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Review article

# Potential therapeutic use of plant flavonoids in AD and PD

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ABSTRACT

*Background:* Millions of people suffer from Alzheimer's disease (AD) and Parkinson's disease (PD) worldwide. Due to their complex pathology, no effective pharmacological treatment has been found to date, despite extensive research. Developing new, effective therapeutic agents to cure these disease remains a major challenge. Although the cause of AD and PD remains illusive, numerous studies indicates that oxidative stress and neuro-inflammation lead to neurodegeneration in the central nervous system and play vital role in AD and PD morbidity and progression. Flavonoids, which are found widely in nature, exhibit anti-oxidative, anti-inflammatory, anti-mutative, anti-microbial, and neuroprotective properties, so have potential to treat these two kinds of diseases.

*Methods:* In this review, we focus on the anti-oxidative and neuroprotective action of flavonoids in attenuating Alzheimer's and Parkinson's disease, and how they might be harnessed in the development of new pharmacological agents to treat these two diseases.

*Result:* Some flavonoid compounds, like hesperidin, naringin, naringenin, tangeretin, nobiletin, silibinin, Epigallocatechin-3-gallate, displayed to be effective in both AD and PD.

*Conclusion:* Considerable studies have demonstrated the anti-AD and anti-PD effects of flavonoids through various in vitro and in vivo models. However, more rigorous studies are needed to be done for flavonoids to develop into effective drugs and apply them to clinical practice.

## 1. Introduction

Alzheimer's and Parkinson's disease, are progressive, chronic and severe conditions characterized by functional loss and neuronal death, and are associated with both motor and cognitive function impairment [1, 2, 3]. The number of patients living with these two diseases increases every year worldwide due to the aging population [4, 5]. AD and PD reduce physical and mental health, and are responsible for an increasingly large burden of disease [6, 7]. Despite considerable effort from many researchers and leading pharmaceutical companies over many years, there are no effective therapies for these two diseases. Developing potent pharmaceutical therapies for AD and PD is a tough challenge due to the complexity of pathological mechanisms and clinical features [8]. Some natural products, like flavonoids, alkaloids, and saponins, have been shown to be effective in preventing and treating neurodegenerative changes, indicating a possible therapeutic role in AD and PD [9, 10, 11, 12, 13]. This article focuses on the potential of flavonoids in Alzheimer's and Parkinson's disease therapy.

Flavonoids are ubiquitous in nature, and play various biological roles. These phytochemicals are polyphenols with two aromatic rings connected by a three-carbon chain (Figure 1 A). According to their chemical structures, flavonoids are classified into groups such as flavones, flavonols, flavanoes, flavanonols, flavanols (catechins), anthocyanidins (anthocyanins), isoflavones, dihydroflavonols, and chalcones (Figure 1 B). Flavonoids have some unique chemical and pharmacological properties due to their special structures [14, 15]. For example, they exhibit oil and water amphipathy, and have complex or electrostatic interactions with a variety of metal ions, reduce and trap free radicals, and combine with proteins [16, 17, 18, 19]. The strong anti-oxidative and neuroprotective activities of flavonoids are a comprehensive reflection of these properties. Flavonoids react with hyperoxidized free radicals, quench unpaired electrons and/or terminate the chain reactions of free radicals, enabling

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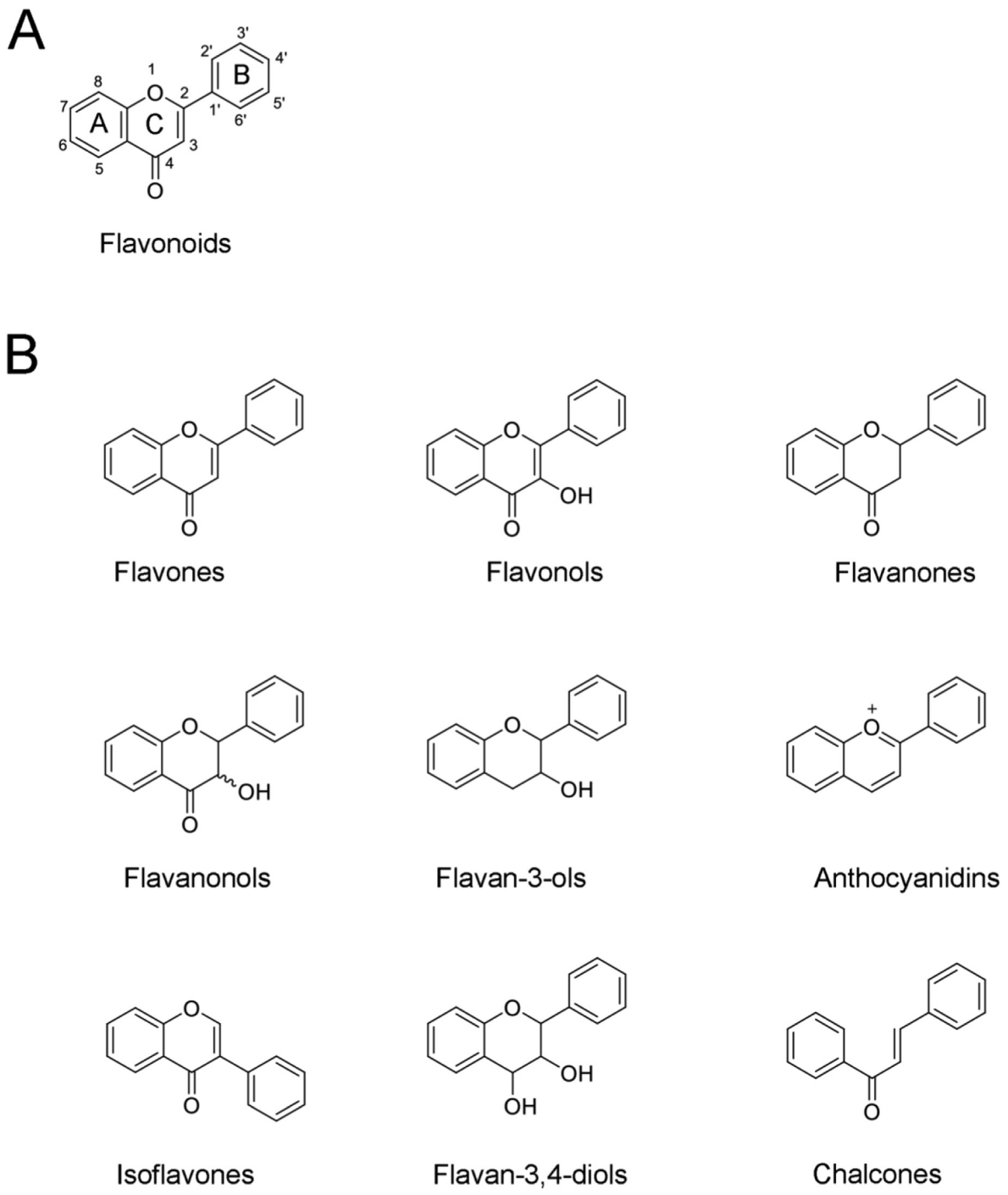



**Figure 1.** The structures of flavonoids (A) The basic structure of flavonoids (B) The structures of the main subgroups.

them to effectively scavenge free radicals. Therefore, flavonoids have been used extensively as powerful antioxidants, and are considered promising candidates for pharmaceutical agents to treat various Alzheimer's and Parkinson's disease [20, 21, 22].

## 2. Neurodegenerative diseases and oxidative stress

Oxidative stress has both beneficial and deleterious effects on the central nervous system. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) play important roles in hippocampal development, synaptic plasticity and axonal form [23, 24, 25]. Moreover, ROS seem to be involved in inflammation [26], signaling transduction [27], immune response [28], apoptosis [29], and are vital in intracellular signaling [30] and growth factor signaling [31, 32]. ROS regulate cytokines [33], tyrosine kinases [34], protein tyrosine phosphatases [35], serine/threonine kinases [36], and nuclear transcription factors [37]. Oxidative stress induces lipid peroxidation and damages nucleic acids and proteins [38]. Polyunsaturated fatty acids, such as arachidonic acid and linoleic acid, are main targets of lipid peroxidation, which induces serious injury to the neuronal membrane [39, 40]. Oxidative stress may damage ribonucleic acid (RNA) and nuclear deoxyribonucleic acid (DNA), especially the mitochondrial DNA [41, 42]. Mitochondrial dysfunction and abnormal energy metabolism are considered the major drivers of neuronal damage [41, 43].

Oxidative stress induces neuronal damage, which is the main pathogeny of AD and PD, and the disease states lead to greater production of ROS and subsequent oxidative injury [44, 45]. Although the molecular mechanisms underlying AD and PD have not been elucidated completely, convincing evidence demonstrates that oxidative stress, which causes numerous biological effects, including abnormal protein secretion and aggregation, mitochondria dysfunction, neuro-inflammation, neuronal death, may be one of the underlying generative mechanisms of these two diseases [46, 47, 48]. Therefore, reduction of oxidative stress is crucial in the treatment of these two diseases, and high-quality antioxidants are potential therapeutic agents.

## 3. Chemical structure and anti-oxidative activity of flavonoids

Flavonoids can not only remove the active free radicals of chain initiation reaction and metal ions of catalytic action, but directly capture the peroxide free radicals in the chain transfer stage and block the chain reaction [49]. According to the D-value of the heat of formation (△ HOF) and radical scavenging rete examination (including DPPH, ABTS and FRAP test), the anti-oxidative activity of flavonoid compounds is closely related to their structures [50]. The main structural factors affecting the anti-oxidative activity of flavonoids includes the number and location of the hydroxyl, ring-C yoke system, the glycoside or methylation of the hydroxyl, the lipid solubility and charge distribution [51, 52].

### 3.1. Phenolic hydroxyl and anti-oxidative activity

Flavonoids are compounds containing polyhydroxy groups. The more phenolic hydroxyl groups in the molecule, the more hydrogen atoms are bonded to the active free radicals and the stronger the phenolic hydroxyl groups anti-oxidation [53]. The ring-B is the main active site for anti-oxidation and scavenging of free radicals [54]. The presence of the o-diphenolhydroxy group on the ring-B greatly enhances anti-oxidative activity, because it scavenges superoxide anions ($O_2^-$). and is considered to be the structural basis for the anti-oxidative properties of flavonoids [55, 56]. Flavonoids with strong anti-oxidative activity generally have a 3′, 4′-catechol structure, among which the 4 hydroxyl group is particularly important [57]. When the number of phenolic hydroxyl groups in the ring-B increases to a certain amount, the anti-oxidative activity no longer increases with the number of phenolic hydroxyl groups. Besides, the o-dihydroxyl group on the ring-A also has anti-oxidative activity [58, 59]. The 5-and 7-hydroxy groups are beneficial to anti-oxidative activity, and can be complexed with metal ions. Moreover, the 7-hydroxy group can increase the anti-oxidative activity in the presence of 4′hydroxyl [60]. The hydroxyl group on the ring-C also affect the anti-oxidative activity of flavonoids. The absence of the hydroxyl group at the C3 position decreases the anti-oxidative activity of flavonoids [57, 61].

### 3.2. Ring-C yoke system and anti-oxidative activity

The existence of ring-A and ring-B conjugate systems through the double bond between C2 and C3 and the 4-position carbonyl group promotes the formation of electron delocalization, which helps the flavonoids form relatively stable free radical intermediates after hydrogen supply and improves their anti-oxidative capacity. The anti-oxidative activity decreases if the double bond is hydrogenated [62].

### 3.3. Other factors

Hydroxyl glycosyl substitution or methylation has an adverse effect on anti-oxidative activity, and the effect is closely related to the substituent position [63, 64]. It is generally believed that 7-oxyglycoside and 6, 8-carboglycoside strongly reduce anti-oxidative activity, while 3-oxyglycoside has little effect [65, 66]. The 4-position carbonyl group also has an effect on the anti-oxidative capacity of flavonoids [65]. The presence of the 4-position carbonyl group prolongs the conjugate system, which is conducive to the formation of more stable free radical intermediates from flavonoids, and therefore is conducive to anti-oxidative activity [62, 67].

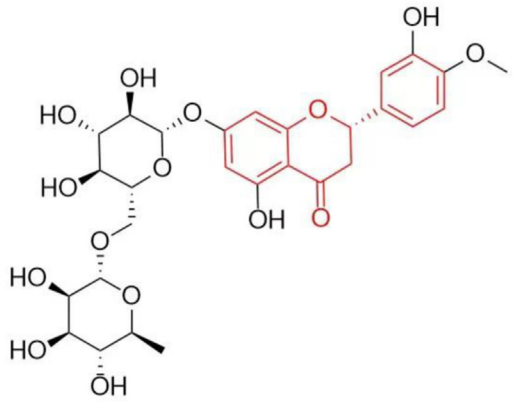
## 4. Flavonoids and Alzheimer's diseases treatment

Alzheimer's disease is the most common neurodegenerative diseases (NDDs), with the gradual increase in the population of the elderly over 65 years old, the number of AD patients is also increasing year by year [5, 68]. Pathologically, it is characterized by atrophy and/or loss of cortical neurons, extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles (NFT) [69, 70]. AD is driven by a complex interplay between genetic and environmental factors. More than 20 genes have been proved to be genetic risk factors for AD, among which the APOE gene is considered the most dangerous factor [70, 71]. Abnormal secretion of Aβ, high phosphorylation and distribution of microtubule-associated protein tau (tau), diminished cerebral glucose metabolism, and the downstream pathological consequences (synaptic dysfunction, mitochondrial dysfunction, neuron atrophy and/or loss, macroscopic atrophy of the cerebellum and/or hippocampus) contribute to neurodegeneration [72, 73] As a major public health problem, although the research into the mechanisms of AD has continued for many years, few treatments have been approved.

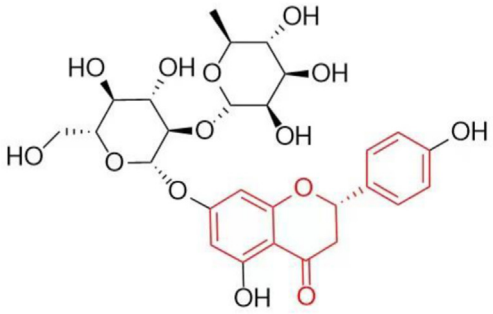
Oxidative stress contributes to Aβ formation and tau pathology. The oxidation of lipids, proteins, and nucleic acids occurs decades prior to Aβ plaque formation, and seems to precede senile plaques and NFTs. Soluble Aβ at pathological levels reduces the activities of key enzymes (such as cytochrome oxidase, Mn-SOD) and disrupts mitochondrial dynamics [74, 75]. Hyper-phosphorylated tau protein, the major component of NFTs and a hallmark of AD, is involved in the neurodegeneration associated with oxidative stress in AD [76, 77]. Oxidative stress leads to mitochondria dysfunction, induces abnormal Aβ secretion and aggregation, makes tau hyper-phosphorylation, synaptic plasticity deficit and learning and memory impairment. Hence, antioxidants are potential therapeutics due to their ability to reduce Aβ level and tau phosphorylation, eliminate ROS, and protect neurons in AD.

Flavonoids have been described as excellent antioxidants, free radical scavengers, and metal chelators [22, 78, 79]. They have been reported to attenuate cholinergic deficits, reduce neurotoxic Aβ abnormal accumulation, and inhibit tau protein hyper-phosphorylation, which makes them to be promising candidate for AD prevention and treatment [80, 81, 82, 83, 84]. Hesperidin, naringin, naringenin, tangeretin, nobiletin, quercetin, rutin, silibinin, anthocyanins, and epigallocatechin-3-gallate are the most-studied flavonoids exhibiting potential therapeutic activities against AD (Figure 2 and Table 1).

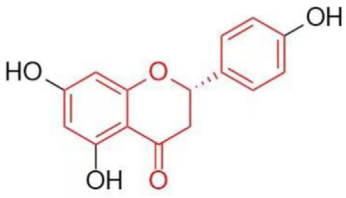
Hesperidin ($C_{28}H_{34}O_{15}$) (2S)-5-hydroxy-2-(3-hydroxy- 4-methoxyphenyl)-4-oxo-3,4-dihydro-2H-chromen-7-yl 6-O-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside, is a flavonoid present primarily in unripe citrus fruit, like orange, grapefruit, lemon, and tangerine juice [85]. This natural compound presents potent anti-oxidative activity, exerts neuroprotective effects and could cross the blood–brain barrier properties [86]. Studies have shown that hesperidin could inhibit evoked glutamate release and attenuates KA-induced neuronal death [86]. Hesperidin was demonstrated to promote neuronal differentiation and mediate neuronal survival [86]. Besides, studies have identified that this compound could activate Akt/Nrf2: Akt/Nrf2 signaling (Akt/Nrf2) and inhibit RAGE/NF-κB signaling (RAGE/NF-κB), through which suppresses oxidative stress, shows neuroprotection and attenuates learning and memory deficits in APPswe/PS1De9 (APP/PS1) transgenic AD model mouse [86]. Moreover, hesperidin has been demonstrated to restore non-cognitive nesting ability and social interaction deficit through reducing Aβ deposition and neuro-inflammatory [87]. Furthermore, hesperidin was reported to reduce β-amyloid precursor protein (APP)



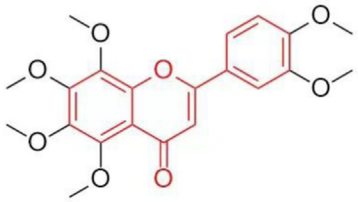

Hesperidin



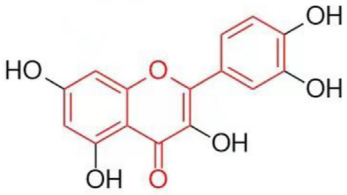

Naringin



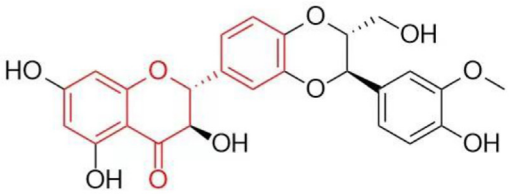

Naringenin



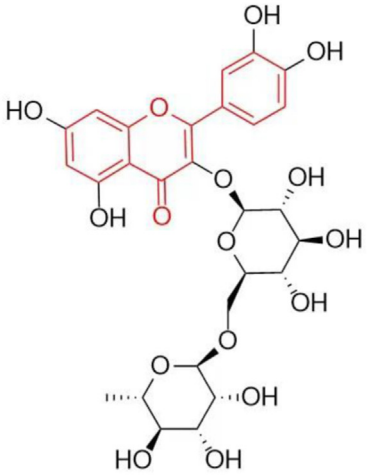

Nobiletin



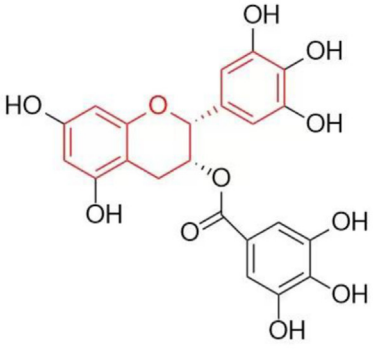

Quercetin




Silibinin




Rutin




Epigallocatechin-3-gallate

**Figure 2.** Chemical structures of flavonoids which exhibited effective activities against AD.

**Table 1.** Characteristics of flavonoids exhibiting effective activities against AD in the review.

| Flavonoid | Molecular | Source | Effects | Model and dose |
|---|---|---|---|---|
| Hesperidin | $C_{28}H_{34}O_{15}$ | unripe citrus fruit, like orange, grapefruit, lemon, etc. | anti-oxidative stress, prevent glutamate excitotoxicity, alleviate mitochondrial dysfunction, reduce Aβ accumulation, attenuate cognitive deficit, etc. | kainic acid (KA)-induced rats model, 10 or 50 mg/kg [138], APP/PS1 mice model, 40 mg/kg for 90 days [87], 100 mg/kg for 10 days [88], APPswe/PS1dE9 transgenic mice, 50 or 100 mg/kg for 16weeks [89]. |
| Naringin | $C_{27}H_{32}O_{14}$ | citrus fruit, like citrus grandis, citrus paradise, etc. | anti-oxidation, anti-apoptotic, anti-inflammation, neuroprotection, memory improvement, etc. | gp120-induced rats model, 30 mg/kg [95], Swiss albino model mice, UCMS mice, 80 mg/kg for 21 days [93], female Wistar rats, 50 mg/kg [93] |
| Naringenin | $C_{15}H_{12}O_5$ | citrus fruit, like citrus grandis, citrus paradise, etc. | anti-oxidation, anti-nociceptive, anti-inflammation, etc. | KO2-induced mice model, 50,150 mg/kg [139], Aβ-induced rats model [98], lipopolysaccharide (LPS)-induced rats model, 25, 50, or 100 mg/kg/day [99], intracerebroventricular-streptozotocin (ICV-STZ) induced rats model, 50 mg/kg for 2 weeks [100], $AlCl_3$+D-gal induced rats model, 50 mg/kg) for two weeks [101] |
| Nobiletin | $C_{21}H_{22}O_8$ | peel of citrus fruits, like shiikuwasa, oranges, lemons, etc. | anti-oxidation, improve learning and reduce memory impairment, reduce soluble Aβ and Aβ plaque, reverse tau hyperphosphorylation, etc. | OBX-, Aβ-, MK-801, LPS-induced mice model; Tg AD model mice, 30 mg/kg, 100 mg/kg [104, 105, 106, 108, 109, 110] |
| Quercetin | $C_{15}H_{10}O_7$ | onions, apples, broccoli, and red wine, etc. | anti-oxidation, anti-inflammation, anti-apoptotic, etc. | Aβ-induced rats model, 100 mg/kg for 18 day [115], APPswe/PS1dE9 transgenic AD model mice, 20, 40 mg mg/day for 16 weeks [116], triple transgenic AD model (3xTg-AD) mice, 25 mg/kg for 3 months [117], thalassemic patients, 500 mg/day [114] |
| Rutin | $C_{27}H_{30}O_{16}$ | *Ruta graveolens* L., Scphora japonica L., etc. | improve memory deficit, scavenge superoxide radicals, increase antioxidant enzymatic activity, etc. | Aβ induced rats model, 100 mg/kg [119], female Wistar rats, 100 mg/kg [93] |
| Silibinin | $C_{25}H_{22}O_{10}$ | dried fruits and seeds of *Silybum marianum* (L.) Gaertn | anti-oxidation, anti-inflammation, anti-aging, ameliorates memory deficits, etc. | STZ- induced rats' model, $A\beta_{25\text{-}35}$ induced mice model, 25, 50, and 100 mg/kg [124, 128]; UVB-irradiated mice model, 50 mg/kg [125] |
| Anthocyanins | a kind of polyphenolic flavonoid | fruits, flowers, grains, and vegetables | anti-oxidation, reduce Aβ production, prevent tau phosphorylation, protect neurons damage, improve synapse function, enhance learning and memory, etc. | APP/PS1 mice model, 12 mg/kg [127] LPS-induced mice model, 24 mg/kg [129]; Aβ-induced mice model, 4 mg/kg [131]; ovariectomized rat, 200 mg/kg [134] |
| Epigallocatechin-3-gallate | $C_{37}H_{30}O_{18}$ | green tea | anti-oxidation, inhibit Aβ fibrillation, restrain tau phosphorylation, improve learning and memory, etc. | morphine-induced rats' model, 5 and 50 mg/kg [137] |

expression and Aβ accumulation, inhibit inflammatory markers (like NF-κB), attenuate cognitive impairment, and alleviate mitochondrial dysfunction and oxidative stress [88, 89].

Naringin ($C_{27}H_{32}O_{14}$), 4', 5, 7-trihydroxyflavanone-7- rhamnoglucoside, is another flavonoid present in citrus grandis, citrus paradise, and other citrus. This phytochemical exhibits strong anti-oxidative, anti-apoptotic and anti-inflammatory activities [90, 91, 92]. Studies have demonstrated that naringin treatment significantly decreased the expression of purinergic receptor P2X7 (P2X7) and a member of nuclear factor-kappaB (P65), reduced the agonist of P2X7 (BzATP) activated current, and could improve glycoprotein 120 (gp120) induced learning and memory dysfunction [98]. Furthermore, it has been identified that narigin could enhance memory in stressed and unstressed mice probably by decreasing AChE activity and by inhibition of inducible NOS [93, 94]. Naringin was reported to have neuroprotective potential with beneficial effects on spatial, emotional and episodic memories [93, 94]. Naringenin ($C_{15}H_{12}O_5$), 4′,5,7-trihydroxyflavanone, is the aglycone of naringin and blood–brain barrier penetrating compound. This natural compound also exhibits excellent anti-oxidative activity probably via activation of the NO-cGMP-PKG-KATP channel signaling involving the induction of Nrf2/HO-1 pathway [95]. Studies have shown that naringenin could rescue Aβ evoked neurotoxicity through maintaining the mitochondrial membrane potential and resisting ROS production [96]. naringenin was identified to reduce Aβ plaque probably by increasing Aβ degradation enzymes [97]. Moreover, studies have demonstrated that naringenin pretreatment could ameliorate Aβ-induced learning and memory impairment through mitigation of lipid peroxidation and apoptosis [98]. In addition, naringenin was reported to alleviate LPS-induced cognitive deficits and neuroinflammation by attenuation of oxidative stress and AChE and modulation of Nrf2/NF-κB/TNFα/COX2/iNOS/TLR4/GFAP [99]. Naringenin was reported to protect against intracerebroventricular-streptozotocin (ICV-STZ) induced cognitive deficits, neuronal injury and oxidative stress [100]. Naringenin was proven to protect $AlCl_3$+D-gal induced AD-like behavioral disturbances and AD-like symptoms [101].

Nobiletin ($C_{21}H_{22}O_8$), 5,6,7,8,3′,4′-hexameth-oxyflavone, is a polymethoxylated flavone found in the peel of citrus fruits such as *Citrus depressa* (shiikuwasa), *Citrus sinensis* (oranges), and *Citrus limon* (lemons). It has been proven to be a retinoic acid-related orphan receptor (ROR) agonist [102]. Nobiletin was identified to modulate cellular antioxidant defense systems and increase the activity of glutathione peroxidase (GPx) [103, 104]. In addition, nobiletin was shown to halt acetylcholinesterase-positive fiber density decrease, reduce soluble Aβ and Aβ plaque levels, and ameliorate the generation of free radicals [105, 106]. Moreover, nobiletin was demonstrated to reverse tau hyperphosphorylation, activate ERK signaling, trigger cAMP transcription, and suppress caspase 3 and Bax expression [107, 108]. This natural flavone attracted great attention when its anti-dementia and neuroprotective properties were discovered [103, 104]. Studies have demonstrated that nobiletin could improve learning and reduce memory impairment in olfactory-bulbectomized (OBX), Aβ, MK-801 (dizocilpine maleate) -induced AD model mice, and could ameliorate these problems in transgenic AD model mice (such as amyloid precursor protein Tg mice, 3XTg-AD mice) [105, 109, 110].

Quercetin ($C_{15}H_{10}O_7$), 3, 3′, 4', 5, 7-pentahydroxyflavone, is a flavonoid present in onions, apples, broccoli, and red wine. It has been proved to inhibit many enzyme systems, including tyrosine protein kinase, phospholipase A2, phosphodiesterase, mitochondrial ATPase, PI3-kinase, and protein kinase C [111, 112]. This natural phytochemical was proven to reduce the oxidative damage caused by iron overload [113]. Quercetin was reported to reduce iron overload and exhibit anti-oxidative, anti-inflammation, cardio-protective, neuroprotective, and anti-apoptotic properties [114]. Quercetin was identified to decrease MDA, increase SOD and GSH [115]. Studies showed that quercetin could modulate Nrf-2 translocation from cytoplasm to nucleus, protect mitochondrial dysfunction [116]. Besides, Quercetin was identified to inhibit Aβ plaque aggregation and neurofibrillary tangles formation [116, 117]. Studies identified that pretreatment quercetin could improve cognitive memory probably by decreasing Aβ level, antioxidant activity and increasing Nrf2/HO-1 pathway (Nrf2/HO-1) [115]. Quercetin was proven to improve cognitive functioning in the APPswe/PS1dE9 transgenic AD model mouse by reducing plaque mitochondrial dysfunction through the activation of AMPK [116]. Quercetin was identified to reverse histological hallmarks of AD and protect cognitive and emotional function in aged triple transgenic AD model (3xTg-AD) mice [117]. Rutin ($C_{27}H_{30}O_{16}$), 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl-6-O-(6-deoxy-α-L-mannopyrano-syl)-β-D-glucopyranoside, is a glycone of quercetin with a flavonol structure. This compound was reported to scavenge superoxide radicals, increase antioxidant enzymatic activity, and reduce lipid peroxidation and cytokine production [118]. Moreover, rutin was identified to improve memory deficit induced by Aβ through the MAPK and brain-derived neurotrophic factor (BDNF) pathways [119]. In addition, this compound was proven to alleviate episodic memory deficits and have beneficial effects on spatial, emotional and episodic memories [119].

Silibinin ($C_{25}H_{22}O_{10}$) (2R, 3R)-3, 5, 7-trihydroxy-2-[(2R, 3R)-3-(4-hydroxy-3-methoxyphenyl)-2- (hydroxymethyl)- 2, 3-dihydro-1, 4-benzodioxin-6-yl]-2,3-dihydro-4H-chromen-4-on, also called silybin and silymarin, is a flavonoid isolated from the dried fruits and seeds of *Silybum marianum* (L.) Gaertn [120]. it has anti-oxidative, anti-inflammatory, anti-radiation, anti-aging, and delaying skin aging activities [121, 122, 123]. This natural flavonoid has been shown to modulate the pro-inflammatory cytokines IL-1β and IL-4, the antioxidant enzyme glutathione (GSH), malondialdehyde (MDA), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) [124]. It is reportedly involved in the inflammatory process and autophagy [125]. In addition, studies have demonstrated that silybin could suppress $A\beta_{25-35}$ induced abnormal increase in nitrotyrosine, and inhibit the overexpression of iNOS and TNF-α [126]. Moreover, silybin has been identified to decrease STZ-induced tau hyperphosphorylation (ser404), alleviate $A\beta_{25-35}$ and streptozocin-induced memory deficits, reverse learning and memory damage [127, 128].

Anthocyanins, a kind of polyphenolic flavonoid commonly present in fruits, flowers, grains, and vegetables, present antioxidant, anti-inflammatory, and anti-apoptotic properties [127, 129]. Studies have demonstrated that anthocyanins could reduce the levels of Aβ, BACE-1, and APP, and elevate the levels of synaptophysin, postsynaptic density protein 95 (PSD95), synaptosome associated protein23 (SNAP23), glutamate receptor 1 phosphorylated at serine 845 (p-GluR1 (Ser845)), and cyclic AMP response element binding protein phosphorylated at serine 133 (p-CREB (Ser133)) [130,131]. In addition, anthocyanins were reported to increase phosphorylated phosphoinositide 3-kinase (p-PI3K), protein kinase B phosphorylated at serine 473 (p-Akt (Ser473)), glycogen synthase kinase 3β phosphorylated at serine 9 (p-GSK3β (Ser9)) levels, and decrease the phosphorylation level of tau at Ser413 and Ser404 [127]. Studies also have demonstrated that anthocyanins could reduce the ratio of ratio of Bax to Bcl-2 (Bax/Bcl2), inhibit Cyt c, caspase-9, cleaved caspase-3, and poly (ADP-ribose) polymerase-1 (PARP-1) [132, 133]. Moreover, anthocyanins have been reported to reduce Aβ production, prevent tau phosphorylation, protect neurons damage, improve synapse function, and enhance learning and memory [134].

Epigallocatechin-3-gallate (EGCG, $C_{37}H_{30}O_{18}$) is a major flavonoid in tea. This compound has been shown to inhibit Al (III)-induced Aβ fibrillation, and remold the preformed, mature, toxic fibrils into low toxic amorphous aggregates [135]. In addition, EGCG was identified to restrain tau phosphorylation, inhibit tau aggregation and recast tau oligomers to an unfolded monomeric state [136]. Furthermore, studies also have shown that EGCG could improve learning and memory impairment [137].

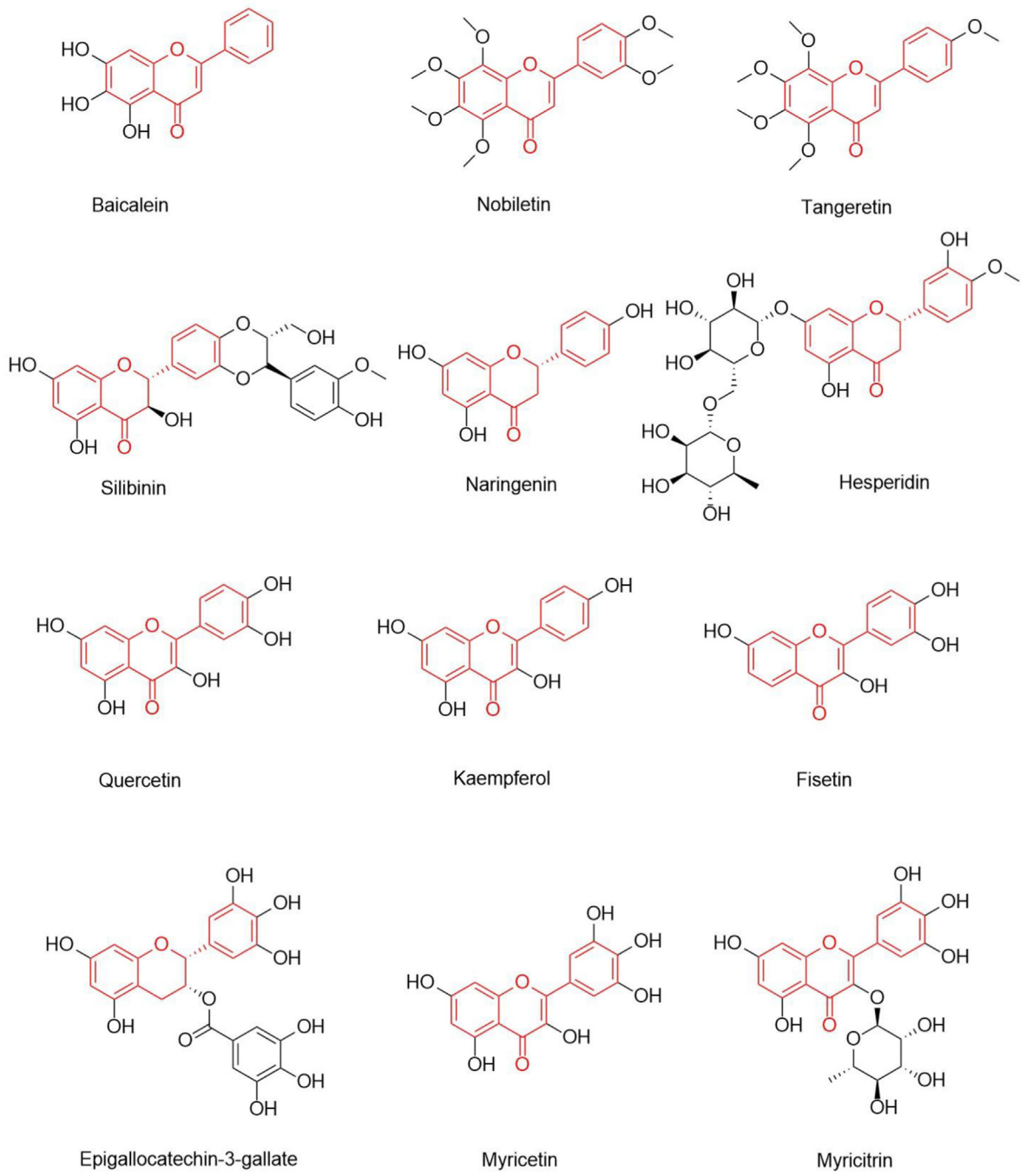



**Figure 3.** Chemical structures of flavonoids which have shown efficacy in PD.

## 5. Flavonoids and Parkinson's diseases treatment

Parkinson's disease, the second most common neurodegenerative disease after AD, is increasing in prevalence worldwide [4, 140]. Chronic and progressive loss of dopaminergic neurons and presence of intracellular Lewy bodies in the substantia nigra (SN) are two major hallmarks of PD. Lesions occurring in the SN induce a decrease in dopamine (DA) content and weakening DA nerve function. This breaks the balance between dopaminergic neurons and cholinergic neurons, resulting in serious movement disturbances, such as tremors, rigidity, and bradykinesia and/or cognitive dysfunction [141, 142]. Although the causes of the lesions of SN and the consequent dopaminergic neurons damage remain unclear, studies have demonstrated that cellular oxidative stress plays a central role in this process. Natural antioxidants are believed to reduce the risk of PD [143, 144], and thus in recent years, the pharmaceutical industry and researchers have turned their attention to flavonoids due to their excellent antioxidative activity and other therapeutic properties [22, 145, 146]. Baicalein, nobiletin, tangeretin, silibinin, naringenin, hesperidin, quercetin, kaempferol, fisetin, epigallocatechin-3-gallate, myricitrin, and myricetin are the most studied flavonoids for their value in PD treatment (Figure 3 and Table 2).

Baicalein ($C_{15}H_{10}O_5$), 5,6,7-trihydroxyflavone, a natural flavonoid extracted from the roots of *Scutellaria baicalensis* Georgi, possesses neuroprotective, anti-oxidative, anti-inflammatory, and antiapoptotic properties [147]. Studies have shown that this compound could protect against 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenylpyridinium ($MPP^+$), glutamate, Aβ, hydrogen peroxide ($H_2O_2$), 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP), and methamphetamine-induced neurotoxicity.

**Table 2.** Characteristics of flavonoids showing efficacy in PD in the review.

| Flavonoid | Molecular | Source | Effects | Model and dose |
|---|---|---|---|---|
| Baicalein | $C_{15}H_{10}O_5$ | the roots of *Scutellaria baicalensis* Georgi., etc. | anti-oxidation, prevent α-synuclein accumulation, disaggregate α-synuclein fibrils, prevent dopaminergic neuron loss, attenuate behavioral impairments, etc. | collagenase-induced ICH rats model, 50 mg/kg [153]; $AlCl_3$-induced rats model, 5 mg/kg and 10 mg/kg [154]; MPTP-induced mice model, 10 mg/kg and 50 mg/kg [152] |
| Nobiletin | $C_{21}H_{22}O_8$ | peel of citrus fruits, like shiikuwasa, oranges, lemons, etc. | anti-oxidation, prevent $MPP^+$-induced DA neuron damage, increase TH activity, reduce motor impairment and cognitive deficits, etc. | MPTP-induced rats' model, 10 mg/kg [157] |
| Tangeretin | $C_{20}H_{20}O_7$ | citrus fruit, like grapefruit, tangerines, mandarins, oranges, etc. | anti-oxidation, protect 6-OHDA-/MPTP/P-induced DA declination, dopaminergic neuron damage, reduce behavioral deficits, etc. | 6-OHDA-insuced rats' model, 10 mg/kg [164]; MPTP-induced rats' model, 50, 100 or 200 mg/kg [166] |
| Silibinin | $C_{25}H_{22}O_{10}$ | dried fruits and seeds of *Silybum marianum* (L.) Gaertn | anti-oxidation, prevent MPTP-caused $TH^+$ neuronal loss, decrease dopamine depletion, ameliorate motor behavior, etc. | METH induced mice model [168] $MPP^+$ induced model, 10, 50, or 100 mg/kg [169] |
| Naringenin | $C_{15}H_{12}O_5$ | citrus fruit, like, citrus grandis, citrus paradise, etc. | anti-oxidation, protect 6-OHDA-induced $TH^+$ neuronal loss, increase DA and its metabolic levers, etc. | hypercholesterolemic diet (HCD) rats' model, 50 mg/kg [173]; isoflurane induced rats' model, 25,50,100 mg/kg [176] |
| Naringin | $C_{27}H_{32}O_{14}$ | citrus fruit, like, citrus grandis, citrus paradise, etc. | anti-oxidation, prevent $MPP^+$-induced DA neurotoxicity, activate mTORC1 and anti-inflammation, etc. | KA-induced mice model, 80 mg/kg [177] |
| Hesperidin | $C_{28}H_{34}O_{15}$ | unripe citrus fruit, like orange, grapefruit, lemon, etc. | anti-oxidation, reduce 6-OHDA-induced memory impairment and depression-like behavior, improve synapse formation and function, enhance memory, etc. | 6-OHDA-induced mice model, 50 mg/kg [179] MTX-induced rats model, 100 mg/kg [180]; adult mice, 10 mg/kg [181] |
| Quercetin | $C_{15}H_{10}O_7$ | onions, apples, broccoli, and red wine, etc. | anti-oxidation, protect 6-OHDA-/MPTP-induced DA depletion, improve behavior impairment, etc. | Cadmium (Cd) induced mice model, 25, 50, 100 mg/kg [182]; $CdCl_2$ induced rats model, 20 mg/kg [183]; 6-OHDA induced rats model, 50 mg/kg [185] |
| Kaempferol | $C_{15}H_{10}O_6$ | kaempferol galanga L, etc. | anti-oxidation, reduce behavior impairment and increase striatal DA and its metabolites, etc. | I/R rats model, 1.75, 3.49, 6.99 mM [192]; ovariectomized (OVX) rats model, 10 mg/kg [193] |
| Fisetin | $C_{15}H_{10}O_6$ | strawberries and lower levels in apples and persimmons, etc. | anti-oxidation, protect MPTP/$MPP^+$-induced dopaminergic toxicity, $TH^+$ loss, and decrease α-synuclein aggregation, etc. | D-gal induced rats' model, 15 mg/kg [195] |
| Epigallocatechin-3-gallate | $C_{37}H_{30}O_{1}8$ | green tea, etc. | anti-oxidation, protect DA depletion and DA neuronal loss, inhibit a-synuclein aggregation and Aβ fibrillogenesis, etc. | sevoflurane-induced mice model, 25, 50, 75 mg/kg [198]; 6-OHDA-induced rats model, 10 mg/kg [200, 201, 205]; MPTP-induced mice model,25,50 mg/kg [204, 206] |
| Myricetin | $C_{15}H_{10}O_8$ | berries, vegetables, tea and wine. | anti-oxidation, reduce $MPP^+$-induced DA-like cell loss, prevent 6-OHDA-/6-hydroxydopamine-induced TH+ and DA neuron degeneration, etc. | 6-OHDA induced rats' model, 0.5 mg/mL [208] |
| Myricitrin | $C_{21}H_{20}O_{12}$ | *Myrica cerifera*, *Myrica esculenta*, *Ampelopsis grossedentata*, etc. | anti-oxidation, reduce 6-OHDA-/$MPP^+$-induced DA neurotoxicity, dopaminergic neuronal loss, etc. | 6-OHDA induced mice model, 30 mg/kg [212] |

α-syn plays a vital role in PD pathomechanism, diagnosis and treatment [148, 149]. Studies have demonstrated that baicalein could prevent α-synuclein accumulation, and disaggregate mature α-synuclein fibrils [150, 151]. Furthermore, this flavonoid has been shown to attenuate behavioral impairments [152], and prevent dopaminergic neuron loss in the SN [153, 154]. In addition, baicalein was reported to restore mitochondrial function, reduce the activation of microglia and astrocytes, and increase the levels of neurotransmitters such as DA, 3,4-dihydroxyphenylacetic acid (DOPAC), and homo vanillic acid (HVA) [155].

Nobiletin, a RORs agonist, can inhibit neuro-inflammation, regulating apoptotic signaling and protect dopaminergic neurons [156, 157, 158]. This natural compound has been reported to prevent $MPP^+$-induced DA neuron damage in the SN [157]. Furthermore, nobiletin has been shown to increase TH activity by stimulating Ca2+/calmodulin-dependent protein kinase II (CaMKII)- and PKA-dependent phosphorylation, leading to reduce MPTP-induced motor impairment and cognitive deficits [157, 159, 160].

Tangeretin ($C_{20}H_{20}O_7$), 5,6,7,8-Tetramethoxy-2-(4-methoxyphenyl)-4-benzopyrone, a flavonoid isolated from the peel of citrus fruit such as grapefruit, tangerines, mandarins, and oranges, is a potent inhibitor of Notch-1 [161]. This compound has been proven to inhibit reactive oxygen species production and $p47^{phox}$ phosphorylation, enhancing the expression of heme oxygenase-1 and the DNA binding activity of nuclear factor-erythroid 2-related factor 2 to the antioxidant response element, and thus possess a potent antioxidant effect in LPS-stimulated microglia [162, 163]. Studies demonstrated that tangeretin can reduce 6-OHDA-induced decline in tyrosine hydroxylse-positive ($TH^+$) cells and improve the reduction of striatal DA in a dose-dependent manner [164]. In addition, this natural flavonoid has been reported to upregulate the mRNA levels of UPR-target genes in dopaminergic neurons and astrocytes after chronic MPTP/probenecid (MPTP/P) injections [165]. Tangeretin was also reported to protect against MPTP/P-induced dopaminergic neuron damage, maintain striatonigral integrity, and reduce behavioral deficits [166].

Silibinin exhibits excellent anti-oxidative and anti-inflammatory activities [167]. Treatment with silibinin in aging animals can decrease dopamine depletion, ameliorate motor behavior, reduce MDA content and increase GSH content [168]. Studies have also demonstrated that silibinin could prevent MPTP-caused $TH^+$ neuronal loss in the striatum and SN [169].

Naringenin is a flavonoid present in tomatoes, grapes, grapefruit and other citrus fruits, which has been demonstrated to have anti-nociceptive, anti-inflammatory, and anti-oxidative activities [170, 171]. Studies have shown that naringenin treatment could increase nuclear factor erythroid 2-related factor 2 (Nrf2) protein levels and activate the antioxidant response element pathway in a 6-OHDA-induced PD model [172]. In addition, pre-treatment with naringenin can protect 6-OHDA-induced ROS damage, striatum and SNC $TH^+$ neuronal loss [173, 174]. Moreover, naringenin has been reported to increase DA and its metabolic levers, like DOPAC and HVA [175].

Naringin, naringenin 7-O-rutinoside, has been reported to inhibit oxidative stress and reduce neuronal loss and neuro-inflammation, and therefore has been suggested to have potential as a therapeutic agent against NDDs [176]. Naringin has been shown to prevent $MPP^+$-induced nigrostriatal DA neurotoxicity through anti-inflammatory activity [177]. In addition, naringin was reported to activate mechanistic target of rapamycin complex 1 (mTORC1) and anti-inflammation in DA neurons [176, 178].

Hesperidin has been demonstrated that it's treatment could effectively reduce the activity of glutathione peroxidase and catalase, and significantly decrease total reactive antioxidant potential, thereby could reduce 6-OHDA-induced memory impairment and depression-like behavior [179, 180]. Furthermore, this nature flavonoid has been proven to induce neuron synapse formation and function between the hippocampus and cortex, and improve memory [181].

Quercetin has been shown to protect against oxidative damage, reduce DA depletion, improve behavior, and maintain the resting membrane potential of neurons in MPTP-induced PD model mice [182, 183]. Studies have demonstrated that quercetin treatment could increase striatal DA, improve neuronal survival, and raise antioxidant enzyme levels in 6-OHDA-induced PD model mice [184, 185, 186]. In addition, quercetin was demonstrated to attenuate the loss of mitochondrial complex-I activity and enhance endogenous antioxidant enzyme activity [187]. Quercetin has been revealed to upregulate the phosphorylation of protein kinase D1, protein kinase B (Akt), cyclic AMP response element binding protein (CREB), and BDNF expression in DA neuronal cells [188]. Rutin, troxerutin ($C_{33}H_{42}O_{19}$), and isoquercitrin ($C_{21}H_{20}O_{12}$), the glycosides of quercetin, have been shown to prevent 6-OHDA-induced neurotoxicity [189]. Moreover, troxerutin was reported to improve apomorphine-induced behavior impairment, prevent nigral $TH^+$ neuronal loss, lessen striatal lipid peroxidation, and diminish mitochondrial oxidative stress [190, 191].

Kaempferol ($C_{15}H_{10}O_6$), 3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one, is a flavonoid mainly isolated from the rhizome of *kaempferol galanga* L., which has been shown to possess neuro-protective effect [192]. Studies have demonstrated that this compound could reduce behavior impairment and increase striatal DA and its metabolites [193]. In addition, this flavonoid has been proven to protect against neurotoxicity and preserve the striatal glutamatergic response by autophagy in a PD model [194].

Fisetin ($C_{15}H_{10}O_6$), 3,7,3′, 4' tetrahydroxyflavone, abundant in strawberries and lower levels in apples and persimmons, is a dietary flavonoid. This natural compound protects brain tissue against oxidative stress, apoptosis and neurodegeneration [195, 196]. Studies have shown that fisetin could protect against MPTP/$MPP^+$-induced dopaminergic toxicity, prevent $TH^+$ loss, and decrease α-synuclein and inflammation [197].

Epigallocatechin-3-gallate has been shown to protect against mitochondrial oxidative stress-induced neuronal apoptosis through CREB/BDNF/TrkB, PI3K/Akt/mTOR, and PI3K/AKT/eNOS signaling [198, 199]. Furthermore, this compound has been identified to protect against 6-OHDA-induced neuronal toxicity by stimulating protein kinase C (PKC) and modulating cell survival/cycle genes [200, 201, 202]. Moreover, studies have demonstrated that EGCG could inhibit a-synuclein aggregation and Aβ fibrillogenesis [203, 204]. EGCG also has been proven to protect striatal DA depletion and DA neuronal loss in MPTP-/6-OHDA-induced PD model mice [205, 206].

Myricetin ($C_{15}H_{10}O_8$), 3, 5, 7, 3′, 4′, 5′-hexahydroxy-flavone, occurs in berries, vegetables, tea and wine. This nature compound was reported to reduce $MPP^+$-induced DA-like cell loss and nuclear condensation by suppressing ROS production and inhibiting mitogen-activated protein kinase 4 (MKK4) and c-Jun N-terminal kinases (JNK) [207]. In addition, studies have demonstrated that myricetin could prevent 6-OHDA- and 6-hydroxydopamine-induced TH+ and DA neuron degeneration [208].

Myricitrin ($C_{21}H_{20}O_{12}$), 3, 5, 7, 3′, 4′, 5′-hexahydroxyflavone 3-O-rhamnoside, the glycoside of myricetin, is abundant in the root bark of *Myrica cerifera*, *Myrica esculenta*, *Ampelopsis grossedentata*, *Nymphaea lotus*, and *Chrysobalanus icaco*. This compound possesses anti-oxidative, anti-inflammatory, and anti-nociceptive, and neuro-protective activities [209]. Studies have identified that, like myricetin, myricitrin could reduce $MPP^+$-induced mitochondrial dysfunction, prevent 6-OHDA-induced mitochondrial oxidation, restore mitochondrial damage, ameliorate apoptosis dysfunction, and protect against DA neurotoxicity through DJ-1 activity [210, 211]. Furthermore, studies have shown that myricitrin could amend 6-hydroxydopamine-induced SN dopaminergic neuronal loss [212].

## 6. Conclusion

The prevalence of AD and PD is on the rise worldwide, and effective pharmacological treatments are needed urgently. Considerable evidence supports the involvement of oxidative stress in the development and progression of these two NDDs. Oxidative stress induces overproduction of ROS and RNS, along with mitochondrial dysfunction, neuroinflammation and neurodegeneration, and plays a vital role in the pathological processes of these two diseases. Therefore, antioxidants are promising candidates for AD and PD therapeutics.

This review provides an overview of the research on the effects of various plant flavonoids on AD and PD. Interestingly, some flavonoid compounds, like hesperidin, naringin, naringenin, tangeretin, nobiletin, silibinin, Epigallocatechin-3-gallate, displayed to be effective in both AD and PD. Tt is well known that oxidative stress induced damages may be one of the major pathological mechanism in both AD and PD. Oxidative stress leads to abnormal protein (such as Aβ and a-synuclein), neuroinflammation mitochondrial dysfunction, and neuronal loss (including cholinergic neurons and dopaminergic neurons). Besides, some flavonoid metabolites (especially some specific products of bacterial transformation) attracted researchers and pharmacy's attention, for their stronger bioactivities [213]. Such as anthocyanins phenolic acid metabolites (including 4-Hydroybenzoic acid, protocatechuic acid, gallic acid, vanillic acid, 3-O-methygallic acid, syringic acid) have been demonstrated to anti-oxidant, anti-neuroinflammation, interfere proteins aggregation, and show good neuroprotective activities [214].

Evaluation of studies have demonstrated the anti-AD and anti-PD effect of flavonoids through various in vitro and in vivo models. However, more rigorous studies are necessary to confirm dosage, the possible targets, the absorption and trans-blood brain barrier (BBB) permeability, address safety and other issues. It will be many years before flavonoids are developed into effective pharmaceuticals and applied in clinical settings. Nevertheless, with continued progress in neuroimaging techniques (like PET-CT, DTI, fMRI, NIRS, ECoG) and biochemical biomarkers, the pathological processes of AD and PD will be clarified, and effective strategies of flavonoids for treating AD and PD will also be found.

## Declarations

### *Author contribution statement*

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No data was used for the research described in the article.

### *Declaration of interest's statement*

The authors declare no conflict of interest.

### *Additional information*

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