Review

Exploitation of Quercetin Antioxidative Properties in Potential Alternative Therapeutic Options of Neurodegenerative Diseases

Viorica Rarinca [1,2], Mircea Nicoara [1,3,*], Dorel Ureche [4,*] and Alin Ciobica [2,5,6]

[1] Doctoral School of Geosciences, Faculty of Geography and Geology, Alexandru Ioan Cuza University of Iasi, No 20A, Carol I Avenue, 700505 Iasi, Romania; rarinca_viorica@yahoo.com
[2] Doctoral School of Biology, Faculty of Biology, "Alexandru Ioan Cuza" University of Iași, Carol I Avenue, 20A, Iasi, Romania
[3] Department of Biology, Faculty of Biology, Alexandru Ioan Cuza University of Iasi, No 20A, Carol I Avenue, 700505 Iasi, Romania
[4] Faculty of Sciences, Department of Biology, Ecology and Environmental Protection, University "Vasile Alecsandri" of Bacau, Romania
[5] Center of Biomedical Research, Romanian Academy, no 8, Carol I Avenue, 700506 Iasi, Romania
[6] Academy of Romanian Scientists, no 54, Independence Street, Sector 5, 050094 Bucharest, Romania
* Correspondence: mirmag@uaic.ro

Abstract: Oxidative stress (OS) is a condition in which there is an excess of reactive oxygen species (ROS) in the body, which can lead to cell and tissue damage. This occurs when there is an overproduction of ROS or when the body's antioxidant defense systems are overwhelmed. Quercetin is part of a group of compounds called flavonoids. It is found in high concentrations of vegetables, fruits, and other foods. Over the past decade, a growing number of studies have highlighted the therapeutic potential of flavonoids to modulate neuronal function and prevent age-related neurodegeneration. Therefore, quercetin has been shown to have antioxidant, anticancer, and anti-inflammatory properties, both in vitro and in vivo. Due to its antioxidant character, quercetin alleviates oxidative stress, thus improving cognitive function, reducing the risk of neurodegenerative diseases. On the other hand, quercetin can also help support the body's natural antioxidant defense systems, thus being a potentially practical supplement for managing oxidative stress. This review focuses on experimental studies supporting the neuroprotective effects of quercetin in Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and epilepsy.

Keywords: oxidative stress; neurodegenerative diseases; quercetin; neuroprotective effects

1. Introduction

Excessive oxidative stress is the result of disturbing the balance between oxidation and antioxidant systems, with a tendency to oxidize. Oxidative stress can cause many reactions, such as protease stimulation, neutrophil infiltration, and the explosion of oxidative intermediates [1]. In addition, OS is thought to play a key role in progressive degeneration and/or death of nerve cells, especially in neurodegenerative diseases, where it acts as a mediator of the side effects of several neurotoxic substances and as a mechanism of age-related degenerative processes [2]. The ROS scavenger is often used to counteract the effects of oxidative stress in neurons [3,4]. Numerous studies have shown that quercetin, by eliminating oxygen radicals and by metal chelating operations, attenuates neuronal damage mediated by oxidative stress [5,6].

To survive, aerobic multicellular organisms need molecular oxygen (O_2), to the detriment of oxygen, which is susceptible to radical formation due to its electronic structure. Reactive oxygen species are the natural by-product of normal oxygen metabolism and play significant roles in homeostasis and cellular signaling. Oxidative stress increases in the cellular environment when oxygen homeostasis is not maintained. ROS are oxygen free radicals or small molecules derived from oxygen, such as peroxyl radical (ROO•), hydroxyl radical ($^{\cdot}OH$), superoxide anion ($\bullet O_2^-$), and alkoxyl ($RO^{\cdot}$). ROS could also come from non-radicals such as ozone (O_3), hypochlorous acid (HOCl),

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singlet oxygen ($^1O_2$), and hydrogen peroxide (H_2O_2). These non-radicals are oxidizing agents or are easily converted to radicals [7,8].

Neurological diseases are a consequence of genetics, environmental factors, and even age [9]. During periods of environmental stress, such as ultraviolet A (UVA) and ultraviolet B (UVB) radiation, exposure to heat, and ionizing radiation, their levels could increase dramatically. A study by Erden et al., 2001 [10] showed that exposure to UVA radiation can induce ROS production leading to damage to cellular elements, but also the benefits that antioxidant quercetin brings to cells, protecting them from the harmful effects of radiation.

Neurodegeneration is characterized by progressive deterioration of the structure and function of neurons and is accompanied by severe cognitive deficits. Aging is the main risk factor for neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. Mitochondrial dysfunction and oxidative stress also trigger neurodegeneration. Recent studies have supported the mechanisms by which quercetin supports brain health [11].

First studies involving flavonoids to reduce oxidative stress have been performed since the end of the twentieth century [12]. Numerous in vitro and in vivo studies have reported the neuroprotective properties of quercetin [11,13,14]. Thus, it has been observed to protect neurons from oxidative damage and reduces lipid peroxidation as well (see Figure 1). On the other hand, besides its antioxidant properties, quercetin can inhibit the formation of amyloid-β proteins in the fibrils, counteracting cell lysis, and inflammatory cascade [13]. Flavonoids, but also foods containing flavonoids can have multiple beneficial effects in the treatment of conditions involving oxidative stress, such as Alzheimer's disease, Parkinson's disease, aging itself, atherosclerosis, and ischemia [12,15,16].

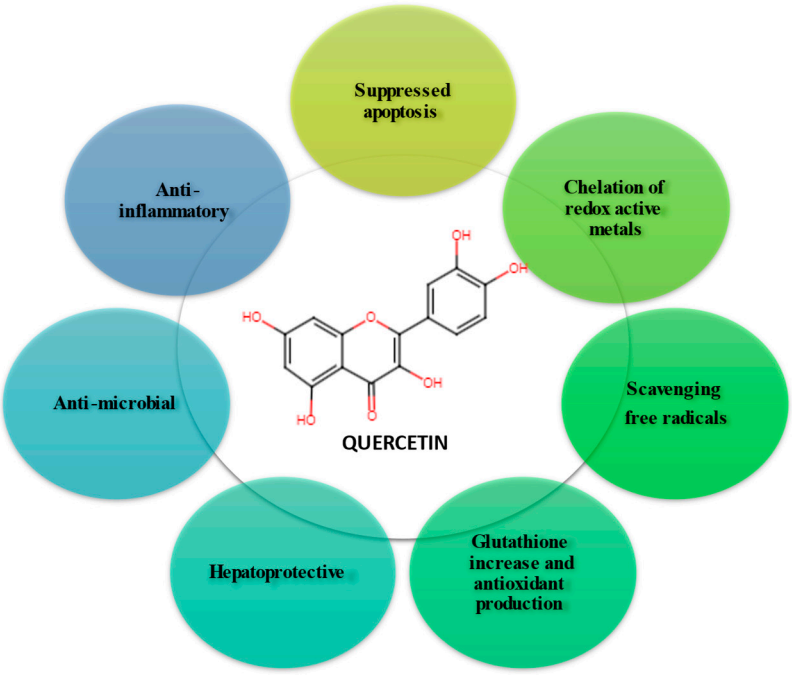

Figure 1. Main effects of quercetin [14,16,17].

Quercetin or 2-(3,4-dihydroxy phenyl)-3,5,7- trihydroxychromen-4-one is commonly found in our diet and is found in abundance as a secondary metabolite in vegetables and fruits. According to the USDA (United States Department of Agriculture) database on flavonoid concentration in foods [18] and Table 1, the highest quercetin concentrations are in capers, dill weed, oregano, onions, cranberries, cherries, and red fruits; in addition to fruits and vegetables, they are also found in beverages such as red wine and black tea. It has also been isolated and marketed as a dietary supplement, in the form of free aglycone, used in doses of 1000 mg per day, exceeding the usual levels of food intake, which is 200-500 mg per day in individuals who consume large amounts of vegetables and fruits [18,19].

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Table 1. Quercetin content (mg 100 g^{-1} or mg 100 mL^{-1}) in selected foods and beverages [18].

	Source			Quercetin
Food	**Common Name**	**Scientific Name**	**Active Portions**	**mg 100 g^{-1} weight**
Fruits	Acerola	*Malpighia emarginata*	Fruits	4.74
	Apple	*Malus domestica*	Fruits	19.36
	Cranberry	*Vaccinium oxycoccus*	Fruits	25.0
	Apricots	*Prunus armeniaca*	Fruits	1.63
	Blackberries	*Rubus* spp.	Fruits	3.58
	Blueberries	*Vaccinium* spp.	Fruits	7.67
	Cherries	*Prunus avium*	Fruits	17.44
	Cranberries	*Vaccinium macrocarpon*	Fruits	14.84
	Grapefruit	*Citrus paradisi*	Fruits	0.50
	Grapes	*Vitis vinifera*	Fruits	1.04
Vegetables	Capers, raw	*Capparis spinosa*	Flower buds	233.84
	Onions, raw	*Allium cepa*	Bulbs	20.30
	Dill weed, fresh	*Anethum graveolens*	Leaves	55.15
	Oregano	*Origanum vulgare*	Leaves	42.00
	Tarragon, fresh	*Artemisia dracunculus*	Leaves	10.00
	Chicory	*Cichorium intybus*	Leaves	6.49
Beverage				**mg 100 mL^{-1}**
	Black tea			2.50
	Red wine			3.16

Source: Phenol Explorer and USDA Database for the Flavonoid Content of Selected Foods.

Quercetin is a more potent antioxidant than other antioxidant nutrients, such as vitamin C, vitamin E, and β-carotene [20]. Due to the five hydroxyl groups present in its structure that can bind to ROS, quercetin has a higher antioxidant potential than many other flavonoids [21,22]. In addition to its antioxidant activity, quercetin has effects anti-cancer [6–10], and anti-inflammatory [21,28–30], antiviral [31–33], antibacterial properties [34–38], cardioprotective effects [39], neuroprotective effects vs. brain ischemia [1,40].

In many studies, quercetin is also reported to have adverse effects, such as induction of mutations, chromosomal aberrations, and single-stranded deoxyribonucleic acid (DNA) ruptures in various eukaryotic cell systems in vitro [41].

Quercetin is less toxic than curcumin or gallic acid, due to the LD_{50} value of 484 μg mL^{-1}, while the LD_{50} values for curcumin it is 135 μg mL^{-1} and for gallic acid it is 304 μg mL^{-1} [42].

This review focuses on the preventive and therapeutic capacity of quercetin in neurological and neurodegenerative diseases along with its potential mechanisms of action. Furthermore, we also summarized the biological sources and other pharmacological activities of this antioxidant compound.

Quercetin acts as a protector of neurons against severe oxidative stress, but also against free radical attack by easily intercalating its molecules in DNA, thus forming a protective barrier against stronger intercalators and/or ROS attack [43].

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2. Methodology

This updated review covers the neuroprotective effects and potential alternative therapeutic options of quercetin in neurological disorders. The literature databases searched for information used in the present review until inception (May 2023) were: PubMed (https://pubmed.ncbi.nlm.nih.gov/), ScienceDirect (https://www.sciencedirect.com/), Scopus (https://www.scopus.com/), and Google Scholar (https://scholar.google.com/).

We used "quercetin", "neurological disorders", "Alzheimer's disease", "Parkinson's disease", "neurodegenerative diseases", "oxidative stress", "neuroinflammation" and "amyloid beta" as the keywords for the literature search.

The chemical structure was revised by consulting the open PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and the scientific names of the plants were revised according to PlantList (http://www.theplantlist.org/). The purpose is to include in vitro and in vivo experimental studies that highlighted the main neuroprotective effects of quercetin. To this review, only full-text articles in English from the years 2013–2023 were chosen, with some important publications from earlier years. Finally, 115 articles are referred to in this review.

3. Oxidative stress

OS is a condition in which there is an imbalance between production of ROS and the body's ability to neutralize them, causing damage to lipids, proteins, and DNA. ROS are naturally produced by the body as a by-product of normal metabolism but can also be produced by environmental factors such as exposure to pollution, radiation, and certain chemicals. In the context of neurological disease, oxidative stress has been shown to play a role in the development and progression of several conditions.

Recent studies have shown that quercetin can protect against oxidative stress-induced cell death by inhibiting the activity of caspase-3 [44] and increasing the body's antioxidant capacity by regulating glutathione (GSH) levels [45]. Quercetin has also been shown to reduce inflammation and oxidative stress and improve wound healing in animal models of Alzheimer's disease [43] and reduce inflammatory pain by inhibiting oxidative stress pathways [46] (see Figure 2). These findings suggest that quercetin may be beneficial in reducing oxidative stress and inflammation in humans.

In AD, OS has been shown to accelerate the formation of amyloid plaques in the brain, which are a hallmark of the disease. Also, in PD, OS can cause the death of dopaminergic neurons, leading to loss of motor function. And in HD, stress can increase levels of the glutamate neurotransmitter in the brain, which can lead to neuron death and worsening symptoms. Thus, Figure 2, we highlighted the main enzymes that have the role of protecting the body from oxidative stress and have neuroprotective effects in the case of neurodegenerative diseases.

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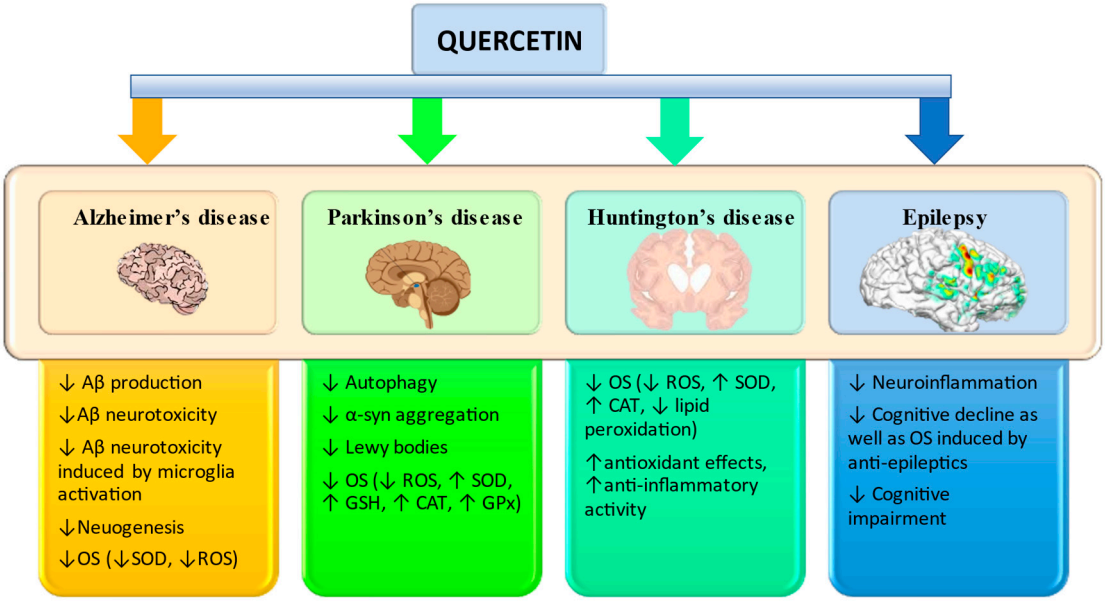

Figure 2. Diagram with possible neuroprotective effects of quercetin. Abbreviations: ↑, increase; ↓, decrease; Aβ, amyloid beta-peptide; CAT, catalase; GPx, superoxide dismutase; GSH, glutathione; OS, oxidative stress; ROS, reactive oxygen species; SOD, superoxide dismutase [14,16,47].

3.1. Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disease, accounting for about two-thirds (60-80%) of all cases of dementia, and it affects mainly the elderly (aged 65 or older) [48]. The pathogenesis of AD is commonly associated with extracellular accumulation of amyloid-β (1-40, 1-42) aggregates and hyperphosphorylation of tau proteins, leading to neurofibrillary tangles (NFT) and synaptic dysfunction [13,49–51]. An estimated 44 million people worldwide are affected by AD or a related form of dementia, with a prevalence rate of 4.6 million new cases each year. The prevalence rate of AD increases with age: the rate doubles every 5 years from the age of 60 [52,53].

Oxidative stress plays an important role in AD, which, through ROS generation, can amplify or initiate the disease. The reduction reaction of hydrogen peroxide results in the production of reactive oxygen species, thus damaging brain tissue and disrupting brain cell repair [54,55]. Thus, the administration (ad) of quercetin before the treatment decreases the damage to the cell membrane induced by the oxidative stress caused by H_2O_2 [55].

AD is characterized by neuronal loss, which is preceded by extracellular accumulation of $A\beta_{1-40}$, and $A\beta_{1-42}$. Antioxidants such as quercetin increase the resistance of neurons to oxidative stress by modulating cell death mechanisms. Thus, quercetin protects the mouse hippocampal cell line HT-22 from glutamate-induced oxidative toxicity and lipid peroxidation, by blocking the production of free radicals [54]. Also, pretreatment of primary hippocampal cultures with quercetin significantly attenuated $A\beta_{1-42}$ induced cytotoxicity, protein oxidation (protein carbonyl, 3-nitrotyrosine), lipid peroxidation (protein-bound 4-hydroxy-2-nonenal), and apoptosis. There were also observed protective effects against $A\beta_{1-42}$ toxicity by modulating oxidative stress at lower concentrations (5 and 10 μM), while in the cases of higher concentrations (20 and 40 μM), effects were not only non-neuroprotective but toxic [13].

However, recent research shows that the more hydroxyl groups the structure of the molecule contains, the stronger the anti-amyloidogenic activity. Therefore, one of the potential benefits of quercetin is its ability to act as an anti-amyloidogenic agent due to its five hydroxyl groups (see Figure 2), which means it can prevent the formation of amyloid plaques in the brain [56,57].

Numerous studies demonstrate anticancer and apoptosis-inducing effects in vitro on a variety of cancer cell lines, including murine neuroblastoma HT-22 cells [54,58,59]. Quercetin was found to be non-cytotoxic and strongly protected HT-22 cells from fibril formation [59]. In addition, Ishige et

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al., 2001, [54] using the HT-22 mouse hippocampal cell line found three distinct mechanisms of flavonoid protection in cell death, including increased intracellular GSH, direct decrease in ROS levels, and prevention of Ca^{2+} influx.

In a study on the stable cell line of the Swedish mutant of amyloid precursor protein (APP695 transfected SH-SY5Y) no effects of quercetin were observed in the middle-late stage of AD; instead, effects were observed in the mid-early stage, when the reduction of β-amyloid converting enzyme 1 (BACE1) activity was recorded [57].

The optimal concentration of quercetin required for effective destabilization of Aβ fibrils has been found to be in the range of 0.1–1 μM [58,60]. Thus, in a study using neurons of the rat hippocampal region, optimal doses of quercetin administration were beneficial for protecting against $Aβ_{25-35}$-induced amnesic injury by reducing lipid peroxidase, ROS, and GPx [60]. In another study on pheochromocytoma (PC12) cells, quercetin was found to increase the survival rate of H_2O_2-damaged cells, decrease lipid peroxidation and GSH level, and provide mitochondrial protection mechanisms [55]. On the other hand, Yu et al., 2020, [61] have shown that quercetin has beneficial effects, so it can increase PC12 cell survival damaged by $Aβ_{25-35}$, antagonize toxicity Aβ, promote cell proliferation, and provide some neuroprotective effects.

Quercetin-3-glucuronide (Q3G), a glucuronide conjugate of quercetin, has been identified as a potential intervention for AD due to its ability to target the brain. Thus, several studies have shown that Q3G may be able to alleviate neuroinflammation and reduce oxidative stress in nerve cells, both of which being associated with AD [62,63]. Additionally, Q3G has been found to specifically localize in human brain tissue, suggesting that it may be able to cross the blood-brain barrier and reach areas of the brain affected by AD [62]. Thus, Ho et al., 2013, [64] observed that quercetin-3-O-glucuronide significantly reduced the generation of β-amyloid peptides by cultures of primary neurons generated by the mouse model Tg2576 AD.

A high concentration of quercetin was found in Ginkgo biloba, thus showing that *Ginkgo biloba* extract (EGb761) and its constituents, quercetin and ginkgolide B, which by intraperitoneal administration (i.p.) have protective effects against the cytotoxic action of $Aβ_{1–42}$, thereby ameliorating oxidative phosphorylation deficits, and mitochondrial dysfunction in AD [65]. Another plant used in pharmacotherapy and in which quercetin is found is *Acanthopanax henryi*, that it can potentiate cholinergic activity by inhibiting acetylcholinesterase (AchE) [66].

Table 2. Protective effects against oxidative stress, neuroinflammation and Aβ accumulation, induced by quercetin in vitro.

Types of quercetin	Concentration of quercetin	Model	Exposure	Effects	Ref.
Quercetin	Dosage: 2.2 μM Duration: 24 h.	HT-22 mouse hippocampal cell	H_2O_2	↓lipid peroxidation, ↑intracellular GSH, ↓ROS	[54]
	Dosage: 10-100 μmol L^{-1} Duration: 10 min	PC12 cells	H_2O_2	↓lipid peroxidation, ↓GSH, mitochondrial protection mechanisms.	[55]
	Dosage: 10 μM	APP695-transfected SH-SY5Y cells	$Aβ_{25–35}$	↓ROS, ↓BACE, ↓Aβ, ↓GSH, ↓lipid peroxidation	[57]
	Dosage: 10 and 50 μM Duration: 7 days	HT-22 mouse hippocampal cells	$Aβ_{1–42}$ or $Aβ_{1–40}$	↓Aβ peptides, ↓the performed mature fibrils	[58]
	Dosage: 2.4 μg mL^{-1}	HT-22 murine neuroblastoma cells	$Aβ_{25–35}$	↓amyloidogenic Aβ peptides, inhibited Aβ fibril formation.	[59]
Quercetin-3′-glucoside	Dosage: 10, 20, 40, and 80 μmol L^{-1} Duration: 24 h, 48 h, and 72 h	PC12 cells	$Aβ_{25–35}$	↑ the survival rate of PC12 injured by Aβ25-35, promote cell proliferation, and antagonize the toxicity of Aβ, ↑ CREB/BDNF signaling pathway, ↓ROS	[61]

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Q3G	Dosage: 50 mg kg^{-1} Ad: gavage Duration: 24 h, 48 h, and 72 h	APP695-transfected $A\beta_{1-42}$ SH-SY5Y cells	↓Aβ peptides, ↑CREB signaling, ↓Aβ aggregation, ↑mitogen-activated protein	[64]
	Dosage: 50 mg kg^{-1} Ad: gavage Duration: 4 months	Tg2576 AD primary neuron cultures	↑neuronal survival, ↑c-Jun N-terminal kinases, ↓stress-induced impairments	
Quercetin/*Ginkgo biloba*	Dosage: 1.5-6 μg mL^{-1} Ad: i.p.	SHSY5Y human neuroblastoma cells	$A\beta_{1-42}$ ↓ Akt signaling pathways, ↓Aβ toxicity, ↓platelet-activating factor	[65]
Quercetin/ *Acanthopanax henryi*	Dosage: 2.5, 5, 10, 20, and 40 μg mL^{-1}	Cell free system	↓ AchE activity, ↑antioxidant activity	[66]

In mitochondria, the first free radical to form is the superoxide radical, which is catalyzed by superoxide dismutase (SOD) and can cause irreversible damage to nucleic acids, proteins, phospholipids and / or signaling pathways, thus contributing to apoptosis and intoxication [67].

Thus, it has been observed that the administration of quercetin can attenuate the levels of the SOD enzyme, reduce the amount of lactate dehydrogenase (LDH) release and protect human brain microvascular endothelial cells (hBMECs) from fibrillar β-amyloid1–40 ($fA\beta_{1-40}$)-induced toxicity [68]. In vivo studies in triple transgenic mice model of AD (3xTg-AD) have shown that quercetin can disaggregate amyloid fibrils, such as extracellular amyloid β-peptide, tauopathy astrogliosis, and microgliosis in the hippocampus and amygdala, and improves their spatial memory and learning [69,70]. Additionally, the results showed that quercetin tended to improve active behaviors of 3xTG-AD mice and decreased neurodegeneration markers in mice [70]. Additionally, in the case of APPswe/PS1dE9 transgenic mice it was observed that long-term quercetin consumption prevents memory loss, Aβ-induced neurotoxicity, and mitochondrial dysfunctions [71].

Furthermore, Hayakawa et al., 2015, [72] have shown that quercetin has memory enhancing effects in older mice and delays the deterioration of memory in the early stages of Alzheimer's, since it reduces eIF2a and ATF4 expression by inducing GADD34 in the brain. Also, quercetin can partially block the effect of other genes that play an important role in Alzheimer's disease, such as tumor necrosis factor-alfa (TNF-α), IL-1β, IL-6 [73].

Quercetin has the effect of reducing anion superoxide levels that increased with H_2O_2 and Aβ treatment in hippocampal neurons [74,75]. On the other hand, oral (p.o.) treatment with 500 mg kg^{-1} b.w. quercetin for 10 days can significantly increase brain apoE levels and reduce insoluble Aβ levels in the cortex of 5xFAD amyloid model mice [76].

Interestingly, this memory impairment was markedly ameliorated by oral treatment with quercetin nanoencapsulated in zein nanoparticles (25 mg kg^{-1} every 48 h for 2 months), while the administration of free quercetin was not able to reverse the faulty behavior, despite a higher administration frequency [77].

In a study involving homozygotic transgenic mouse line B6.129S7-Sod2tm1Leb/J, where quercetin was administered orally at a dose of 50 mg kg^{-1} body weight (b.w.) twice a week for four weeks, the results showed that quercetin had a protective effect against hydrogen peroxide- and paraquat-induced oxidative stress in the mice [74].

Scopolamine administration causes short-term and long-term memory loss because it blocks muscarinic cholinergic receptors in the brain and interferes with learning and memory [78,79]. There are studies that have found that quercetin alleviates scopolamine-induced memory deficits by protecting against neuroinflammation and neurodegeneration by inhibiting oxidative stress and acetylcholinesterase activity, reverses synaptic loss in the cortex and hippocampus of the brain of adult mice, and suppresses memory impairment [78,79].

Aluminum is a toxic metal that has neurological effects, including Alzheimer's disease, by generating ROS [80]. Increased production of reactive oxygen species leads to the disruption of

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cellular antioxidant defense systems and to the release of cytochrome c from mitochondria into the cytosol, resulting in apoptotic cell death [80,81]. Thus, the administration of 10 mg kg^{-1} b.w quercetin reduces the effects induced by aluminum, thus reducing oxidative stress, in addition, it prevents cytochrome c translocation [80].

In addition, Hou et al., 2010 [82] have shown that flavonols can antagonize A toxicity Aβ and improve the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus of double transgenic mice.

Table 3. Protective effects against oxidative stress, neuroinflammation, and Aβ accumulation, induced by quercetin in vivo.

Types of quercetin	Concentration	Model	Exposure	Effects	Ref.
Quercetin	Dosage: 5 or 10 mg kg^{-1} b.w.; Ad: p.o.; Duration: once daily;	hBMECs	$fA\beta_{1-40}$	↓SOD, ↓LDH	[68]
	Dosage: 25 mg kg^{-1} b.w.; Ad: i.p.; Duration: every 2 days for 3 months;	3xTg-AD mice		↓tauopathy, ↓β-amyloidosis, ↑memory, ↑learning↓ microgliosis, ↓astrogliosis	[69]
	Dosage: 100 mg kg^{-1} b.w.; Ad: gavage; Duration: every 48 h for 12 months;	3xTg-AD mice		↓neurodegeneration, ↓β-amyloidosis	[70]
	Dosage: 20 and 40 mg kg^{-1} b.w.; Ad: p.o.; Duration: 16 weeks;	adult male C57BL mice		↑ MMP, ↑ATP levels, ↓ROS	[71]
	Dosage: 20 mg; Ad: p.o.; Duration: 5 weeks;	APP23 AD mice model	Aβ	↓eIF2α, ↓ATF4, ↓GADD34, ↑memory in aged mice, ↓memory deterioration in the early stage of AD, ↓memory dysfunction, ↓OS	[72]
	Dosage: 1% in mouse chow; Ad: p.o.; Duration: from 3 to 13 months;	double transgenic female mice		↓neuroinflammation, ↓neurodegeneration, ↓ IL-1β	[73]
	Dosage: 50 mg kg^{-1} b.w.; Duration: 2 times a week for 4 weeks;	homozygotic transgenic mouse line B6.129S7-Sod2tm1Leb/J	H_2O_2 and Aβ	↓ROS levels, improved the typical morphology of mitochondria, prevented mitochondrial dysfunction	[74]
	Dosage: 100 mg kg^{-1} b.w.; Ad: p.o.; Duration: 22 days;	adult male Sprague-Dawley rats	Aβ1–42	↑expression of Nrf2/HO-1 in rat brain, ↓Aβ1-42 level, ↓antioxidant activity	[75]
	Dosage: 25 mg kg^{-1}; Ad: p.o.; Duration: 2 times a week for 2 months;	SAMP8 mice		↑ the cognition and memory impairments, ↓ astrogliosis	[77]
	Dosage: 12.5 and 25 mg kg^{-1};	mice	Scopolamine	↓OS, ↓AchE activity	[78]
	Dosage: 30 mg kg^{-1} b.w.; Ad: i.p.;	male albino Wistar rats	Scopolamine	abridged transfer latency, ↓avoidance response, ↓3,4-methylenedioxyamphetamine,	[79]

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	Duration: every day for 8 days; Dosage: 10 mg kg $^{-1}$ b.w.; Ad: p.o.; Duration: every day for 12 weeks;	male albino Wistar rats	aluminum	acetylcholinesterase levels, ↑CAT, ↑ GSH levels ↓ROS production, ↑mitochondrial superoxide dismutase activity	[80]
Quercetin/ ginkgo flavonols	Dosage: 4.8% in extract, all based on weight;	Double Transgenic (TgAPP/PS1) mice	-	Reversed the spatial learning deficit	[82]

Several studies have shown that type 2 diabetes is a risk factor for the onset of AD [83,84]. Moreover, changes in glucose regulation that accompany type 2 diabetes appear to affect regions of the hippocampus involved in age-related memory loss [84].

The link between AD and type 2 diabetes is not fully understood. However, uncontrolled blood sugar can increase the risk of AD [85]. Some researchers have referred to AD as "diabetes of the brain" or "type 3 diabetes" [86–88]. Environmental factors and comorbidities, as well as other diseases that a certain person suffers from, can make them more susceptible to the onset of AD, but all studies so far point to the fact that the accumulation of amyloid is the fundamental cause of dementia.

3.2. Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disorder worldwide, affecting 1% of the global population aged 65 years and older; it has significant morbidity and mortality [89]. An increasing percentage of research indicates the association of Parkinson's disease with microglial activation, resulting in an increase in various inflammatory mediators and neuroinflammation [90,91]. 1-Methyl-4-phenylpyridinium (MPP+) is the ultimate toxic agent formed by metabolism of MPTP and can activate glial cells to induce neuroinflammation [92]. Research has shown that MPP+ induces microglial activation and degeneration of dopaminergic neurons, as well as generation of ROS in dopaminergic neurons [93]. On the other hand, quercetin administration protects microglia cells against MPP+- induced increases in mRNA protein level of IL-1, IL-6 and TNF-α, due to its antioxidant action [92]. In addition to the loss of dopaminergic neurons in the substantia nigra pars compacta, PD is also characterized by the abnormal accumulation and aggregation of α-synuclein (α-Syn) in the form of Lewy bodies [94,95]. Thus, the formation of α-Syn fibrillations can be inhibited by quercetin and oxidized quercetin through their 1:1 covalent binding [95].

Another neurotoxic synthetic organic compound used by researchers to selectively destroy dopaminergic and noradrenergic neurons is 6-hydroxydopamine (6-OHDA) [96,97]. It is a hydroxylated analogue of dopamine and is a benzenetriol with hydrogens on the phenyl ring at positions 2, 4 and 5. Isoquercetin, a flavonol derived from quercetin, has also been found to have protective effects against 6-OHDA-induced oxidative damage in a rat model of Parkinson's disease, they observed that antioxidant enzymes, catalase (CAT), SOD, GPX and GSH levels, which were previously attenuated by 6-OHDA, increased significantly [96,97].

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Table 4. Protective effects against oxidative stress and neuroinflammation, induced by quercetin in vitro, in the case of Parkinson's disease.

Types of quercetin	Concentration	Model	Exposure	Effects	Ref.
Quercetin	Dosage: 0.1 μM	Microglial (N9)-neuronal (PC12) cells	MPP	↓iNOS gene expression, ↓ROS, ↓ cellular death, ↓DNA fragmentation, ↑apoptosis, ↓nuclear translocation of apoptosis-inducing factor, ↓caspase-3activation	[92]
	Dosage:10 mM	PC12 cells	α-Synuclein	↓Aβ fibrillation	[95]
Isoquercetin	Dosage: 10, 50, and 100 μM	PC12 cells	6-OHDA	↓ROS, ↑SOD, ↑GSH, ↑CAT, ↑GPx	[96]
Quercetin glycoside	Dosage: 10, 50, and 100 μM	PC12 cells	6-OHDA	↑antioxidant activity, ↑GSH, ↑GPx	[97]

In vitro studies have shown that quercetin can improve mitochondrial quality control, reduce oxidative stress, and increase levels of antioxidant enzymes [92,95–97]. Instead, in vivo studies in mice and 6-OHDA-induced PD rat models demonstrated that quercetin can improve locomotor and muscle activity, increase striatal dopamine levels, and protect neurons from mitochondrial dysfunction [98–102].

Studies have shown that quercetin has neuroprotective effects against MPTP-induced neurotoxicity in Wistar rats and adult male C57BL/6 mice [98–100]. Quercetin was found to reduce oxidative stress and neuroinflammatory cytokines in rats [98,99], as well as restores motor and non-motor symptoms (depression and cognitive impairment) of PD in rats injected with rotenone [103,104]. Additionally, quercetin supplementation was found to improve striatal cholinergic function and reduce rotenone-induced oxidative stress in rats [104].

On the other hand, administration of fish oil can attenuate rotenone-induced oxidative impairments and mitochondrial dysfunctions in rat brain [105]. Combined oral supplementation with fish oil and quercetin has been found to enhance neuroprotection in a chronic rotenone rat model, suggesting potential relevance for Parkinson's disease [105].

Table 5. Protective effects against oxidative stress and neuroinflammation of quercetin in vivo in the case of Parkinson's disease.

Types of quercetin	Concentration	Model	Exposure	Effects	Ref.
Quercetin	Dosage: 25 mg kg^{-1} Ad: p.o.	Wistar rats	Haloperidol MPTP	↓cataleptic score, ↑actophotometer activity score, ↑GSH, ↓lipid peroxidation, ↓ROS	[98]
	Dosage: 25 and 50 mg kg^{-1}, Ad: intragastrically Duration: 14 days	Wistar rats	MPTP	↓TNF-α, ↓IL-1β and ↓IL-6, ↓glutamate level,	[99]
	Dosage: 50, 100 and 200 mg kg^{-1} Ad: p.o. Duration: 14 days.	adult male C57BL/6 mice	MPTP	↓striatal dopamine depletion, ↓level of acetylcholine, ↑AchE activity, ↑motor deficits, ↑GPx, ↑SOD	[100]
	Dosage: 100, 200 and 300 mg kg^{-1} Duration: 14 days	Wistar rats	6-OHDA	↑spatial memory, ↓OS, ↓AchE activity, ↑antioxidant activity, ↓neuronal damage	[101]
	Dosage: 20 mg kg^{-1} Ad: i.p. Duration: 1 month.	Wistar rats	6-OHDA	↓neuroplastic changes in neural circuits, ↓excitability in neurons involved in epilepsy, ↓NMDA receptor functionality	[102]

	Dosage: 25-75 mg kg^{-1} Duration: 12 h intervals for 4 days	Wistar rats	Rotenone	↓nigral GSH depletion, ↓ROS, ↓striatal DA loss, ↑mitochondrial complex, ↓neuronal death	[103]
	Dosage: 50 mg kg^{-1}, Ad: p.o. Duration: 14 days	Wistar rats	Rotenone	↑AchE activity, ↑SOD, ↓GPx, ↓CAT	[104]
Quercetin + fish oil	Dosage: 25 mg kg^{-1} Ad: p.o. Duration: 28 days	Wistar rats	Rotenone	↑mitochondrial functions, ↑GSH, ↑antioxidant defenses	[105]

3.3. Huntington's disease

Along with Alzheimer's and Parkinson's, Huntington's disease (HD) is a major health problem worldwide, with a major financial impact [106]. Huntington's disease is an autosomal dominant, inherited disorder, treatment of which is clinically available but provides only symptomatic relief. These drugs are available by prescription and have side effects such as anxiety and depression.

For an experimental model of Huntington's disease, 3-nitropropionic acid (3-NPA) is administered, which alters the mitochondrial metabolism, decreases cellular ATP level, and includes the nerve cell death, by increasing OS.

In a study by Sandhir and Mehrotra [107], in which female Wistar rats were used as model organisms, in which quercetin was orally administered at a dose of 25 mg kg^{-1} for 21 days, for 17 of these 21 days concomitantly with 3-NPA, was observed an attenuation of motor deficits which were assessed using the narrow-beam walking test and fingerprint analysis. Furthermore, molecular changes induced by 3-NPA acid were observed, which were reversed, thus increasing the level of oxidative stress, and lowering the ATP concentration [107].

On the other hand, a study by Chakraborty [108] failed to confirm the beneficial effect of quercetin on the 3-NP-induced striatal neuronal lesion. However, the conditions of the two studies varied little, Chakraborty used male rats as model organisms, and the duration of administration of 3-NP and quercetin was 4 days, and the concentration was higher (25-50 mg kg^{-1}), than that which was administered by Sandhir and Mehrotra, [107] where the dose was administered subchronically (25 mg kg^{-1}). Although quercetin had no effects on 3-NP-induced striatal neuronal injury, it significantly attenuated neurotoxin-induced anxiety, decreased microglial proliferation, and increased the number of astrocytes in the lesion core [108].

In addition, quercetin in combination with other antioxidants, such as lycopene, decreases anxiety and depression [109]. Furthermore, the use of dietary antioxidants as adjuvants with n-3 fatty acids is increasingly being used, as they offer a higher degree of protection. Thus, the efficacy of quercetin in combination with fish oil was observed in a rat model previously treated with 3-NPA, where it decreased OS, and improved motor function [110].

Quinolinic acid (QA) is also a paradigm of Huntington's disease, and co-administration of antioxidants such as quercetin with sesamol minimizes neurochemical, behavioral, and biochemical alterations in rat brains [111]. However, these data appear inconsistent and unequivocal conclusions cannot be drawn.

Table 6. Protective effects against oxidative stress and neuroinflammation, induced by quercetin in vitro in the case of Huntington's disease.

Types of quercetin	Concentration	Model	Exposure	Effects	Ref.
Quercetin	Dosage: 25 mg kg^{-1} Ad: p.o. Duration: 21 days;	Wistar rats	3-NPA	↑ATP, ↑activity of complex II and V enzyme of respiratory chain complex, ↓ROS, ↑SOD, ↑CAT, ↓lipid peroxidation	[107]
	Dosage: 25–50 mg kg^{-1} Ap: i.p.; Duration: 4 days	Sprague Dawley rats	3-NPA	↓gait despair, ↓microglial proliferation, ↓anxiety, ↑astrocyte numbers in the lesion core, ↓motor coordination deficits, ↓serotonin metabolism	[108]

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Quercetin + lycopene	Dosage: 50 mg kg^{-1}, Duration: 14 days	Wistar rats	3-NPA	↓anxiety, ↓depression	[109]
Quercetin + fish oil	Dosage: 25 mg kg^{-1}	Wistar rats	3-NPA	↓OS, ↑motor function	[110]
Quercetin + sesamol	Dosage: 25, 50, and 100 mg kg^{-1}, Ad: i.p. Duration: 14 days before and 14 days after quinolinic acid administration	Wistar rats	QA	↓behavioral, biochemical, and neurochemical alterations in the rat brain, ↑antioxidant effects, ↑anti-inflammatory activity	[111]

3.4. Epilepsy

Epilepsy is a neurological disorder characterized by recurrent spontaneous seizures, being caused by an imbalance in excitatory and inhibitory neurotransmission [112]. Glutamate and γ-amino butyric acid (GABA) are the major excitatory and inhibitory neurotransmitters in the CNS [113]. A GABA receptor antagonist is pentylenetetrazol (PTZ), which is used to create a chemically induced seizure model in animals [113].

In a study using PTZ-induced seizure model rats, quercetin administration at 10 mg kg^{-1} intraperitoneally 30 min before PTZ injection significantly prolonged the onset and reduced the severity of the seizure, but, at an increased concentration of 40 mg kg^{-1}, quercetin failed to prevent the effects of PTZ [113]. Also, Nassiri-Asl et al., [111] showed that administration of 35 mg kg-1 PTZ after 50 mg kg-1 quercetin reduces seizure severity during kindling and improves performance in a passive avoidance task in kindled rats. In addition, Choudhary et al., 2011, [114] isolated and evaluated the antiepileptic potential of the flavonoid fractions of *Anisomeles malabarica* leaves, both acute and chronic. In the acute treatment (25 and 50 mg kg^{-1}, i.p.) with toxic effects observed, respectively chronic treatment for one week (6.25 and 12.5 mg kg^{-1}, i.p.) a significant antiepileptic effect was observed without causing side effects neurotoxic [114].

Table 7. Protective effects against oxidative stress and neuroinflammation, induced by quercetin in the case of epilepsy.

Types of quercetin	Concentration	Model	Type of test	Exposure	Effects	Ref.
Quercetin	Dosage: 5, 10, 20, 40 mg kg^{-1}	Albino rats	in vivo	PTZ	↑antiseizure effect, ↑anticonvulsant effect	[113]
	Dosage: 25, 50, and 100. mg kg^{-1} Ad: i.p.	Wistar rats	in vivo	PTZ	↑anticonvulsant effects, ↓seizure severity, ↓lipid peroxidation, ↑antioxidant effect, ↑memory retrieval in the passive avoidance task	[115]
Quercetin/ *Anisomelesma labarica*	Dosage: 25 and 50 mg kg^{-1} Ad: i.p.	Wistar rat	in vivo	PTZ	↓ locomotor activity and motor activity performance	[114]
	Dosage: 6.25 and 12.5 mg kg^{-1} Ad: i.p. Duration: 1 week	Wistar rat	in vivo	PTZ	potentiating the GABAergic system, inhibition of the NMDA receptor and Na^+ channels.	

4. Conclusions

Research on quercetin's neuroprotective effects suggests that it can be used to protect against various neurodegenerative diseases. Quercetin has been shown to reduce OS and inflammation, which are both associated with neurodegeneration. It has also been found to reduce hippocampal tau phosphorylation, which is a marker of AD.

In addition, quercetin has been found to act through numerous mechanistic targets to provide neuroprotection, including the modulation of receptor pathways. It has also been found to have protective effects when combined with vitamin C, lycopene, fish oil, or sesamol.

Overall, research suggests that quercetin may be an effective agent for the prevention of progressive age-related neurodegenerative diseases such as AD, PD, HD, or epilepsy, respectively. However, more research is needed to draw more concrete conclusions about the efficacy of quercetin in these disorders.

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