ M for 24 h)	0.1–16 $\mu$ M for 24 h	–	–	Cell viability $\uparrow$ NGF, VEGF, and BDNF $\uparrow$ Bcl2 and MMP $\uparrow$ SYP and PSD95 $\uparrow$ p-PI3K	[151]

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Table 1 (continued)

Cell line/animal	Neurotoxin/duration	Drug concentration/duration	Behavioral parameters	Behavioral changes	Mechanism of action	Reference
Primary culture	A $\beta$ <sub>25–35</sub> (25 $\mu$ M for 24 h)	0.1–10 $\mu$ M for 24 h	–	–	and p-Akt $\uparrow$ ROS, Bax, caspase-3, and cyt-C $\downarrow$ Cell viability $\uparrow$ Bcl2 and MMP $\uparrow$	[152]
Primary culture	A $\beta$ <sub>25–35</sub> (10 $\mu$ M for 24 h)	0.1–5 $\mu$ M for 24 h	–	–	ROS, Bax, and caspase-3 $\downarrow$ Mitochondrial complex I, II, III, and IV activity and ATP content $\uparrow$ Mito Tfam levels and Mito-cyt-C $\uparrow$ mtDNA copy numbers $\uparrow$ mtDNA transcript levels $\uparrow$ 8-OHdG and cytosolic-C $\downarrow$ Intracellular ROS level $\downarrow$ Mitochondrial ROS level $\downarrow$	[153]
<b>Lycopene-in vivo studies</b>						
Sprague-Dawley rats	A $\beta$ <sub>1–42</sub> (3 $\mu$ l for one day)	2.5 or 5 mg/kg bw for 3 weeks	MWM	Improvement in spatial learning performance and alteration in locomotor activity	Mitochondrial complex I, II, III, and IV activity and BDNF $\uparrow$ CAT, SOD, and GSH $\uparrow$ NO, MDA, and LPO levels $\downarrow$ AChE, TNF- $\alpha$ , and IL-6 $\downarrow$ Caspase-3 activity $\downarrow$	[154]
Sprague-Dawley rats	A $\beta$ <sub>1–42</sub> (10 $\mu$ l for one day)	1, 2, and 4 mg/kg bw for 3 weeks	MWM, elevated plus maze, and actophotometer test	Attenuation of poor latency performance and improvement in learning and memory performance	Mitochondrial complex I, II, III, and IV activity $\uparrow$ CAT, SOD, and GSH $\uparrow$ NO, MDA, and LPO levels $\downarrow$ AChE, TNF- $\alpha$ , TGF- $\beta$ 1, and IL-6 $\downarrow$ Caspase-3 activity $\downarrow$	[155]
APP/PS1 mice and WT C57/BL6J mice	–	4 mg/kg bw	MWM	Amelioration of spatial learning and memory impairments	CD105, VEGF, and NeuN $\uparrow$ p-Akt, LXR $\alpha$ , and LXR $\beta$ $\uparrow$ A $\beta$ aggregation, GFAP, and iNOS $\downarrow$	[156]
Sprague-Dawley rats	A $\beta$ <sub>1–42</sub> (3 $\mu$ l for 1 day)	5 mg/kg bw for 3 weeks	MWM	Improvement in spatial learning and cognitive function	TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 $\downarrow$ TLR4 and p-NF- $\kappa$ B $\downarrow$ APP and PS1 $\downarrow$	[157]
C57BL/6J mice	LPS (0.25 mg/kg bw for 9 days)	30 mg/kg bw for 5 weeks	MWM and Y-maze test	Prevention of losses in spatial learning and memory	IL10 and MMP3 $\uparrow$ GSH, CAT, and SOD $\uparrow$ APP and BACE1 $\downarrow$ iNOS, COX-2, IL-6, and MMP9 $\downarrow$ A $\beta$ aggregation $\downarrow$ Iba-1 activation $\downarrow$	[150]
Albino Wistar rats	Fructose (10% for 16 weeks)	4 mg/kg bw for 10 weeks	MWM	Recovery of impaired learning and memory	IR, IGF-1R, PI3K, and p-Akt $\uparrow$ SOD, CAT, GPx, and GSH $\uparrow$ PPAR $\gamma$ expression $\uparrow$ ROS, AChE, LPO, and PCC $\downarrow$ TNF- $\alpha$ , IL-1 $\beta$ , and p-NF- $\kappa$ B $\downarrow$	[158]
Sprague-Dawley rats	A $\beta$ <sub>1–42</sub> (10 $\mu$ l for 14 days)	5 mg/kg bw for 5 weeks	MWM	Mitigation of spatial memory and learning dysfunction	IL-10 and TGF- $\beta$ 1 levels $\uparrow$ A $\beta$ accumulation $\downarrow$ TNF- $\alpha$ and IL-1 $\beta$ levels $\downarrow$ TLR4 and p-NF- $\kappa$ B $\downarrow$	[159]
<b>Ferulic acid – in vitro studies</b>						
PC12 cells	LPS (1 $\mu$ g/mL for 24 h)	2.5, 5, 10, 20 and 40 $\mu$ M for 24 h	–	–	CREB, p-CREB, and PDE4 $\uparrow$ TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 $\downarrow$	[164]
SH-SY5Y cells	A $\beta$ <sub>1–42</sub> (20 $\mu$ l for 72 h)	10–50 $\mu$ M for 72 h	–	–	A $\beta$ <sub>42</sub> aggregation $\downarrow$	[165]
SH-SY5Y cells	A $\beta$ <sub>1–42</sub> (5 $\mu$ l for 24 h)	1–50 $\mu$ M for 24 h	–	–	Cell viability $\uparrow$ A $\beta$ <sub>42</sub> aggregation $\downarrow$ Intracellular ROS formation $\downarrow$ Mitochondrial ROS formation $\downarrow$ Repair of membrane damage $\downarrow$	[166]
BV-2 cells	LPS (100 ng/mL for 24 h)	2.5, 7.5, and 22.5 $\mu$ M for 24 h	–	–	Cell viability $\uparrow$ PGE2, IL-1 $\beta$ , and NO $\downarrow$	[167]
BV-2 cells	LPS (1 $\mu$ g/mL for 12 h)	55 $\mu$ M for 24 h	–	–	iNOS, COX-2, and TLR4 $\downarrow$ p-AMPK, p-ULK1, and Beclin1 $\uparrow$ LC3, LAMP2A, and TFEB $\uparrow$	[168]

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Table 1 (continued)

Cell line/animal	Neurotoxin/duration	Drug concentration/duration	Behavioral parameters	Behavioral changes	Mechanism of action	Reference
					IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and p-65 $\downarrow$	
<b>Ferulic acid – <i>in vivo</i> studies</b>						
ICR mice	Trimethyltin chloride (2.5 mg/kg bw for one day)	20 or 50 mg/kg bw for 4 weeks	Y-maze and passive avoidance test	Attenuation of memory impairment and behavioral disabilities	ChAT activity $\uparrow$	[169]
Male APP/PS1 mice	–	50 mg/kg bw for 4 months	MWM, Open-field test, NOR, and fear conditioning test	Recovery of impaired learning and memory	PSD95 and Syn1 $\uparrow$ APP and APP $\beta$ $\downarrow$ Neuronal loss $\downarrow$ BACE-1 and PS1 $\downarrow$ Cerebral blood flow $\uparrow$	[170]
APP/PS1 transgenic mice and C57 mice	–	20 mg/kg bw for 30 days	MWM	Reduction in spatial memory deficits	Cerebral blood flow $\uparrow$ A $\beta$ plaque deposition $\downarrow$ APP, BACE1, and p-NF- $\kappa$ B $\downarrow$	[171]
PSAPP transgenic mice and WT mice	–	30 mg/kg bw for 90 days	Y-maze, NOR, and radial arm water maze test	Recovery of episodic memory, spatial working memory, and spatial reference learning and memory deficits	Synaptophysin $\uparrow$ Oxidative stress $\downarrow$ A $\beta$ deposits $\downarrow$ C99 and BACE1 $\downarrow$ IL-1 $\beta$ , TNF- $\alpha$ , Iba-1 and GFAP $\downarrow$	[172]
APP/PS1 mice	–	5.3 or 16 mg/kg bw for 6 months	Y-maze test and NOR	Enhancement of behavioral performance and memory function	A $\beta$ <sub>1–42</sub> deposits $\downarrow$ A $\beta$ <sub>1–40</sub> deposits $\downarrow$ IL-1 $\beta$ levels $\downarrow$	[173]
Sprague-Dawley rats	A $\beta$ <sub>1–42</sub> (10 $\mu$ l for 7 days)	50, 100, and 250 mg/kg bw for 3 weeks	–	–	PKB and p-PKB $\uparrow$ IL-1 $\beta$ and GFAP activation $\downarrow$ p-p38 and p-ERK1/2 expression $\downarrow$ Caspase-3 and FasL expression $\downarrow$	[174]
Transgenic <i>C. elegans</i>	A $\beta$ <sub>1–42</sub> over-expression	1, 10, and 100 $\mu$ M for 24–96 h (different assays at different time points)	–	–	HLH-30 activation $\uparrow$ A $\beta$ monomers, oligomers, and deposits $\downarrow$ PolyQ40 aggregation $\downarrow$	[175]
<b>Ellagic acid – <i>in vitro</i> studies</b>						
SH-SY5Y cells	A $\beta$ <sub>1–42</sub> (10 $\mu$ l for 12 h)	100–300 $\mu$ M for 24 h	–	–	Cell viability $\uparrow$ Morphology of A $\beta$ <sub>42</sub> aggregates $\downarrow$ A $\beta$ oligomer levels $\downarrow$	[179]
PC-12 cells	H <sub>2</sub> O <sub>2</sub> (40 $\mu$ M) and A $\beta$ <sub>25–35</sub> (0.01 $\mu$ M) for 24 h	0.5–5.0 $\mu$ g/ml for 24 h	–	–	Cell viability $\uparrow$ Intracellular ROS $\downarrow$ calcium ion influx $\downarrow$	[180]
SH-SY5Y cells	d-galactose (200 mM for 24 h)	0.01–10 $\mu$ M for 24 h	–	–	Cell viability $\uparrow$ GSH content $\uparrow$ MDA and ROS formation $\downarrow$ $\beta$ -GAL, AGEs, and TNF- $\alpha$ level $\downarrow$	[181]
BV-2 cells	LPS (1 $\mu$ g/mL for 24 h)	25, 50, and 100 $\mu$ M for 24 h	–	–	p-p38 and p-ERK1/2 expression $\downarrow$ TNF- $\alpha$ and NO activity $\downarrow$	[182]
<b>Ellagic acid – <i>in vivo</i> studies</b>						
APP/PS1 double-transgenic and WT-C57BL/6 mice	–	50 mg/kg bw for 2 months	MWM	Improvement in learning and memory performance	A $\beta$ <sub>1–42</sub> deposits $\downarrow$ BACE1, APP and pThr668-APP $\downarrow$ pSer199-tau and pSer396-tau $\downarrow$ pTyr216-GSK3 $\beta$ activation $\downarrow$ Percentage of apoptotic cells $\downarrow$ Caspase-3 expression $\downarrow$ CAT and GSH content $\uparrow$	[183]
Sprague-Dawley rats	STZ (3 mg/kg for 1 day)	25 and 50 mg/kg bw for 5 weeks	Y-maze and radial arm maze test	Improvement in memory score and cognitive performance	Synaptophysin $\uparrow$ MDA, CRP, and AChE activity $\downarrow$ GFAP and A $\beta$ -plaques $\downarrow$ SOD and GSH content $\uparrow$	[184]
Sprague-Dawley rats	AlCl <sub>3</sub> (50 mg/kg for 4 weeks)	50 mg/kg bw for 4 weeks	NOR	Improvement in episodic memory	TBARS activity $\downarrow$ Neuronal loss $\downarrow$ NFTs and NPs $\downarrow$ APP and caspase-3 expression $\downarrow$	[185]
Sprague-Dawley rats	A $\beta$ <sub>1–42</sub> (10 $\mu$ g/kg for one day)	10, 50, and 100 mg/kg bw for 7 days	Y-maze, radial arm maze test, NOR, and passive avoidance test	Prevention of learning and memory deficits	CAT, GSH, and Nrf2 $\uparrow$ MDA, NO, AChE, and BChE $\downarrow$ TLR4 and NF- $\kappa$ B $\downarrow$ CA1 neuronal loss $\downarrow$	[186]

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Table 1 (continued)

Cell line/animal	Neurotoxin/duration	Drug concentration/duration	Behavioral parameters	Behavioral changes	Mechanism of action	Reference
Sprague-Dawley rats	Scopolamine (2 mg/kg for 1 day)	25, 50, and 100 mg/kg bw for 3 weeks	MWM and passive avoidance test	Attenuation of learning and memory deficits	CAT and SOD ↑ MDA content ↓	[187]
<b>Caffeic acid – in vitro studies</b>						
PC12 cells	Aβ <sub>1-42</sub> (10 μl for 24 h)	10 or 20 μg/mL for 24 h	–	–	Cell viability ↑ Calcium levels ↓ AT8 and phosphorylation of tau ↓ Phosphorylation of GSK-3β ↓	[194]
HT22 cells	Acrolein (25 μl for 24 h)	5–50 μM for 24 h	–	–	Cell viability ↑ GSH levels and MMP ↑ ADAM-10, p-Akt, and LR-11 ↑ p-Erk and p-GSK-3β ↑ Intracellular ROS production ↓ p-p38 and p-JNK1 ↓ RAGE and BACE1 ↓	[195]
<b>Caffeic acid – in vivo studies</b>						
Sprague-Dawley rats	HFD for 30 weeks	200 mg/kg bw for 12 weeks	MWM	Amelioration of learning and memory impairments	SOD and CAT levels ↑ p-GSK-3β and synaptophysin ↑ GSSG activity ↓ APP and BACE1 ↓ Aβ <sub>1-42</sub> , PSD95, and drebrin ↓ p-tau (Ser 396), p-tau (Ser 404), and p-tau (Thr 181) ↓	[196]
Sprague-Dawley rats	Aβ <sub>1-40</sub> (5 μl for 1 day)	100 mg/kg bw for 2 weeks	MWM	Prevention of learning deficits and increased cognitive function	GSH and CAT levels ↑ AChE activity and NO level ↓ IL-6 and TNF-α activities ↓ p53, p-p38, and p-NF-κB-p65 ↓ Caspase 3 protein expression ↓ GSH levels ↑	[197]
Sprague-Dawley rats	ICV-STZ (3 mg/kg for 1 and 3 days)	10, 20, and 40 mg/kg bw for 3 weeks	MWM, object recognition test, and spontaneous locomotor activity	Improvement in discriminating ability and alleviation of spatial learning and memory deficits	AChE activity and NO level ↓ MDA content and protein carbonyl ↓	[198]
C57BL/6 mice	Aβ <sub>1-40</sub> (5 μl for one day)	50 mg/kg bw for 2 weeks	MWM and Y-maze	Improvement in spatial working memory and cognitive performance	Nrf2 and HO-1 expression ↑ p-PI3K and BDNF expression ↑ SYN, SNAP-23, and SNAP-23 ↑ PSD-95 expression ↑ BACE1 and Aβ <sub>1-42</sub> deposits ↓ GFAP and Iba-1 expression ↓ IL-1β, TNF-α, and p-NF-κB-p65 ↓	[199]
ApoE <sup>-/-</sup> mice and WT-C57BL/6J	–	20 mg/kg bw for 8 weeks	MWM and Y-maze	Amelioration of cognitive decline and spatial memory impairment	ABCA1 and ABCG1 ↑ Aβ accumulation ↓ TNF-α, IL-6, and MCP-1 ↓	[200]
<b>Galic acid – in vitro studies</b>						
Neuro-2A cells and BV-2 cells	Aβ <sub>1-40</sub> (5 μl for 24 h)	5, 25, and 50 μM for 24 h	–	–	Cell viability ↑ IL-1β and TNF-α expression ↓ COX-2 and iNOS expression ↓ p-NF-κB-p65 expression ↓	[204]
<b>Galic acid – in vivo studies</b>						
ICR mice	Aβ <sub>1-40</sub> (5 μl for 7 days)	10 or 30 mg/kg bw for 4 weeks	Y-maze and passive avoidance test	Restoration of memory deficits and cognitive function	IL-1β and TNF-α expression ↓ COX-2 and iNOS expression ↓ p-NF-κB-p65 expression ↓	[204]
APP/PS1 and WT-C57BL/6 N mice	–	30 mg/kg bw for 4 weeks	MWM, NOR, and Y-maze	Mitigation of spatial learning and reference memory deficits	PSD-95 expression ↑ GFAP and Iba-1 expression ↓ Aβ accumulation ↓	[205]
APP/PS1 mice	–	20 mg/kg bw for 6 months	Y-maze, radial arm maze test, and NOR	Attenuation of spatial learning and working memory	APP, C99, and BACE1 ↓ GFAP and Iba-1 expression ↓	[206]

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Table 1 (continued)

Cell line/animal	Neurotoxin/duration	Drug concentration/duration	Behavioral parameters	Behavioral changes	Mechanism of action	Reference
Sprague-Dawley rats	AlCl <sub>3</sub> (200 mg/kg bw for 60 days)	100 or 200 mg/kg bw for 8 weeks	Y-maze and MWM	impairment and reversal of episodic memory impairment Improvement in learning and memory status	↓ Aβ deposition SOD, CAT, and GSH content ↑ Na <sup>+</sup> , Ca <sup>2+</sup> , and Zn <sup>2+</sup> ↑ Dopamine and serotonin ↑ Norepinephrine ↓ K <sup>+</sup> and CU <sup>2+</sup> ↓ H <sub>2</sub> O <sub>2</sub> , MDA, and NO levels ↓ NFTs and NPs ↓	[207]
Sprague-Dawley rats	ICV-STZ (3 mg/kg bw for 1 and 3 days)	100 or 200 mg/kg bw for 26 days	MWM and passive avoidance test	Mitigation of spatial learning and memory impairment	SOD, CAT, and GPx content ↑ MDA levels ↓	[208]
Sprague-Dawley rats	Sodium arsenite (2.5 mg/kg for 28 days)	50 or 100 mg/kg bw for 4 weeks	MWM, elevated plus maze, forced swim test, and light-dark activity box test	Attenuation of anxiety-like behavior and improvement in learning and memory performance	SOD, CAT, and GPx content ↑ ACHE activity and MDA levels ↓	[209]
Sprague-Dawley rats	Aβ <sub>1-40</sub> (1 μg/1 μL for 1 day)	50, 100, and 200 mg/kg bw for 10 days	–	–	Aβ accumulation ↓	[210]
<b>Epigallocatechin-3-gallate – in vitro studies</b>						
BV2-cells	Aβ <sub>25-35</sub> (25 μM for 24 h)	2, 5, and 10 μM for 24 h	–	–	Cell viability ↑ Bcl2 and GSH levels ↑ MDA and ROS production ↓ iNOS and NO production ↓ Bax expression ↓	[218]
U373MG cells	Aβ <sub>25-35</sub> (30 μM for 24 h) and IL-1β (10 ng/mL for 24 h)	0.2–200 μM for 24 h	–	–	Cell viability ↑ MKP-1 expression ↑ IL-6, IL-8, and VEGF ↓ PGE <sub>2</sub> , COX-2, and p-NF-κB-p65 ↓ p-p38 and p-JNK ↓	[219]
BV2-cells	LPS (1 μg/mL for 1 h)	0–350 μM for 24 h	–	–	Cell viability ↑ IL-6, TNF-α, and NO production ↓ MIF, CCL2, and TNFS10 ↓ STAT1, TRAF2, and TRAF3 ↓ TRAF5 and NFKB2 ↓	[220]
SH-SY5Y cell and BV-2 cells	Aβ <sub>1-40</sub> (10 μM for 6 h) and LPS (1 μg/mL for 1 h)	10 μM for 24 h	–	–	AKT3, mTOR, and NF-κB2 Cell viability ↑ IL-1β, IL-18, and Iba-1 expression ↓ Aβ accumulation ↓ Caspase-1 and caspase-1 p20 ↓ Caspase-11 p26 and NLRP3 ↓ p-NF-κB-p65, p-IκB-α, and TLR4 ↓	[221]
<b>Epigallocatechin-3-gallate – in vivo studies</b>						
APP/PS1 mice and WT mice	–	2 mg/kg bw for 28 days	–	–	IL-1β, IL-18, and Iba-1 expression ↓ Aβ accumulation ↓ Caspase-1 and Caspase-1 p20 ↓ Caspase-11 p26 and NLRP3 ↓ p-NF-κB-p65, p-IκB-α, and TLR4 ↓	[221]
APP/PS1 mice and WT mice	–	50 mg/kg bw for 8 weeks	MWM and NOR	Alleviation of memory and cognitive deficits	Synapsin-1 and synaptophysin ↑ Synaptotagmin and PSD93 ↑ PSD95, MAP-2, and GluR1 ↑ IL-4, IL-10, and IL-13 ↑ Aβ accumulation ↓ Tau phosphorylation ↓ Iba-1, IL-6, TNF-α, and IL-1β ↓	[222]
Sprague-Dawley rats	Aβ <sub>1-40</sub> (1 nM/μL for 1 day)	100, 250, and 625 mg/kg bw for 8 weeks	MWM	Improvement in learning and memory function	Ach, GPx and SOD content ↑ Tau aggregation ↓ Tau phosphorylation and BACE1 ↓	[223]

(continued on next page)

Table 1 (continued)

Cell line/animal	Neurotoxin/duration	Drug concentration/duration	Behavioral parameters	Behavioral changes	Mechanism of action	Reference
ICR mice	LPS (0.250 mg/kg bw for 7 days)	15 or 3 mg/kg bw for 4 weeks	MWM	Amelioration of memory impairment and cognitive dysfunction	A $\beta$ <sub>1-42</sub> expression ↓ MDA and AChE ↓ A $\beta$ accumulation ↓ APP, C99, and BACE1 ↓ iNOS and COX-2 expression ↓ IL-1 $\beta$ , TNF- $\alpha$ , and IL-16 ↓ GFAP and caspase-3 expression ↓	[224]
APP/PS1 mice and WT mice	HFD for 12 weeks	40 mg/kg bw for 12 weeks	MWM and NOR	Improvement in spatial learning and memory function	ADAM10, p-CDK5, and pAKT ↑ GSK3 $\beta$ and pGSK3 $\beta$ , and p-CREB ↑ APP and BACE1 ↓ GFAP, ATF4, and CHOP ↓ p-JNK, p-ERK, and TRL4 ↓ IRE1/p-IRE1 and ATF6 ↓ Prevotella ↑	[225]
C57BL/6 mice	HFD for 8 weeks	5, 15, and 45 mg/kg bw for 8 weeks	Barnes maze and NOR	Improvement in cognitive function and amelioration of cognitive decline	Gut flora and diversity ↑ <i>Bifidobacteriales</i> ↓	[226]
<b>Theaflavins – in vivo studies</b>						
ICR mice	d-galactose (120 mg/kg bw for 56 days)	15, 30, and 60 mg/kg bw for 8 weeks	Y-maze and NOR	Alleviation of memory and cognitive deficits	<i>Ach</i> and <i>ChAT</i> activity ↑ <i>SOD</i> , <i>GSH</i> , <i>GS</i> , and <i>GLS</i> ↑ <i>Nrf2</i> , <i>Prx2</i> , <i>GSH-px1</i> , and <i>SOD 1</i> ↑ <i>MDA</i> , <i>GLU</i> , and <i>AChE</i> activity ↓	[231]
C57BL/6J mice	LPS (10 $\mu$ g for 1 h)	10 or 50 mg/kg bw for 3 days	Y-maze and tail suspension test	Attenuation of concomitant cognitive impairment and Alzheimer-like behavior	<i>Dendritic spine density</i> ↑ <i>MIP-1<math>\alpha</math></i> - and <i>TNF-<math>\alpha</math></i> ↓	[232]
<b>Vanillin – in vitro studies</b>						
PC12 cells	A $\beta$ <sub>1-40</sub> (20 $\mu$ M for 12 h)	0, 10, 30, and 100 $\mu$ M for 24 h	–	–	Cell viability ↑ <i>SOD</i> , <i>CAT</i> , and <i>GSH</i> ↑ <i>MMP</i> and <i>Bcl2</i> ↑ <i>LDH</i> leakage ↓ <i>MDA</i> and <i>ROS</i> production ↓ <i>Caspase-3</i> , <i>Bax</i> , and <i>apoptosis</i> ↓	[237]
BV2-cells	LPS (200 ng/mL for 24 h)	0–400 $\mu$ M for 24 h	–	–	Cell viability ↑ <i>iNOS</i> and <i>COX-2</i> expression ↓ IL-1 $\beta$ , TNF- $\alpha$ , and IL-16 ↓ p-p38, p-JNK, and p-ERK ↓ p-NF- $\kappa$ B-p65, and p-I $\kappa$ B- $\alpha$ ↓	[238]
<b>Vanillin-in vivo studies</b>						
Swiss Albino mice	Scopolamine (2 mg/kg bw for 10 days)	10 or 20 mg/kg bw for 10 days	Passive avoidance, elevated plus maze, and MWM	Reversal of memory and behavioral deficits	<i>GSH</i> and <i>CAT</i> ↑ <i>AChE</i> and <i>TBARS</i> ↓ IL-6 and TNF- $\alpha$ ↓	[239]
Swiss Albino mice	AlCl <sub>3</sub> (5 mg/kg for 90 days) and d-galactose (60 mg/kg bw for 90 days)	40 mg/kg bw for 3 months	NOR, elevated plus maze, and MWM	Mitigation of memory and behavioral deficits	<i>GSH</i> and <i>CAT</i> ↑ BDNF and neuron density ↑ <i>AChE</i> and <i>TBARS</i> ↓ <i>BACE1</i> and <i>caspase-3</i> ↓ A $\beta$ accumulation ↓	[240]
ICR mice	Scopolamine (1 mg/kg bw for 28 days)	40 mg/kg bw for 4 weeks	Passive avoidance and MWM	Attenuation of spatial learning impairment and cognitive dysfunction	ID-1 protein expression ↑ ID-1-immunoreactive cells ↑ NeuN-immunoreactive neurons ↑ DCX-immunoreactive cells ↑ Ki-76-immunoreactive cells ↑	[241, 242]

induced brain AChE inhibition, enhanced antioxidant activity, and improved learning and memory behavior in the A $\beta$ -induced AD rat model [251]. Recent *in vitro* and *in vivo* studies have shown that the water-soluble FA analogs 1-feruloyl glycerol (FA-G1) and 1-feruloyl diglycerol (FA-DG1) inhibit NO production, suppress iNOS expression, and inhibit the NF- $\kappa$ B pathway in a concentration-dependent manner. In addition, treatment with these analogs inhibited A $\beta$ -induced neuronal cell death and A $\beta$  aggregation, destabilized pre-aggregated A $\beta$  to a

similar extent, and subsequently protected hippocampal neurons [252, 253].

Konar et al. reported that CA phenethyl ester (CAPE) had potent neuroprotective effects in a *Drosophila* AD model and a scopolamine-induced model of amnesia. Their results showed that CAPE treatment increased levels of the neurotrophin BDNF, the neural progenitor marker nestin, and the differentiation marker NeuN in the cerebral cortex and hippocampus [254]. Similarly, intraperitoneal administration of CAPE

**Table 2**

Summarizes the latest preclinical research findings on the effect of dietary small molecules bioactive compounds against AD.

Dietary small molecules	Bioactive constituents	BBB crossing ability	Type of study	Observed effects	Reference
Chrysin	4-oxo-2-phenyl-4H-chromene-5,7-diyl bis(piperidine-1-carboxylate)	Able	<i>In vitro</i> and <i>in silico</i>	Oral bioavailability ↑ Antioxidant activity ↑ AChE and BuChE ↓ Aβ aggregation ↓	[243]
7,8-DHF	7-O-β-d-glucosyl-8-hydroxyflavone, 7-hydroxy-8-O-β-d-glucosyl flavone, and 7,8-di-O-β-d-glucosylflavone	Not able	<i>In vitro</i> and <i>in silico</i>	APP and BACE inhibition ↓	[244]
Naringenin	Compound 3c and 5a	Able	<i>In vitro</i> and <i>in silico</i>	Cell viability ↑ Antioxidant activity ↑ AChE and BuChE ↓ Aβ aggregation ↓ Tau phosphorylation ↓ NO and TNF-α ↓	[245]
Naringenin	Compounds 5f and 7k	Able	<i>In vitro</i> , <i>in vivo</i> , and <i>in silico</i>	Cell viability ↑ Antioxidant activity ↑ AChE and BuChE ↓ Aβ aggregation ↓ NO and TNF-α ↓ Cognitive function ↑	[246]
Naringenin	5-hydroxy-2-(4-hydroxyphenyl)-4-oxochroman-7-yl piperidine-1-carboxylate	Able	<i>In vitro</i> and <i>in silico</i>	Oral bioavailability ↑ Antioxidant activity ↑ AChE and BuChE ↓ Aβ aggregation ↓ Cognitive function ↑	[247]
FA	Compounds 4g and 7f	Able	<i>In vitro</i> , <i>in vivo</i> , and <i>in silico</i>	Cell viability ↑ Antioxidant activity ↑ AChE and BuChE ↓ Aβ aggregation ↓ Cognitive function ↑	[248, 249]
FA	TM-10	Able	<i>In vitro</i> , <i>in vivo</i> , and <i>in silico</i>	Cell viability ↑ Antioxidant activity ↑ Autophagy activation ↑ AChE and BuChE ↓ MAO-A and MAO-B ↓ Acute toxicity ↓ Aβ aggregation ↓ Cognitive function ↑	[250]
FA	Compounds 6j and 6k	Able	<i>In vitro</i> , <i>in vivo</i> , and <i>in silico</i>	Cell viability ↑ Antioxidant activity ↑ MDA, AChE, and BuChE ↓ BACE-1 activity ↓ Acute toxicity ↓ Cognitive function ↑ Oral bioavailability ↑	[251]
FA	Compounds FA-G1 and FA-DG1	Not able	<i>In vitro</i> and <i>in vivo</i>	Cell viability ↑ Aβ aggregation ↓ NO production ↓ iNOS and p-NF-κB-p65 ↓ Neuronal cell death ↓	[252, 253]
CA	CAPE	Not able	<i>In vitro</i> and <i>in vivo</i>	NF200 and NeuN ↑ BDNF, nestin, and NeuN ↑ Neuromuscular activity ↑ Cognitive function ↑	[254]
CA	CAPE	Not able	<i>In vitro</i> and <i>in vivo</i>	PSD95, MAP-2, and GFAP ↓ Memory function ↑ Neuronal density ↑ Nrf2 and HO-1 ↑ GSK3β and p-GSK3β ↓ Oxidative stress ↓ GFAP and Iba-1 expression ↓ Caspase-9 expression ↓	[255]
CA	FA-97	Not able	<i>In vitro</i> and <i>in vivo</i>	Cell viability ↑ GSH and SOD activity ↑ Nrf2, HO-1, and NQO-1 ↑ Neuronal density ↑ Bcl2 expression ↑ LDH leakage ↓ MDA and ROS production ↓ Bax, caspase-9, and cyt-C ↓ Memory function ↑	[256]
Vanillin	Compounds 9e, 9h, 9i, 9t and 9z	Not able	<i>In vitro</i> and <i>in silico</i>	Cell viability ↑ AChE, BChE, and DPPH ↓ Aβ aggregation ↓ Neuronal cell death ↓	[257]

prevented oxidative stress and was accompanied by the induction of Nrf2 and HO-1 via the modulation of GSK3 $\beta$  in the hippocampus. Additionally, CAPE treatment in A $\beta$ -induced AD mice decreased A $\beta$ -induced neuronal apoptosis and neuroinflammation, and improved spatial learning and memory, protecting the mice against cognitive deficits [255]. Another study reported that CAPE-4-O-glucoside (FA-97) attenuated oxidative stress by inhibiting ROS, MDA, and PCOation levels, as well as inducing cellular GSH and SOD and apoptosis in H<sub>2</sub>O<sub>2</sub>-induced SH-SY5Y and PC12 cells. Mechanistically, FA-97 promotes the nuclear translocation and transcriptional activity of Nrf2 that is associated with upregulated expression of HO-1 and NQO-1. In addition, FA-97 prevents scopolamine-induced learning and memory impairments by reducing oxidative stress and neuronal apoptosis, protecting against cholinergic system dysfunction, and increasing the expression of HO-1, NQO-1, and nuclear Nrf2 in the hippocampus and cortex of AD mice [256]. Yelamanda Rao et al. [257] observed that the five acrylamide analogs 9e, 9h, 9 l, 9t, and 9z from vanillin protected against H<sub>2</sub>O<sub>2</sub>-induced SK-N-SH cell death. The results showed that these analogs had excellent neuroprotective effects, inhibited AChE and BChE activity, and had good radical-scavenging activity. In addition, acrylamide analogs were strong modulators of A $\beta$  aggregation; they irretrievably disrupted A $\beta$ <sub>42</sub> fibril morphology, decreased the aggregates, and reduced A $\beta$ -induced toxicity in neurons.

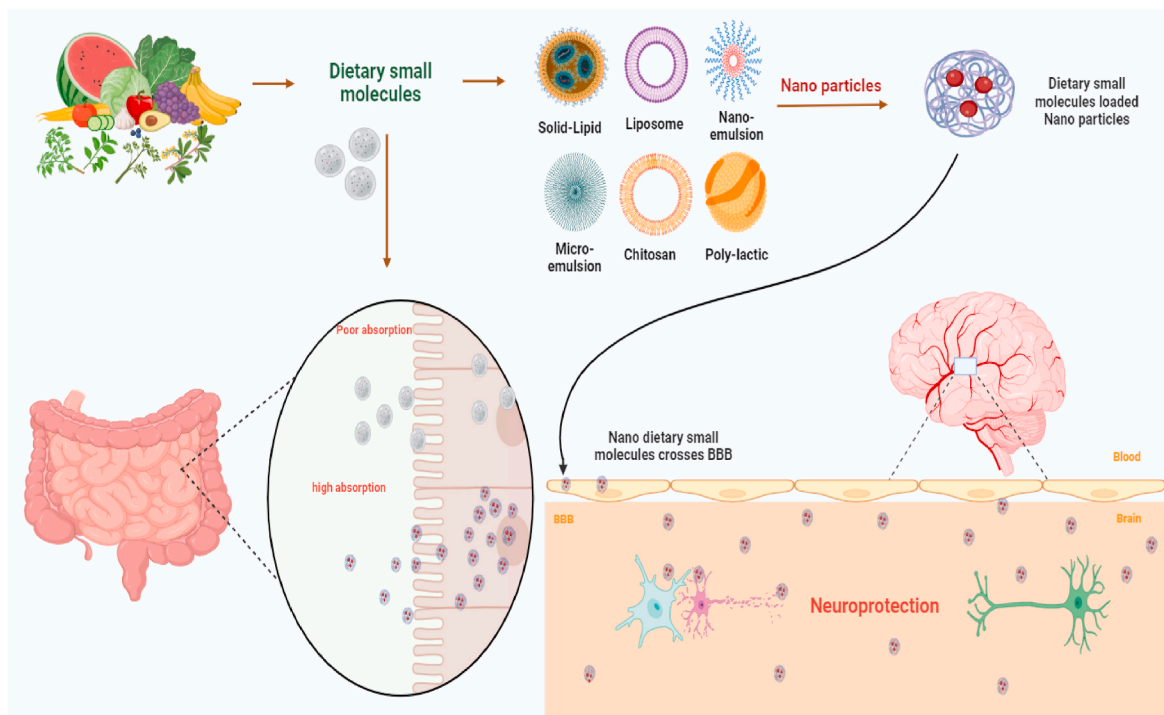
## 6. Potential of dietary small molecule-based nanotherapy in AD

Nanocarriers can increase a drug's bioavailability and lipophilicity, which can improve its therapeutic effect. Drug stability has been another target for nanocarriers; they were designed to improve encapsulation efficiency and allow for more precise control over drug release, which is essential for treating a variety of diseases [258,259]. Therefore, nanotechnology has the potential to improve the therapeutic efficacy of medicines by producing the desired pharmacological response in humans. Several nanodelivery systems with dietary small molecule payloads have demonstrated effectiveness in modulating oxidative

stress, A $\beta$  deposition, and hyperphosphorylation of tau, chronic neuroinflammation, and various signaling pathways that mediate aging-associated NDDs, particularly in AD (Fig. 8).

In aged female mice with A $\beta$ <sub>1-42</sub>-induced AD, treatment with chrysin-loaded lipid-core nanocapsules (LNCs) (1 and 5 mg/kg) for 2 weeks provided gradual release and increased bioavailability as well as greater accumulation in brain tissues compared with free chrysin. Furthermore, LNC administration improved spatial learning and memory, decreased non-protein thiols levels (NPSH) and reactive species (RS), and increased GR, GPx, GST, and CAT activity in the prefrontal cortex and hippocampus. Treatment also upregulated BDNF expression, reduced proinflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$  and increased expression of the anti-inflammatory cytokine IL-10 in the prefrontal cortex and hippocampus of the mice [260]. Similarly, chrysin-loaded chitosan nanoparticles (Chr-Chi NPs) were evaluated for neuroprotection activity in an A $\beta$ -induced zebrafish AD model. The results demonstrated that Chr-Chi NP treatment effectively improved memory, cognition, and synaptic connections and reduced A $\beta$  aggregates, thus decreasing neuronal cell death and the generation of ROS [261]. Another study reported that the administration of chrysin in an oil-in-water nanoemulsion (chrysin-NE) was easy to digest, was significantly absorbed by human intestinal cells (Caco-2), and enhanced the bioavailability of chrysin [262]. Recently, chrysin-loaded solid lipid nanoparticles (CN-SLNPs) showed enhanced oral bioavailability and increased the encapsulating capacity of chrysin in SLNs in A $\beta$ -induced AD rats at low concentrations. In addition, CN-SLNP treatment significantly increased all the antioxidant and non-antioxidant enzymes while significantly reducing TBARS and AChE activity in the hippocampus of A $\beta$ -induced AD rats. Furthermore, histopathological evidence and behavioral analysis showed that CN-SLNPs restored hippocampal neuronal loss and prevented memory impairments in A $\beta$ -induced AD rats [263]. Table 3 summarizes the latest preclinical research findings on the neuroprotective effect of nano-formulated dietary small molecules against AD.

Md et al. observed that naringenin-loaded nanoemulsion



**Fig. 8.** Illustrates the potential uses of dietary small molecules nanoformulations in AD. Dietary small molecules lower BBB permeability, poor solubility, and low bioavailability, they have failed to reduce disease progression and treat AD. The development of dietary small molecules-loaded nanocarrier systems can reduce these barriers while improving neuroprotective benefits. BBB: blood brain barrier.



**Table 3**

Summarizes the latest preclinical research findings on the effect of nano-formulated dietary small molecules against AD.

Dietary small molecules	Limitation	Nanocarrier	Nanocarrier size (nm)	Neurotoxin/duration	Drug concentration/duration	Mechanism of action	Reference
Chrysin	Poor oral bioavailability	Lipid-core nanocapsule	368–419	A $\beta$ <sub>1–40</sub> (3 $\mu$ L for 1 day)	1 or 5 mg/kg bw for 14 days	Oral bioavailability $\uparrow$ Memory function $\uparrow$ NPSH, GSH, SOD, and CAT $\uparrow$ BDNF and IL-10 $\uparrow$ IL-1 $\beta$ and TNF- $\alpha$ $\downarrow$	[260]
Chrysin		Chitosan		A $\beta$ <sub>1–40</sub> (3 $\mu$ L for 1 day)			[261]
Chrysin	Low bioaccessibility	Nanoemulsion	161	–	–	Bioaccessibility $\uparrow$ Cell viability $\uparrow$ Antioxidant activity $\uparrow$ AChE and BChE activity $\downarrow$ Cognitive performance $\uparrow$ GSH, SOD, CAT, and GPx $\uparrow$ Vitamin-C $\uparrow$ TBARS and AChE $\downarrow$ Neuronal cell loss $\downarrow$ GFAP-positive astrocyte $\downarrow$	[262]
Chrysin	Poor pharmacokinetic profile	Solid lipid nanoparticles	240.0 $\pm$ 4.79	A $\beta$ <sub>1–40</sub> (3 $\mu$ g for 1 day)	50 mg/kg bw for 21 days	Cognitive performance $\uparrow$ GSH, SOD, CAT, and GPx $\uparrow$ Vitamin-C $\uparrow$ TBARS and AChE $\downarrow$ Neuronal cell loss $\downarrow$ GFAP-positive astrocyte $\downarrow$	[263]
Naringenin	Low aqueous solubility and low bioavailability	Nanoemulsion	113.83 $\pm$ 3.35	A $\beta$ <sub>1–40</sub> (2 $\mu$ M for 84 h)	0.125, 0.250, 0.5 $\mu$ M for 24 h	Solubility $\uparrow$ Cell viability $\uparrow$ ROS production $\downarrow$ APP and BACE1 $\downarrow$ A $\beta$ level, tau, and pT231 $\downarrow$ Cognitive performance $\uparrow$ Spatial learning and memory $\uparrow$ GSH, Nrf2, and p-CREB $\uparrow$ Neuronal survival $\uparrow$ MDA, iNOS, and COX-2 $\downarrow$ MMP9, TNF- $\alpha$ , and NF- $\kappa$ B-p65 $\downarrow$ A $\beta$ level and Tau $\downarrow$ Neuronal damage $\downarrow$ A $\beta$ -plaques formation $\downarrow$ GFAP-positive astrocyte $\downarrow$	[264]
Luteolin	Low solubility and low permeability	Chitosan	412.8 $\pm$ 3.28	ICV-STZ (3 mg/kg for 1 day)	50 mg/kg bw for 21 days	Cognitive performance $\uparrow$ Spatial learning and memory $\uparrow$ GSH, Nrf2, and p-CREB $\uparrow$ Neuronal survival $\uparrow$ MDA, iNOS, and COX-2 $\downarrow$ MMP9, TNF- $\alpha$ , and NF- $\kappa$ B-p65 $\downarrow$ A $\beta$ level and Tau $\downarrow$ Neuronal damage $\downarrow$ A $\beta$ -plaques formation $\downarrow$ GFAP-positive astrocyte $\downarrow$	[265]
Luteolin	Low solubility and low permeability	Nanobilosomes	153.2 $\pm$ 0.98	ICV-STZ (3 mg/kg for 1 day)	50 mg/kg bw for 21 days	Cognitive performance $\uparrow$ Spatial learning and memory $\uparrow$ Neuronal survival $\uparrow$ MMP9 and TNF- $\alpha$ $\downarrow$ A $\beta$ level and Tau $\downarrow$ Neuronal damage $\downarrow$ A $\beta$ -plaques formation $\downarrow$ GFAP-positive astrocyte $\downarrow$ Iba-1-positive astrocyte $\downarrow$	[266]
Lycopene	Poor oral bioavailability	Microemulsion	<100	A $\beta$ <sub>1–40</sub> (10 $\mu$ M for 1 day)	4 mg/kg bw for 21 days	Cognitive performance $\uparrow$ Spatial learning and memory $\uparrow$ Reelin, nestin, and Pax6 $\uparrow$ BrdU <sup>+</sup> , Dcx <sup>+</sup> , and BrdU <sup>+</sup> $\uparrow$ Neun <sup>+</sup> , BrdU <sup>+</sup> , and Dcx <sup>+</sup> $\uparrow$ p-GSK-3 $\beta$ and p- $\beta$ -Catenin $\uparrow$	[267]
Lycopene		Microemulsion		A $\beta$ <sub>1–40</sub> (10 $\mu$ M for 1 day)	4 mg/kg bw for 21 days	Memory function $\uparrow$ GSH, SOD, CAT, and GPx $\uparrow$ MDA levels $\downarrow$	[268]
FA	Poor aqueous solubility	Chitosan	185	ICV-STZ (3 mg/kg for 1 day)	80 mg/kg bw for 28 days	Solubility $\uparrow$ Oral bioavailability $\uparrow$ Memory function $\uparrow$ GSH and SOD content $\uparrow$ MDA, NO, and AChE activity $\downarrow$	[269]
EA	Low absorption and low permeability	Poly (lactic-co-glycolic acid)	277	AlCl <sub>3</sub> (50 mg/kg for 28 days)	10 mg/kg bw for 14 days	Solubility $\uparrow$ Oral bioavailability $\uparrow$ Memory function $\uparrow$ Neuronal survival $\uparrow$ GSH and SOD content $\uparrow$ TBARS content $\downarrow$ Neuronal damage $\downarrow$ NFT and A $\beta$ -plaque formation $\downarrow$	[270]
CA	Poor oral bioavailability and drug instability	Liposome	140	A $\beta$ <sub>1–40</sub> (10 $\mu$ M for 1 h)	0.8 $\mu$ M for 2 h	Oral bioavailability $\uparrow$ Stability $\uparrow$	[271]

(continued on next page)

Table 3 (continued)

Dietary small molecules	Limitation	Nanocarrier	Nanocarrier size (nm)	Neurotoxin/duration	Drug concentration/duration	Mechanism of action	Reference
EGCG	Instability and low bioavailability	Poly (lactic-co-glycolic acid)	124.8 ± 5.2	Transgenic model	40 mg/kg bw for 90 days	Aβ aggregation ↓ Aβ fibril formation ↓ Physicochemical stability ↑ Synaptic neurons ↑ Memory function ↑	[272]
EGCG	Poor bioavailability and inefficient delivery	Nanolipids	<100	–	3.125–30 μM for 18 h and 100 mg/kg bw for 8 h	Aβ-plaque and GFAP ↓ Oral bioavailability ↑ Stability ↑ α-secretase ↑	[273]

significantly alleviated the direct neurotoxic effects of Aβ on SH-SY5Y cells; this was associated with a downregulation of APP and BACE expression, indicating reduced amyloidogenesis, and decreased the levels of phosphorylated tau in Aβ-exposed SH-SY5Y cells [264].

Recent studies found that luteolin-loaded Chi and bilosome NPs provided obvious improvement in the acquisition of short- and long-term spatial memory, increased neuronal survival rate with a reduction in the number of Aβ-plaques, improved antioxidant enzyme status, and reduced pro-inflammatory mediator levels. In addition, luteolin-loaded Chi NPs suppressed both Aβ aggregation and hyperphosphorylated tau protein in the hippocampus and cerebral cortex in ICV-STZ-induced AD mice [265,266]. Interestingly, Ning et al. [267] demonstrated that in Aβ-induced AD rats, lycopene-loaded microemulsion (LME-NPs) improved spatial learning and memory, significantly increased reelin, nestin, and Pax6 gene expression, which regulate neurogenesis, as well as increased BrdU<sup>+</sup>, Dcx<sup>+</sup>, BrdU<sup>+</sup>/Neun<sup>+</sup>, and BrdU<sup>+</sup>/Dcx<sup>+</sup> cells in the dentate gyrus of the hippocampus and subventricular regions, thus promoting neurogenesis. Treatment also reduced the number of Iba1<sup>+</sup> and Iba1<sup>+</sup>/BrdU<sup>+</sup> cells, thus reducing the neuroinflammatory response. In addition, LME-NPs upregulated the Wnt/β-catenin pathway by upregulating Wnt3a, β-catenin, Dishevelled (Dvl), and p-GSK3β and downregulating p-β-catenin and GSK3β. More recently, LME-NP supplementation dramatically decreased MDA production and restored antioxidant capacity, alleviated neuronal loss, attenuated astrocytosis and microgliosis, normalized apoptotic parameters, inhibited amyloidogenic processing, and activated the non-amyloidogenic pathway, together with upregulating synaptic protein expression and restoring synaptic plasticity [268].

Another recent study demonstrated that FA-coated Chi-SLNPs successfully improved anti-AD efficacy, provided superior nasal mucoadhesion and permeation, and extended drug release. It has also been reported that FA-coated Chi-SLNPs improved cognitive ability in ICV-STZ-induced AD rats by reducing escape latency, significantly improving body weight gain and various other biochemical parameters; histopathological changes were also observed in the hippocampus and cerebral cortex [269]. Moreover, poly (lactic-co-glycolic acid)-EA-NPs significantly enhanced antioxidant activity and reduced brain neurotoxicity in rats with AlCl<sub>3</sub>-induced AD by reducing oxidative stress, reducing the AD-vacuolation of neurons, chromatolysis, NFTs, and senile plaques in the brain and restoring Nissl granules as well as modulating behavioral performance [270]. Transferrin-targeted CA-loaded liposome-NPs showed suitable encapsulation efficiency and physical stability for at least 2 months. They prevented Aβ aggregation, fibril formation, and disaggregation of mature fibrils [271]. Furthermore, dual-drug-loaded PEGylated PLGA NPs (EGCG/AA NPs) induced tight junction disruption and opened the BBB *in vitro* and *ex vivo*. In addition, EGCG/AA NP treatment produced a marked increase in synapses as judged by synaptophysin expression, reduced neuroinflammation, Aβ plaque formation, and cortical levels of soluble and insoluble Aβ<sub>(1-42)</sub> peptide; this subsequently enhanced spatial learning and memory in APP/PS1 AD mice [272]. Finally, Smith et al. found that nanolipid EGCG NPs improved oral bioavailability and enhanced neuronal α-secretase in SweAPP N2a cells [273].

## 7. Combination therapeutic effects of dietary small molecules in AD

Accumulating evidence has suggested that multidrug therapeutic targets associated with multifactorial molecular mechanisms could prove to be effective in treating AD. A recent study indicated that flavones such as apigenin, 7,8-DHF, quercetin, and wogonin were investigated for Tau aggregation inhibitory activity and neuroprotection in SH-SY5Y cells. Among the four tested flavones, 7,8-DHF, apigenin, and quercetin reduced oxidative stress, Tau aggregation, and caspase-1 activity by improving the expression of HSPB1 and Nrf2 and activated TRKB-mediated ERK signaling as well as upregulate CREB and its downstream antiapoptotic Bcl2 expression in SH-SY5Y cells expressing ΔK280 Tau<sub>RD</sub>-DsRed folding reporter [94]. Tao et al. [274] found that luteolin (100 mg/kg bw) combined with exercise training significantly improved learning and memory, reversed the increase in Aβ, and inhibited the activation of astrocytes and microglia (as shown by GFAP and Iba-1 markers, respectively) in a mouse AD model induced by Aβ<sub>1-42</sub> oligomers. This model also showed decreased levels of autophagy markers (p-ULK1 and p62) as well as increases in autophagy-related proteins LC3I and LC3II in the hippocampus and cortex following luteolin treatment. Notably, luteolin combined with exercise therapy led to more intact hippocampal and cortical areas, with a greater improvement than that seen with monotherapy. However, luteolin and L-theanine can act together in the anti-Alzheimer's effects by improving memory function, norepinephrine metabolisms, hippocampal insulin signaling, and reducing neuroinflammation in Aβ-induced AD rats [275]. *In vitro* and *in vivo* research findings reported that combined treatment with palmitoylethanolamide and luteolin (co-ultra PEALut) promoted neuronal survival, upregulated the protein and mRNA BDNF and GDNF expression, significantly reduced iNOS and GFAP expression, and reduced the neuronal apoptosis as well as neuroinflammation [140, 276].

Interestingly, combination treatment with lycopene and vitamin E significantly improved spatial and passive memory, decreased MDA levels and increased GPx activity in the serum, and decreased tau phosphorylation at Thr231/Ser235, Ser262, and Ser396 in the brains of P301L transgenic mice [277]. Ohashi et al. reported that FA combination with curcumin treatment was confirmed to effectively inhibit Aβ aggregation, decrease mitochondrial and extracellular ROS levels by increasing the cell viability, and improve the mitochondrial function in Aβ exposure SH-SY5Y cells. Combination treatment produced an overall higher neuroprotective effect than treatment with FA or curcumin alone [166]. In another study, it was found that a combination treatment of FA, atractylenolide III, and paeoniflorin can exert neuroprotective and anti-inflammatory effects on LPS-induced autophagy and neuroinflammation in BV-2 microglial cells by significantly increasing the expression of autophagy-related proteins p-AMPK, Beclin1, p-ULK1, LC3, and TFEB and decreased the expression of p62 and significantly reduced the production of inflammatory factors such as IL-6, IL-1β, and TNF-α [168]. A similar study has also been reported that FA, curcumin, and phosphatidylserine exposed to APP<sup>sw</sup>/PS1<sup>de9</sup> transgenic mice and evaluated neuroprotective and cognitive function. The results

showed that FA, curcumin, and phosphatidylserine treatment exhibited a significant improvement in memory function, BDNF expression, and acetylcholine level and strongly inhibited aggregation of A $\beta$ -plaque and phosphorylated tau formation and reduced the proinflammatory cytokine IL-1 $\beta$  [278].

Interestingly, nutraceutical bioactive products such as EGCG, curcumin,  $\alpha$ -lipoic acid, and docosahexaenoic acid appeared to have the most potent anti-inflammatory and neuroprotective effects by suppressing the A $\beta$ -induced BACE-1 upregulation, attenuated ROS production and beta-sheet structure formation; and strongly reduction of A $\beta$ -plaque aggregation and inhibition of microglial activation [279,280]. In hAbKI mice, combined treatment with EGCG and urolithin A ameliorated behavioral deficits by upregulating the levels of protein and mRNA expression of synaptic function, mitochondrial fusion, autophagy, and mitophagy function, increased dendritic spine length and down-regulating the mitochondrial fission. In addition, EGCG combination with urolithin A strongly inhibited A $\beta$ -plaque aggregation, reduced mitochondrial fragmentation, and increased mitochondrial length and mitophagosomal formations [281]. A similar study reported that both EGCG and voluntary exercise were able to attenuate nest building and Barnes maze performance deficits and lowered soluble A $\beta$ <sub>1-42</sub> levels in the cortex and hippocampus [282]. Moreover, PEGylated-loaded EGCG/ascorbic acid nanoparticles resulted in a significantly enhanced spatial learning and memory and a marked increase in synaptophysin (SYP) expression, synapse function, and reduction of A $\beta$ -plaque burden and cortical levels of soluble and insoluble A $\beta$ <sub>(1-42)</sub> peptide as well as neuroinflammation in APP/PS1 AD mice [272]. Ali et al. [283] conducted a study in AlCl<sub>3</sub>-induced AD rats to evaluate the neuroprotective and inhibitory effects of A $\beta$ -plaque aggregation. The results showed that combination administration of EGCG, Coenzyme Q10, Vitamin E and Selenium significant decrease in A $\beta$ -plaque aggregation and AChE activity, suppressed TNF- $\alpha$ , IL-1 $\beta$  expression, and increased the BDNF protein expression as well as antioxidant enzymes activities (MDA, SOD, TAC).

## 8. Clinical aspects and dietary small molecules

A 12-month, open-label, randomized controlled trial in 40 patients with MCI showed that physical exercise combined with lipophilic micronutrients including lutein and lycopene reduced cognitive impairment, suggesting a potential benefit from multifactorial lifestyle changes. Therefore, combinations of nutritional and physical interventions may have greater effects on cognition in individuals at risk for AD [284]. A randomized placebo-controlled trial in patients with MCI showed that citrus peel extract (0.1, 3, and 400 mg) containing naringenin and auraptene administered over 36 weeks reduced neuronal damage (BDNF, IGF-1, and NF-light), oxidative stress (NO, TBARS, and SOD), and cytokines (pro-inflammatory: CXCL8/IL-8, IL-1 $\beta$ , IL-6, IL-17, TNF- $\alpha$ , IP10, MIP-1 $\alpha$ , CCL2/MCP-1, CCL5/RANTES, IL-18; anti-inflammatory: IL-10, IL1-Ra, soluble TNF receptor I, soluble TNF receptor II) [285]. In a study of the effects of EA treatment (50 mg/kg for 12 weeks) in patients with mild age-related cognitive decline, EA improved blood lipid metabolism, with declines in total cholesterol, triglycerides, and low-density lipoprotein, as well as increased high-density lipoprotein and plasma BDNF levels, and enhanced cognitive function [286]. A 12-month randomized controlled study conducted between September 2016 and August 2017 included 200 older adults with MCI and reported that a dietary supplement containing FA 200 mg/kg and *A. archangelica* extract 40 mg/kg showed clinical effectiveness for cognitive functioning [287].

## 9. Advantages of dietary small molecules and their bioactive constituents

Since ancient times, natural products (e.g., fruits, vegetables, and other medicinal plants) have been used to prevent and treat human

diseases such as NDDs. Most modern medicines are derived from herbs, with many based on traditional knowledge and practices [288]. As reported by the WHO, approximately 80% of individuals in developing countries are currently using natural plant-based medicine as well as food products to meet their primary healthcare needs [289]. The science of natural small molecule drug discovery is currently among the most interesting areas of research. Over the last 20 years, research in this field has led to the filing of more than 200,000 patents and the completion of several dozen clinical trials [290]. Almost 25% of the major pharmaceutical compounds (and bioactive derivatives) available today are acquired from natural resources [291]. This is mainly because natural agents have unique advantages, such as reduced toxicity and minimal side effects, considerable chemical diversity, and low cost, as well as favorable chemical and pharmacological properties, including preventive effects on disease. While the value of dietary small molecules and their bioactive derivatives as replacements for pharmaceuticals has been questioned, studies have shown that they are at least as effective as commercially available pharmaceuticals or possibly more effective [292]. In addition, bioactive dietary components do not require extensive toxicity testing and rigorous human trials, which can significantly diminish their time to market [293].

Plant-based foods containing the most bioactive dietary components (cereals, vegetables, fruits, and other medicinal plant sources) have been investigated to assess their activity in the body, and functional foods have emerged as prospective preventive and therapeutic options [294]. Bioactive dietary small molecules have a range of metabolic activities that may be useful for treating illness. These chemicals are secondary metabolites in medicinal plants; they have antimicrobial, neuroprotective, antioxidative, and anti-inflammatory activity and can perform a variety of biological activities, including regulating the immune system; reducing platelet aggregation; regulating hormone, glucose, and lipid metabolism; controlling enzyme detoxification and digestion, and delaying aging [294,295]. However, the biological processes through which plant-based bioactive dietary small molecules promote health remain a mystery. However, these molecules operate in distinct or comparable locations. Bioactive dietary elements have been shown to lower the risk of developing NDDs and infectious diseases [296,297]. Individuals with risk factors for early death can benefit from regular intake of foods rich in polyphenols, flavonoids, and carotenoids since these bioactive dietary small molecules improve memory and cognitive function, decrease neuroinflammation and oxidative stress, and contribute to clearing aggregates of A $\beta$  plaques and tangles by promoting neuronal growth and survival, and reducing AD-related manifestations [298,299]. Importantly, bioactive dietary small molecules can interact with gut microbes and host and/or modify the microbial metabolites that are available to the host. SCFAs promote digestive wellness, metabolic management, immune regulation, glucose and lipid composition, and microbiome antioxidant and neuroprotective activity [297,300]. In recent years, dietary small molecules have been promoted as dietary supplements for hypertension and obesity and as anti-aging preparations [301]. Interestingly, the future use of dietary small molecules and their bioactive compounds as anti-Alzheimer's as anti-obesity agents is the use of combination therapies. By combining dietary small molecules, herbal supplement, and other drug combinations that target different aspects of neuroprotective signaling pathways, it may be possible to achieve synergistic effects and improve overall therapeutic efficacy. This could lead to favors for targeted drug development that modulate early-stage mild cognitive impairment associated with AD, offering more precise and effective treatment options.

Natural dietary products can also be used in the food and cosmetics industries. Several dairy products with dietary supplements have already been commercialized [302]. The antioxidant potential of dietary small molecules is also of great interest in food packaging and storage because they can prevent food spoilage, with antioxidants used in a controlled atmosphere to limit oxygen availability [303]. Green tea (EGCG and TFs) is becoming a very popular beverage worldwide

because of its health benefits, attributed to its high polyphenol content, especially the monomeric catechins. Enzymes have been used in tea processing mainly to improve the quality of tea beverages. Generally, cell-wall-digesting enzymes improved the extraction efficiency including polyphenols and thereby the antioxidant capacity of the extract. It can be seen that green tea consumption may protect cognitive function by reducing AD pathology and improving anti-oxidative stress capacity. Green tea extract can also be used in lipid-bearing foods to delay lipid oxidation and to enhance the shelf-life of various food products [211,212,228]. Dietary small molecules have become a modern food trend to add nutritional fortification to foods to increase the content of essential micro-nutrients and improve their nutritional quality. Cakes contain high carbohydrates and fats, while other nutrients, including proteins, minerals, and vitamins are fewer. Adding available, cheap, and nutritious edible plants to the cakes can enhance their health and nutritional safety. Many studies have shown that cake made with dietary small molecules powder is rich in protein, vitamins, and dietary fiber. It has high nutritional value and good taste [304]. Recently, dairy products-derived snacks mixed with other plant materials have received extensive attention. For example, sweet and salty biscuits rich in calcium and protein were prepared by mixing dietary supplements. Fermented snacks made from cassava flour, soybean flour, and horseradish leaf powder rich in Vitamin A provided a new strategy for improving the diet of people with nutritional deficiencies. Snacks are one of the fastest-growing segments of the food industry. However, providing nutrition through the inclusion of fruits and vegetables in puffed snacks is a relatively new concept. Importantly, dietary supplements can be easily blended with oats to create extruded puffed snacks with a significantly improved nutrient profile compared to that of commercially available snacks [301]. However, more attention should be paid to other phenolic compounds that are not regulated by current legislation and that have the potential to be used as food additives, such as phenolic acids and other classes of dietary products. Dietary small molecules could also be useful in cosmetics and could be used to prevent skin aging and cutaneous disorders since ROS are key drivers of aging [305]. In addition, their ability to prevent lipid peroxidation allows them to extend shelf-life, as they do for foods [306]. Dietary small molecules could also be used in cosmetic formulations such as body lotion, shampoo, hair restorer, hair color, and soaps [307]. Since dietary small molecules are safe for consumption, their use as dietary supplements in natural, green, and healthy foods may soon become a trend in the food and drug development industry.

## 10. Limitation and future directions

Indeed, dietary small molecules and their bioactive constituents are an important natural compound that has multiple health benefits. However, the use of dietary small molecules as targeted AD therapy has some limitations. The advances, challenges, and future perspectives that remain to be considered include the following. (1) Molecules like polyphenols are unstable when pH, temperature, humidity, or light level changes and they cause toxicity and adverse events at specific concentrations. Therefore, future research must focus on improving the extraction yield and stability of these molecules, minimizing side effects, and increasing health-promoting activity. In addition, since natural dietary small molecules are usually safe, recommendations on daily dosing and treatment duration must be provided for safe and effective use. (2) The pharmacokinetic and pharmacodynamic features of dietary small molecules can compromise their therapeutic efficacy. These include poor water solubility, low bioavailability, rapid metabolism, and susceptibility to physical and chemical degradation. Therefore, further pharmacokinetic and pharmacological studies are needed to improve these features. (3) Based on the rich functionality of dietary small molecules, separation of functional components, discovery of new structural compounds, structural identification, active function research, and structure-activity relationship studies should be

investigated. (4) The BBB is a biological membrane that restricts the entry of compounds, thus hindering treatments from reaching the brain. Characteristics of the BBB should be thoroughly investigated to facilitate the discovery of structural compounds from dietary small molecules that can successfully cross the barrier and target the disease. (5) Nanotechnology is a novel and promising solution for improving oral bioavailability and providing other health-promoting and neuroprotective effects. However, it is difficult to determine the range of useful doses, treatment durations, and drug-delivery methods. Extensive research is needed to investigate these areas (6) Dietary small molecules (e.g., luteolin, EGCG, and TFs). can modulate the gut microbiota and exert a neuroprotective effect through the gut-brain axis. However, studies are limited to the neuroprotective molecular signaling pathways involved. More work is needed to elucidate how dietary small molecules influence the gut microbiota and induce anti-AD effects. (7) Finally, as most *in vivo* studies are currently based on rat or mouse models, well-designed human intervention studies are urgently required to verify the safe and effective dosage of dietary small molecules and their bioactive constituents.

Apart from a few limitation, the main concern is high lipophilicity. Lipophilicity is an important physicochemical property of a compound that has parabolic relationship with *in vivo* brain penetration. High lipophilic natural phytochemicals often experience low BBB access owing to increased non-specific plasma protein bindings and vulnerability to P450 metabolism that led to rapid clearance of compounds. Because of this high lipophilic property, a low concentration of dietary small molecule (naringenin) is observed in the brain, limiting its neuroprotective effect at a low dose. Recent study has addressed this issue and resolved it on their own. For example, nanoemulsion-loaded with naringenin showed higher efficacy over free drug without affecting naringenin neuroprotective function restoration effect in an AD model (264). However, dietary small molecules are a potential bioenhancer, it could be administered with other drugs or herbs to potentiate their therapeutic efficacy in NDDs, like with resveratrol, curcumin, quercetin, and Vitamin E.

## 11. Conclusion

AD is associated with cognitive impairment in a substantial proportion of people, and age-related cognitive decline is associated with alterations in the brain, particularly in the hippocampus and cerebral cortex. These include moderate but chronic neuroinflammation, increased oxidative stress, mitochondrial dysfunction, diminished autophagy, waning neurogenesis, and neuronal synaptic loss. A $\beta$  plaque deposition contributes to the accumulation of neurofibrillary tangles and the progression of neuroinflammation induced by activated microglia; these processes lead to synaptic loss and neurodegeneration. Extensive *in vitro* and animal studies have provided strong evidence that dietary small molecules and their main bioactive ingredients can improve AD pathology via multi-target signaling, making them suitable for multi-target drug design. Dietary small molecules and their bioactive ingredients can inhibit AChE activity, reducing A $\beta$  deposition and inhibiting tau hyperphosphorylation to rescue synaptic dysfunction. In addition, they enhance mitochondrial activity, activate autophagy, and modulate the gut microbiome, as well as having anti-apoptosis, anti-oxidation, and anti-inflammatory activity. Importantly, evidence shows that dietary small molecules and their main bioactive ingredients play an essential role in improving spatial learning and memory in animal models of AD.

## Ethical approval and consent to participate

Not applicable.

## CRedit authorship contribution statement

**Rengasamy Balakrishnan:** Writing – review & editing, Writing – original draft, Validation, Investigation, Conceptualization. **Khoshnur Jannat:** Resources, Formal analysis. **Dong-Kug Choi:** Supervision, Project administration, Funding acquisition.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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