Quercetin in Food: Possible Mechanisms of Its Effect on Memory

Fatemeh Babaei, Mohammadreza Mirzababaei, and Marjan Nassiri-Asl

Abstract: Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is found in vegetables and fruits. It is one of the major flavonoids that is part of human diets. Quercetin has several pharmacological effects in the nervous system as a neuroprotective agent. In this review, we summarize the research on quercetin and its role in memory in both animals and humans. Articles were chosen from the Scopus, PubMed, and Web of Science databases. In this review, we describe and summarize the importance of quercetin's presence in the body, particularly in the brain; its kinetics, including its absorption, metabolism, distribution, and excretion; its behavioral effects; and some of the possible mechanisms of action of quercetin on memory in different animal models. Several important pathways that may be involved in the processes of learning and memory, long-term potentiation, and cognition may be impaired during neurological diseases or other medical conditions. As dietary quercetin is important, provision of its best formulation for delivery to the brain as a nutraceutical and in clinical translational research for the prevention or treatment of Alzheimer's disease and other types of dementia is necessary.

Keywords: Alzheimer's disease, flavonoids, food, memory, quercetin

Introduction

According to the 2015 World Alzheimer report, an estimated 46.8 million people are thought to be living with dementia. This number is expected to increase to 74.7 million by 2030 and 131.5 million by 2050 (Prince et al., 2015; Wu et al., 2017). There are several different types of memory: episodic, verbal, visual, and olfactory. Memory can also be classified as implicit (nonverbal habitual memory) or explicit (active or passive recall of facts) (Arlt, 2013). The main cause of dementia and the most common dementia disorder is Alzheimer's disease (AD). Loss of episodic memory is one of the symptoms of AD. Other types of dementia include Lewy body, vascular, and frontotemporal dementia (Arlt, 2013).

Parkinson's disease (Goldman, Weis, Stebbins, Bernard, & Goetz, 2012) and epilepsy (Felician, Tramoni, & Bartolomei, 2015) are neurological disorders that cause memory impairment. In addition, general medical conditions such as diabetes mellitus (Falvey et al., 2013), pregnancy (Wilson et al., 2011), cerebral hypoxia (Jablonski, Maciejewski, Januszewski, Ulamek, & Pluta, 2011), and the use of alcohol (Sachdeva, Chandra, Choudhary, Dayal, & Anand, 2016) or drugs (Chavant, Favrelière, Chebassier, Plazanet, & Pochat, 2011) can result in cognitive deficits (Arlt, 2013; Sorbi et al., 2012).

Two classes of drugs, acetylcholine esterase inhibitors (AChE) and N-methyl-D-aspartate (NMDA) receptor antagonists, have been used for the treatment of AD (Allgaier & Allgaier, 2014).

In recent years, several studies have discussed the role of flavonoids as a therapeutic strategy in the treatment of AD (Ruan, Ruan, Zhang, Qian, & Yu, 2018; Sureda, Xavier, & Tejada, 2017). It has been shown that the flavone, isoflavone, and chalcone derivatives of flavonoids have AChE inhibitory activity (Uriarte-Pueyo & Calvo, 2011).

JFDS-2018-0273 Submitted 2/3/2018, Accepted 11/7/2018. *Author Babaei is with Dept. of Clinical Biochemistry, Qazvin Univ. of Medical Sciences, Qazvin, Iran. Author Mirzababaei is with Dept. of Clinical Biochemistry, Faculty of Medical Sciences, Tarbiat Modares Univ., 14115-111, Tehran, Iran. Author Nassiri-Asl is with Cellular and Molecular Research Center, Qazvin Univ. of Medical Sciences, 341197-5981, Qazvin, Iran. Direct inquires to author Nassiri-Asl (E-mail: marjannassiriaslm@gmail.com).*

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is one of the major flavonoids that is part of human diets, and approximately 3 to 38 mg of quercetin is consumed per day (Manach, Williamson, Morand, Scalbert, & Rémésy, 2005). Quercetin is found in many fruits and vegetables. Apples, cherries, berries, onions, asparagus, and red leaf lettuce have the highest levels of quercetin, while tomatoes, peas, broccoli, and green peppers have lower levels (Costa, Garrick, Roquè, & Pellacani, 2016). The name quercetin comes from the Latin word "Quercetum," a yellow colored compound that dissolves in alcohol and lipids but is insoluble in cold water and poorly soluble in hot water (David, Arulmoli, & Parasuraman, 2016). Quercetin as a flavonoid and natural product has been suggested for the treatment of AD (Bui & Nguyen, 2017). Possible effects of quercetin on several diseases that cause memory impairment are illustrated in Figure 1.

There are several animal models of AD, and memory impairment including amyloid β (Aβ) (Facchinetti, Bronzuoli, & Scuderi, 2018), the transgenic mouse model of AD (Wang et al., 2014), lipopolysaccharide (Wang et al., 2018), and the streptozotocin (STZ) (Bhutada et al., 2010), scopolamine (Nouriziabari et al., 2018), D-galactose (Dong et al., 2017), hypoxia (Prasad et al., 2013), and ischemia models (Viswanatha et al., 2015).

Methods

For this review, the most important articles published between 2010 and 2018 relating to the effects of quercetin on AD and other memory impairments were selected from the Scopus, PubMed, and Web of Science databases. The keywords used for the search were: quercetin, quercetin and memory, and quercetin and Alzheimer. In this review, we tried to classify all data pertaining to the kinetic and pharmacological effects of quercetin on memory in different disease or animal models. We considered all articles—positive or negative—on quercetin's effects on memory.

Absorption, Metabolism, Distribution, and Excretion

Quercetin is a lipophilic compound with low bioavailability that easily diffuses across the blood–brain–barrier such that it can reach the target organ (that is, the brain) and perform neuroprotective actions (Barreca et al., 2016). The nature of the attached sugar in

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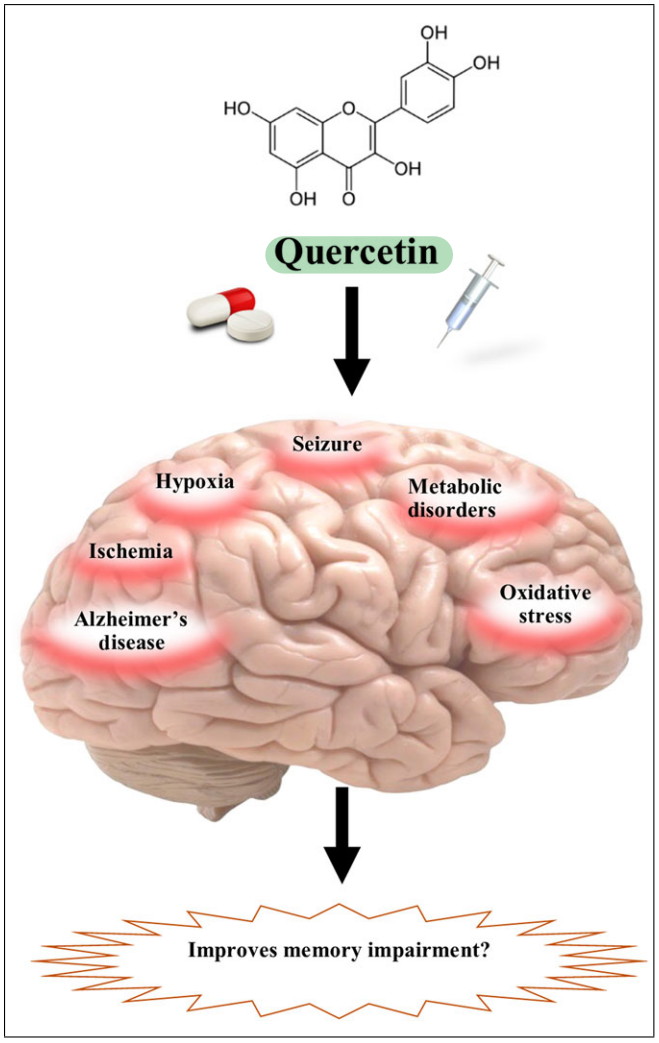

Figure 1–Several causes of memory impairment and quercetin.

quercetin can affect its absorption (D'Andrea, 2015). A glycosyl group such as glucose, rhamnose, or rutinose is attached and replaces one of the OH groups, commonly located at position 3, and produces a quercetin glycoside (Ross & Kasum, 2002). The solubility, absorption, and *in vivo* effects of quercetin can change depending on the glycosyl group. A quercetin glycoside has a high level of water solubility compared with the aglycone form of quercetin. Upon absorption, quercetin is metabolized in the small and large intestines, liver, and kidney (Russo, Spagnuolo, Tedesco, Bilotto, & Russo, 2012).

The mechanisms of metabolism are summarized as follows: Both the glycoside and aglycone forms of quercetin are absorbed in the small intestine. The β-glucosidase enzyme and lactase phlorizin hydrolase present in the intestinal brush border deglycosylate and absorb quercetin in the aglycone form (Day, Gee, DuPont, Johnson, & Williamson, 2003). Subsequently, conjugation reactions occur through uridine diphosphate glucuronosyltransferases, catechol-O-methyltransferase, and the sulfotransferase and quercetin derivatives—quercetin-3-glucuronide, quercetin-3′-sulfate, 3′-O-methylquercetin (isorhamnetin), and 4′-O-methylquercetin—are produced (Wang et al., 2016).

Next, quercetin aglycone is transferred to the liver and metabolized via O-methylation, glucuronidation, and sulfation to produce quercetin-3-glucuronide, quercetin-3′-sulfate, and isorhamnetin-3-glucuronide (Suganthy, Devi, Nabavi, Braidy, & Nabavi, 2016) and enters the blood circulation or undergoes biliary excretion (Arts, Sesink, Faassen-Peters, & Hollman, 2004; Guo & Bruno, 2016). Compounds that are not absorbed in the small intestine reach the large intestine, where colonic microflora degrade the structure of quercetin to phenolic acid compounds that can readily be absorbed and transported via the portal vein to the liver, where they undergo conjugation reactions (Thilakarathna & Rupasinghe, 2013).

It has been shown that 6 to 12 hr after [2-^{14}C] quercetin-4′-glucoside ingestion in rats, radiolabeled hippuric acid, 3-hydroxyphenylacetic acid, and benzoic acid appeared in the urine and 3-hydroxyphenylacetic acid and hippuric acid appeared in the feces (Mullen et al., 2008).

A summary of the presence of quercetin in different organs after oral consumption is shown in Figure 2.

Quercetin in the Brain

It has been shown that after oral administration of quercetin, conjugated forms of it accumulate in the brain (Ishisaka et al., 2011). Quercetin-3-O-glucuronide and isorhamnetin-3-O- glucuronide (methylquercetin-3-O-glucoronide) are found in the brain tissue (Dajas et al., 2015; Huebbe et al., 2010; Ishisaka et al., 2011). However, methylquercetin-3-O-glucoronide was not quantifiable in the mouse brain (Ho et al., 2012). Aglycone quercetin is only scarcely present in the CNS (Dajas et al., 2015).

Quercetin and Memory

Alzheimer's disease

Quercetin (40 mg/kg, p.o., 16 weeks) is known to improve learning and recognition memory, reduce scattered senile plaques, attenuate mitochondrial dysfunction, as indicated by increasing mitochondrial membrane potential and ATP levels and decreasing reactive oxygen species (ROS) production, and increase AMP-activated protein kinase (AMPK) activity in the APPswe/PS1dE9 transgenic mouse model of AD. It has been suggested that activation of AMPK may be one of the mechanisms by which quercetin ameliorates cognitive defects (Wang et al., 2014). An AIN93G diet containing 20% casein and 0.5% quercetin was found to suppress presenilin 1 (PS1) expression and Aβ secretion, and reduce eukaryotic translation initiation factor 2a phosphorylation and the levels of activating transcription factor 4 expression by increasing growth arrest and DNA damaged-inducible gene (GADD34) expression in the brain, ultimately delaying the deterioration of memory and the improvement of contextual and fear memory in the APP23 AD model mice (Hayakawa et al., 2015).

Oral administration of quercetin (60 mg/kg, p.o., 16 weeks) in high cholesterol-fed aged mice inhibited the cholesterol-induced activation of protein phosphatase 2C alpha (PP2Cα) and activated AMPK. Acetyl-CoA carboxylase and HMG-CoA reductase were then inactivated in the brain. Quercetin also decreased the inflammatory markers via the inhibition of NF-κB p65 nuclear translocation, ameliorated cognitive dysfunction, and reduced the expression of β-amyloid converting enzyme 1, which resulted in a reduction of Aβ levels and deposits (Martínez de Morentin, González, & López, 2010).

Quercetin (80 and 100 mg/kg, i.p, 21 days) enhanced spatial learning and memory impairment in STZ-induced AD rats (Ashrafpour, Parsaei, & Sepehri, 2015). Quercetin improved

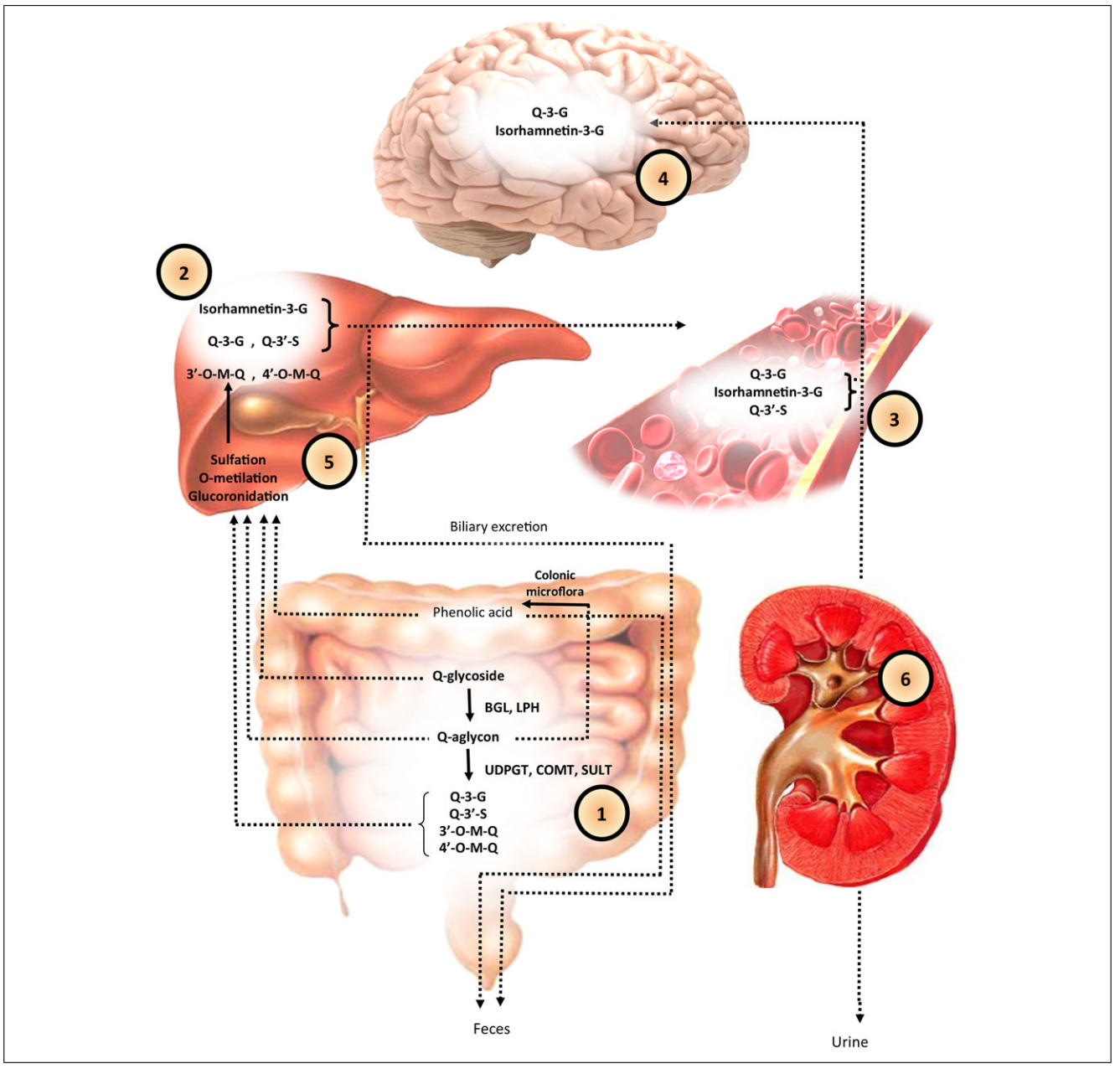

Figure 2–Metabolism of quercetin in digestive system (1) and liver (2), and the passage to blood circulation (3), brain (4), biliary system (5), and kidney (6).
Q, quercetin; BGL, β-glucosidase; LPH, lactase phlorizin hydrolase; UDPGT, uridine diphosphate glucuronyl transferase; COMT, catechol-o-methyl transferase; SULT, sulfo transferase; Q-3-G, quercetin-3-glucuronide; Q-3′-S, quercetin-3′-sulfate; 3′-O-M-Q, 3′-O-methyl-quercetin (isorhamnetin); 4′-O-M-Q, 4′-O-methyl-querecrtin; isorhamnetin-3-G, isorhamnetin-3- glucuronide.

memory recall in aged C57BL/6J mice that were fed a diet containing 0.5% quercetin for 4 weeks (Nakagawa et al., 2016). In animal studies involving STZ-induced diabetic rats, quercetin improved memory impairment. For more details, see Table 1.

Quercetin (25 mg/kg every 48 hr, 3 months) reversed β-amyloidosis, decreased tauopathy, astrogliosis, and microgliosis, increased anxiolytic activity, and improved spatial learning and memory in aged triple transgenic AD model mice (Sabogal-Guáqueta et al., 2015). Oral administration of quercetin (20 mg/kg, 8 days) after injection of amyloid β25-35 ameliorated learning and memory performance, decreased AChE activity, protected vessel integrity, and prevented the loss of surrounding neurons that were altered in Aβ25-35-treated mice. It also modified the changes caused by $A\beta_{25-35}$ injection and inhibited activation of RAGE signaling and restored the ERK/cAMP response element binding protein (CREB)/brain-derived neurotrophic factor (BDNF) signaling pathway, reversing $A\beta_{25-35}$-induced cognitive dysfunction (Table 1) (Liu et al., 2013).

Pretreatment with quercetin (100 mg/kg, 1 month) ameliorated the Aβ-induced degradation of learning and memory loss in mice. The LD_{50} value of orally administrated quercetin in mice was 575 mg/kg. In an *in vitro* assay, quercetin inhibited the PC12 neuronal cell death caused by Aβ-treatment (Li et al., 2017). Poly lactic-co-glycolic acid functionalized quercetin (PLGA@QT)

Table 1–The protective effects of quercetin on memory impairment in animal models by possible mechanisms.

Model	Animal	Dose of quercetin	Mechanism	Reference
STZ-induced memory impairment	Mice	5, 10 mg/kg, p.o.	Reduced elevated levels of MDA, nitrite, and AChE, and increased levels of CBF, ATP, and GSH in the brain	Tota, Awasthi, Kamat, Nath, & Hanif, 2010
	Rats	5, 25, 50 mg/kg, p.o., 40 days	Reduced MDA, ADA, and AChE levels, and increased the NTPDase level in the brain	Maciel et al., 2016
Aβ-induced AD disease	Mice	30 mg/kg, p.o., 14 days, and Q3G	Inhibited lipid peroxidation and NO formation, decreased MDA level and attenuated oxidative stress in the brain	Kim, Lee, Lee, & Cho, 2016
	Mice	20 mg/kg, p.o., 8 days	Decreased AChE activity, reduced expression of RAGE, NF-kB p65, and phosphorylated p38 MAPK, enhanced expression of BDNF, phosphorylated ERK 1/2, and CREB in the cerebral cortex	Liu et al., 2013
Scopolamine-induced memory impairment	Rats	25 mg/kg/d, p.o., 14 days	Decreased AChE, LPO, MDA, and β amyloid $_{1–42}$ levels, and increased GSH level in the brain	Pattanashetti et al., 2017
D-galactose-induced aged animal	Mice	20, 50 mg/kg, p.o., 49 days	Activated Nrf2-ARE signaling pathway and increased the expression of Nrf2, HO-1, and SOD, reduced neuronal cell apoptosis	Dong et al., 2017

AChE, acetylcholinesterase; ADA, adenosine deaminase; ARE, antioxidant response element; ATP, adenosine tri-phosphate; BDNF, brain-derived neurotrophic factor; CBF, cerebral blood flow; CREB, cAMP response element binding protein; ERK1/2, extracellular signal-regulated protein kinase 1/2; GSH, glutathione; HO-1, heme oxygenase-1; LPO, lipidperoxidase; MDA, malondialdehyde; NF-κB, nuclear factor-kappa B; NO, nitric oxide; Nrf2, nuclear factor-erythroid 2-related factor 2; NTPDase, nucleoside triphosphate diphosphohydrolase; p38 MAPK, p38 mitogen-activated protein kinase; Q3G, quercetin-3-β-D-glucoside; RAGE, receptor for advanced glycation end products; SOD, superoxide dismutase; STZ, streptozotocin.

nanoparticles (10 to 40 μg/mL) showed partial protection against Zn^{2+}/Aβ_{42} system neurotoxicity and Aβ_{42} aggregation and increased the viability of neurons in SH-SY5Y cells. PLGA@QT nanoparticles (20 and 30 mg/kg, i.v.) also improved Aβ_{42}-induced spatial learning and memory impairment in APP/PS1 mice. Moreover, systemic toxicity of PLGA@QT NPs (20 mg/kg, i.v.) was not observed in the histological study of mouse tissues 5, 15, or 30 days after injection (Sun et al., 2016).

Oral administration of nanoencapsulated quercetin in zein nanoparticles (NPQ, 25 mg/kg every 48 hr, 2 months) improved the memory and cognition impairments and decreased the astrogliosis in SAMP8 (Senescence-accelerated mouse prone 8) mice. On the contrary, daily oral administration of the same dose of free quercetin did not affect the senescence of the animals. These results revealed that zein nanoparticles improve the oral absorption and bioavailability of quercetin (Moreno et al., 2017).

Non-Alzheimer's diseases

In this part of the review, we summarize the importance of quercetin in various conditions that may be associated with memory impairment in animal studies.

Neurological diseases in different animal models of memory impairment

Quercetin (100, 200, or 300 mg/kg, 2 weeks) improved cognition before and after administration of 6-hydroxydopamine in a rat model of Parkinson's disease in the Morris water maze test (Sriraksa et al., 2012). Pretreatment with quercetin (20 mg/kg, 3 weeks) in the trimethyltin model of learning and memory impairment enhanced learning and memory function in mice. It inhibited AChE activity and ROS accumulation, reduced MDA levels, and showed antioxidant capacity, which was confirmed by a 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) and an ABTS radical scavenging and ferric reducing antioxidant power (FRAP) assay (Choi et al., 2012).

Quercetin liposomes (0.5 mg/20 μL, intranasally, 3 wk), modified ethylcholine mustard aziridinium ion (AF64A)-induced memory defects, elevated levels of MDA, and reduced levels of SOD, catalase, and glutathione in rats (Tong-un, Wannanon, Wattanathorn, & Phachonpai, 2010). Pretreatment with quercetin (60 mg/kg, p.o., 21 days) 3 hr prior to dexamethasone administration improved memory impairment, increased NR2A/B protein levels of NMDA receptors, and restored the hippocampus dentate gyrus cell proliferation in mice (Tongjaroenbuangam et al., 2011). Furthermore, pretreatment with quercetin (20 mg/kg, 7 days) in a cerebral ischemia model resulted in antioxidant activity, FRAP, and DPPH (2, 2-diphenyl-1-picrylhydrazyl) capacity in rats. It inhibited the neurologic, cognitive, and motor defects and brain cerebral infarct and edema formation caused by ischemia-reperfusion injury and decreased the MDA level (Viswanatha et al., 2015).

Additionally, the administration of quercetin (50 mg/kg, i.p.) in the kindling model of epilepsy by pentylenetetrazole (PTZ) reduced seizure severity and enhanced memory retrieval in rats. It increased MDA levels but did not significantly elevate the total sulfhydryl concentration in PTZ-induced kindling rats (Nassiri-Asl et al., 2013).

Quercetin (200, 400, and 800 mg/kg) dose-dependently caused anticonvulsant activity in psychomotor seizure induced via corneal stimulation (0.2 ms square pulse at 6 Hz, 3 s) in mice. The combination of quercetin (200 mg/kg, i.p.) with valproate sodium or levetiracetam was safe, and quercetin did not change the anticonvulsant effects of either drug. Furthermore, quercetin did not result in any changes in the long-term memory (LTM) of mice with both treatments or individually (Nieoczym, Socała, Raszewski, & Wlaź, 2014).

Bioactive dietary polyphenol preparation has been shown to attenuate memory dysfunction in a sleep deprivation (SD) model through activation of the CREB signaling pathway in mice. Quercetin (0.2 and 2 mg/kg) phosphorylated CREB, and administration of both quercetin (0.2 mg/kg) and

malvidin-3-O-glucoside (5 μg/kg) improved SD-induced cognition impairment in mice (Zhao et al., 2015).

Quercetin (25 mg/kg/day, p.o., 14 days) improved memory impairment in a scopolamine model; furthermore, histopathological studies confirmed the suppression of neuronal damage (Pattanashetti, Taranalli, Parvatrao, Malabade, & Kumar, 2017). Additional detail is provided in Table 1. Quercetin (50 mg/kg, i.p.) prevented scopolamine-induced memory impairment in zebrafish (Richetti et al., 2011). Other studies on the effects of quercetin on memory impairment are presented in Table 1.

Oral administration of quercetin (10 mg/kg, 90 days) modified the effects of deltamethrin (DLM), a model of neurotoxicity, on the increase in permeability and mitochondrial swelling, mitochondrial metabolite levels (proteins, lipids, and carbohydrates), enzyme activity (glutathione S-transferase [GST] and superoxide dismutase), amount of cytochrome c and caspase-3, and MDA acid levels caused by DLM in the hippocampus and striatum of rats. Furthermore, the histological results confirmed the protective effects of quercetin on brain cells in the hippocampus and striatum (Gasmi et al., 2017).

Quercetin (50 mg/kg, p.o., 30 days) increased the levels of antioxidant enzymes, including SOD, catalase, GPx, GST, and glutathione reductase in response to polychlorinated biphenyls (PCBs) when used as a neurotoxic agent in the rat hippocampus. It also attenuated learning and memory impairment, anxiety, and stress, and lowered the elevated levels of hydrogen peroxide, hydroxyl radicals, MDA, and the thiobarbituric acid reactive substances induced by PCBs (Selvakumar et al., 2013).

Quercetin (30 mg/kg, p.o., 21 days) ameliorated the cognitive impairment induced by chronic unpredicted stress (CUS) by improving hippocampal insulin signaling and upregulating neuronal GLUT4 (Mehta, Parashar, Sharma, Singh, & Udayabanu, 2017a). Additionally, quercetin (30 mg/kg, p.o., 21 days) reversed all of the effects of CUS on anxiety, depression, short- and LTM impairment, locomotor dysfunction, neural damage, and decreased the levels of oxidative stress markers and proinflammatory cytokines in mice (Mehta, Parashar, & Udayabanu, 2017b). In a similar study that used a CUS model, quercetin (40 and 80 mg/kg, p.o., 28 days) treatment improved memory impairment, decreased the levels of malondialdehyde (MDA), nitrite, corticosterone, AChE, and tumor necrosis factor, and increased the reduced levels of catalase, superoxide dismutase (SOD), and glutathione (GSH) in mice. Coadministration of piperine (20 mg/kg, p.o.) with quercetin enhanced the effectiveness of quercetin, even at a low dose (Rinwa & Kumar, 2017).

Exposure of *Lymnaea stagnalis*, a pond snail, to a heat stressor (1 hr at 30 °C) enhanced LTM formation via DNA methylation and the activation of heat shock proteins (HSPs). Quercetin (100 μmol/L) has been shown to prevent the stressor-induced enhancement of LTM formation by inhibiting the production of HSPs. It has been suggested that quercetin is effective in controlling the negative effects of stressors on memory formation. However, this effect was not produced by epicatechin, another flavonoid (Sunada et al., 2016). Querectin (50 mg/kg) ameliorated learning and memory impairment and the glutathione peroxidase (GPx) activity induced by restraint stress caused by the placement of rats in well-ventilated plexiglass tubes. It also reduced corticosterone and MDA. Quercetin returned the elevated levels of SOD to normal values (Mohammadi, Goudarzi, Lashkarbolouki, Abrari, & Elahdadi Salmani, 2014).

Quercetin (5, 25, or 50 mg/kg, p.o., 45 days) prevented the effects induced by cadmium (Cd) exposure, including memory impairment, anxiogenic effects, the decrement of total thiols (T-SHs) and reduced GSH levels, the reduction of AChE, Na^+, K^+-ATPase, δ-aminolevulinic acid dehydratase, and glutathione reductase activities, and the increment of ROS production, TBRS levels, protein carbonyl content, double-stranded DNA fractions, and GST activity in the cerebral cortex and hippocampus (Abdalla et al., 2014). Furthermore, the spatial, retention, and acquisition memory improved in pups which were exposed to quercetin (50 or 100 mg/kg, i.p., 7 d) and Cd through breast milk (Halder et al., 2016a). Similar effects of quercetin have been reported in pups that received chromium (Halder et al., 2016b).

Animal models for other medical conditions involving memory impairment

Chronic administration of quercetin (20 mg/kg, i.p., 28 days) improved spatial learning and memory and motor coordination in aged rats. Quercetin also increased 5-hydroxytryptophan and 5-hydroxytryptamine levels, and caused elevated tryptophan hydroxylase activity and decreased 5-hydroxyindoleacetic levels, suggesting an inhibitory effect on the MAO-A enzyme. It also ameliorated the age-related reduction in the levels of dopa, dopamine, and noradrenaline, thereby increasing tyrosine hydroxylase activity. Quercetin treatment modified the age-related reduction in the Sirt1 level and increased the level of acetylated NF-κB (Sarubbo et al., 2018).

Pretreatment with quercetin (5, 25, and 50 mg/kg, p.o., 30 days) has been shown to prevent memory impairment in poloxamer-407-induced hyperlipidemic rats, increase the recognition index, and prevent AChE activity from decreasing in the hippocampus. Furthermore, pretreatment with quercetin decreased the total cholesterol and increased HDL cholesterol levels in hyperlipimedic rats (Braun et al., 2017).

In mice that received a high-fat diet, supplementation with a high dose of quercetin (17 mg/kg, p.o., 13 weeks) improved learning and memory impairment, as well as the expression of phosphatidylinositol-4,5-bisphosphate 3-kinase, Akt, nuclear factor E2-related factor 2 (NRF2), CREB, and BDNF. In addition, a high dose of quercetin preserved the normal levels of total antioxidant capacity, SOD, and catalase activity. It also reduced the oxidative damage induced by ROS and MDA (Xia et al., 2015).

Quercetin (5 mg/kg, i.p., 14 days) partially reversed the learning and memory impairment induced by ischemia in rats. Furthermore, quercetin (0.3, 3, and 30 μM) inhibited voltage-dependent sodium channels dose-dependently in hippocampal CA1 pyramidal neurons. These data suggest that its neuroprotective effects may be related to sodium channel blockade (Yao, Han, Zhang, & Yang, 2010). Complementary to these results, administration of quercetin (20 mg/kg, i.p., 7 days) prior to ischemia relieved the neurological deficits, memory impairment, motor dysfunction, and cerebral infarct formation induced by ischemia by increasing the reduced levels of catalase, SOD, and GSH, and decreasing the MDA levels (Viswanatha, Shylaja, & Mohan, 2013). Furthermore, pretreatment with quercetin (100 mg/kg, i.p.) 2 hr before bilateral carotid artery occlusion alleviated the anxiety-like behaviors, learning and memory impairment, and neuronal apoptosis induced by cerebral ischemia-reperfusion injury in mice. Quercetin inhibited apoptosis by increasing the levels of phosphorylated Akt (p-Akt) and decreasing the levels of p-ASK1, p-JNK3, p-c-Jun, and cleaved caspase-3. These results suggest that quercetin exerts a neuroprotective effect via activation of the Akt signaling pathway and inhibition of the JNK signaling pathway (Pei et al., 2016).

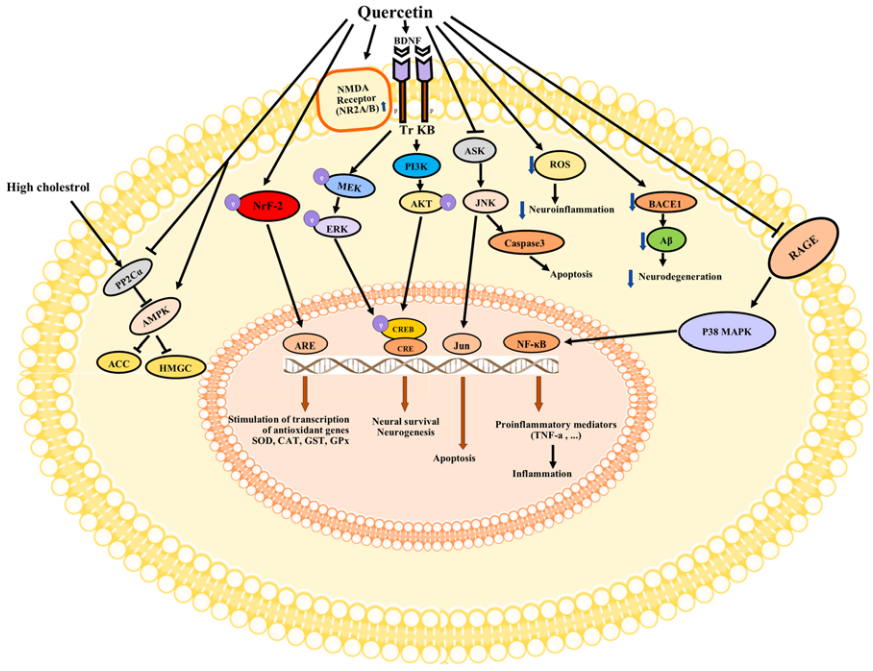

Figure 3–Possible molecular mechanisms of quercetin in improvement of memory impairment. Aβ, amyloid β; ACC, Acetyl-CoA carboxylase; Akt, protein kinase B; ARE, antioxidant responsive element; AMPK, AMP-activated protein kinase; ASK1, apoptosis signal-regulating kinase 1; BACE1, beta-amyloid converting enzyme 1; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element binding protein; CAT, catalase; ERK, extracellular-signal-regulated kinase; GST, glutathione s-transferase; GPx, glutathione peroxidase; HMGCR, HMG-CoA reductase; JNK, Jun amino-terminal kinases; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; NMDA receptor, N-methyl-D-aspartate receptor; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2 [NF-E2]-related factor 2; PI3K, phosphoinositide 3-kinase; PP2Cα, protein phosphatase 2Cα; RAGE, receptor for advanced glycation end-products (AGE); ROS, reactive oxygen species; SOD, super oxide dismutase; TrkB, tropomyosin receptor kinase B (tyrosine receptor kinase B).

Administration of quercetin (50 mg/kg, p.o.) during 7 days of exposure to hypobaric hypoxia in rats improved memory impairment and elevated the reduced GSH levels, glutathione reductase and SOD activity, and decreased GPx activity, caspase 3 expression, ROS levels, and LPO. It also decreased the number of pyknotic cells and Fluoro Jade B-positive neurons in the CA3 area of the hippocampus (Prasad et al., 2013). Similarly, quercetin (100 mg/kg/d, p.o., 7 days) ameliorated memory impairment and hippocampal mitochondrial and synaptic lesions in a hypobaric hypoxia-model by increasing the expression of sirtuin 1 (Sirt1), peroxisome proliferator-activated receptor-gamma coactivator-1alpha, fibronectin type III domain-containing protein 5 (FNDC5), and BDNF. Furthermore, it increased the expression of mitochondrial biogenesis-related proteins, nuclear respiratory factor 1 (Nrf1), and mitochondrial transcription factor A (Tfam), the enzyme activity of respiratory chain complexes, fusion-related proteins Mitofusin 1 and 2 (Mfn1 and Mfn2), and decreased the expression of fission-related proteins Drp1 (Dynamin-related protein 1) and Fission 1 homolog (Fis1). Overall, these data suggest that quercetin enhances mitochondrial biogenesis and modulates mitochondrial dynamics (Liu et al., 2015).

Function of the metabolic forms of quercetin in the brain

Quercetin-3-O-glucuronide, a bioactive dietary compound, has shown several beneficial effects against AD at different concentrations, including the inhibition of Aβ peptide production and the activation of P-CREB in corticohippocampal neuron cultures generated from TG2576 AD mice. It has also been shown to improve long-term potentiation and basal synaptic transmission in hippocampal slices from TG2576 AD mice (Ho et al., 2013). Similarly, as a metabolite of polyphenols in brain, quercetin-3-O-glucuronide promoted the phosphorylation of CaMKII/CREB in an SD model of memory impairment in a dietary polyphenol preparation (Concord grape juice + grape seed extract + resveratrol) (Zhao et al., 2015). Additionally, quercetin-3-O-glucuronide (100 mg/kg, i.p., 14 days) improved memory impairment in a scopolamine model in mice. It increased neural stem cell proliferation and mobilization *in vitro* by enhancing the phosphorylation of Akt and expression of cyclin D1, BDNF, and CXCR4 (Baral, Pariyar, Kim, Lee, & Seo, 2017).

Alternate effects of quercetin on memory

Acute administration of quercetin at doses of 10, 20, and 40 mg/kg in mice was found to impair learning and memory and reduce the expression of phosphorylated Akt, phosphorylated calcium-calmodulin kinase II (pCaMKII), and phosphorylated CREB in hippocampal tissue (Jung et al., 2010).

Human studies

A large community study was conducted in which 1002 residents from western North Carolina were treated with quercetin supplementation (500 or 1000 mg/d, 12 weeks). The results indicated that quercetin had no significant effects on memory, psychomotor speed, reaction time, attention, or cognitive flexibility (Broman-Fulks, Canu, Trout, & Nieman, 2012). Early-stage AD patients who consumed 18 g of onion powder containing quercetin glycosides, equivalent to 80 mg quercetin aglycone (Quergold), for 4 weeks showed improved memory recall (Nakagawa et al., 2016).

Possible mechanism of quercetin's action on memory

As the literature review of animal studies shows, several mechanisms have been suggested as to the possible positive mechanism of quercetin's effects on memory, including the activation of the ERK/CREB/BDNF, Nrf2-ARE, Akt, AMPK signaling pathways or NMDA receptors, and the inhibition of the Ask/JNK/Jun, RAGE signaling pathway, and PP2Cα (Dong et al., 2017; Liu et al., 2013; Martínez de Morentin et al., 2010; Pei et al., 2016; Tongjaroenbuangam et al., 2011; Xia et al., 2015). Refer to Figure 3 for more details on the potential signaling pathways of quercetin.

Conclusion

As the importance of dietary quercetin consumption and its use as a supplement is increasing, this review aimed at summarizing the animal studies that have used quercetin to treat memory impairment in different models of dementia, including models of AD as well as other diseases. In recent years, new formulations of quercetin have been developed that improved its bioavailability in some animal studies. Furthermore, it seems that quercetin-3-O-glucoronide, the major compound found in the animal brain, has a role in non-human studies of AD, unlike quercetin aglycon. Therefore, efforts should focus on finding a reliable formulation of quercetin or active metabolites that can enter the brain. Additionally, translational research is needed to apply the findings of basic science research to clinical research and 1 day be able to prevent or treat AD or other types of dementia in humans. Access to additional data will provide new insights on the role of quercetin and other similar compounds in health and the prevention and treatment of AD in humans.

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Author Contributions

M. Nassiri-Asl designed, wrote, and revised the manuscript. F. Babaei and M. Mirzababaei collected the data and wrote the draft of manuscript.

References

Abdalla, F. H., Schmatz, R., Cardoso, A. M., Carvalho, F. B., Baldissarelli, J., de Oliveira, J. S., & Mazzanti, C. M. (2014). Quercetin protects the impairment of memory and anxiogenic-like behavior in rats exposed to cadmium: Possible involvement of the acetylcholinesterase and Na+,K+-ATPase activities. *Physiology and Behavior*, *135*, 152–167. https://doi.org/10.1016/j.physbeh.2014.06.008

Allgaier, M., & Allgaier, C. (2014). An update on drug treatment options of Alzheimer's disease. *Frontiers in Bioscience (Landmark Edition)*, *19*, 1345–1354.

Arlt, S. (2013). Non-Alzheimer's disease-related memory impairment and dementia. *Dialogues in Clinical Neuroscience*, *15*(4), 465–473.

Arts, I. C., Sesink, A. L., Faassen-Peters, M., & Hollman, P. C. (2004). The type of sugar moiety is a major determinant of the small intestinal uptake and subsequent biliary excretion of dietary quercetin glycosides. *The British Journal of Nutrition*, *91*(6), 841–847.

Ashrafpour, M., Parsaei, S., & Sepehri, H. (2015). Quercetin improved spatial memory dysfunctions in rat model of intracerebroventricular streptozotocin-induced sporadic Alzheimer's disease. *National Journal of Physiology, Pharmacy and Pharmacology*, *5*(5), 411–415. https://doi.org/10.5455/njppp.2015.5.2308201563

Baral, S., Pariyar, R., Kim, J., Lee, H. S., & Seo, J. (2017). Quercetin-3-O-glucuronide promotes the proliferation and migration of neural stem cells. *Neurobiology of Aging*, *52*, 39–52. https://doi.org/10.1016/j.neurobiolaging.2016.12.024

Barreca, D., Bellocco, E., D'Onofrio, G., Nabavi, S. F., Daglia, M., Rastrelli, L., & Nabavi, S. M. (2016). Neuroprotective effects of quercetin: From chemistry to medicine. *CNS and Neurological Disorders and Drug Targets*, *15*(8), 964–975. https://doi.org/10.2174/1871527315666160813175406

Bhutada, P., Mundhada, Y., Bansod, K., Bhutada, C., Tawari, S., Dixit, P., & Mundhada, D. (2010). Ameliorative effect of quercetin on memory dysfunction in streptozotocin-induced diabetic rats. *Neurobiology of Learning and Memory*, *94*(3), 293–302. https://doi.org/10.1016/j.nlm.2010.06.008

Braun, J. B. S., Ruchel, J. B., Adefegha, S. A., Coelho, A. P.V., Trelles, K. B., Signor, C., . . . Leal, D. B. R. (2017). Neuroprotective effects of pretreatment with quercetin as assessed by acetylcholinesterase assay and behavioral testing in poloxamer-407 induced hyperlipidemic rats. *Biomedicine and Pharmacotherapy*, *88*, 1054–1063. https://doi.org/10.1016/j.biopha.2017.01.134

Broman-Fulks, J. J., Canu, W. H., Trout, K. L., & Nieman, D. C. (2012). The effects of quercetin supplementation on cognitive functioning in a community sample: A randomized, placebo-controlled trial. *Therapeutic Advances Psychopharmacology*, *2*(4), 131–138. https://doi.org/10.1177/2045125312445894

Bui, T. T., & Nguyen, T. H. (2017). Natural product for the treatment of Alzheimer's disease. *Journal of Basic and Clinical Physiology and Pharmacology*, *28*(5), 413–423. https://doi.org/10.1515/jbcpp-2016-0147

Chavant, F., Favrelière, S., Chebassier, C. L., Plazanet, C., & Pochat, M. C. P. (2011). Memory disorders associated with consumption of drugs: Updating through a case/noncase study in the French PharmacoVigilance Database. *British Journal of Clinical Pharmacology*, *72*(6), 898–904. https://doi.org/10.1111/j.1365-2125.2011.04009.x

Choi, G. N., Kim, J. H., Kwak, J. H., Jeong, C. H., Jeong, H. R., Lee, U., & Heo, H. J. (2012). Effect of quercetin on learning and memory performance in ICR mice under neurotoxic trimethyltin exposure. *Food Chemistry*, *132*(2), 1019–1024. https://doi.org/10.1016/j.foodchem.2011.11.089

Costa, L. G., Garrick, J. M., Roquè, P. J., & Pellacani, C. (2016). Mechanisms of neuroprotection by quercetin: Counteracting oxidative stress and more. *Oxidative Medicine and Cellular Longevity*, *2016*(2016), 2986796. https://doi.org/10.1155/2016/2986796

D'Andrea, G. (2015). Quercetin: A flavonol with multifaceted therapeutic applications? *Fitoterapia*, *106*, 256–271. https://doi.org/10.1016/j.fitote.2015.09.018

Dajas, F., Abin-Carriquiry, J. A., Arredondo, F., Blasina, F., Echeverry, C., Martínez, M., . . . Vaamonde, L. (2015). Quercetin in brain diseases: Potential and limits. *Neurochemistry International*, *89*, 140–148. https://doi.org/10.1016/j.neuint.2015.07.002

David, A. V. A., Arulmoli, R., & Parasuraman, S. (2016). Overviews of biological importance of quercetin: A bioactive flavonoid. *Pharmacognosy Review*, *10*(20), 84–89. https://doi.org/10.4103/0973-7847.194044

Day, A. J., Gee, J. M., DuPont, M. S., Johnson, I. T., & Williamson, G. (2003). Absorption of quercetin-3-glucoside and quercetin-4′-glucoside in the rat small intestine: The role of lactase phlorizin hydrolase and the sodium-dependent glucose transporter. *Biochemical Pharmacology*, *65*(7), 1199–1206. https://doi.org/10.1016/S0006-2952(03)00039-X

Dong, F., Wang, S., Wang, Y., Yang, X., Jiang, J., Wu, D., . . . Yao, R. (2017). Quercetin ameliorates learning and memory via the Nrf2-ARE signaling pathway in d-galactose-induced neurotoxicity in mice. *Biochemical and Biophysical Research Communications*, *491*(3), 636–641. https://doi.org/10.1016/j.bbrc.2017.07.151

Facchinetti, R., Bronzuoli, M. R., & Scuderi, C. (2018). An animal model of Alzheimer disease based on the intrahippocampal injection of amyloid β-peptide (1–42). *Methods in Molecular Biology*, *1727*, 343–352. https://doi.org/10.1007/978-1-4939-7571-6_25

Falvey, C. M., Rosano, C., Simonsick, E. M., Harris, T., Strotmeyer, E. S., Satterfield, S., & Yaffe, K. (2013). Macro- and microstructural magnetic resonance imaging indices associated with diabetes among community-dwelling older adults. *Diabetes Care*, *36*(3), 677–682. https://doi.org/10.2337/dc12-0814

Felician, O., Tramoni, E., & Bartolomei, F. (2015). Transient epileptic amnesia: Update on a slowly emerging epileptic syndrome. *Revue Neurologique (Paris)*, *171*(3), 289–297. https://doi.org/10.1016/j.neurol.2014.11.010

Gasmi, S., Rouabhi, R., Kebieche, M., Boussekine, S., Salmi, A., Toualbia, N., . . . Djabri, B. (2017). Effects of deltamethrin on striatum and hippocampus mitochondrial integrity and the protective role of quercetin in rats. *Environmental Science and Pollution Research International*, *24*(19), 16440–16457. https://doi.org/10.1007/s11356-017-9218-8

Goldman, J. G., Weis, H., Stebbins, G., Bernard, B., & Goetz, C. G. (2012). Clinical differences among mild cognitive impairment subtypes in Parkinson's disease. *Movment Disorders*, *27*(9), 1129–1136. https://doi.org/10.1002/mds.25062

Guo, Y., & Bruno, R. S. (2016). Endogenous and exogenous mediators of quercetin bioavailability. *The Journal of Nutritional Biochemistry*, *26*(3), 201–210. https://doi.org/10.1016/j.jnutbio.2014.10.008

Halder, S., Kar, R., Galav, V., Mehta, A. K., Bhattacharya, S. K., Mediratta, P. K., & Banerjee, B. D. (2016a). Cadmium exposure during lactation causes learning and memory-impairment in F1 generation mice: Amelioration by quercetin. *Drug and Chemical Toxicology*, *39*(3), 272–278. https://doi.org/10.3109/01480545.2015.1092042

Halder, S., Kar, R., Mehta, A. K., Bhattacharya, S. K., Mediratta, P. K., & Banerjee, B. D. (2016b). Quercetin modulates the effects of chromium exposure on learning, memory and antioxidant enzyme activity in F1 generation mice. *Biological Trace Element Research*, *171*(2), 391–398. https://doi.org/10.1007/s12011-015-0544-8

Hayakawa, M., Itoh, M., Ohta, K., Li, S., Ueda, M., Wang, M. X., . . . Nakagawa, T. (2015). Quercetin reduces eIF2α phosphorylation by GADD34 induction. *Neurobiology of Aging*, *36*(9), 2509–2518. https://doi.org/10.1016/j.neurobiolaging.2015.05.006

Ho, L., Ferruzzi, M. G., Janle, E. M., Wang, J., Gong, B., Chen, T. Y., . . . Pasinetti, G. M. (2013). Identification of brain-targeted bioactive dietary quercetin-3-O-glucuronide as a novel intervention for Alzheimer's disease. *The FASEB Journal*, *27*(2), 769–781. https://doi.org/10.1096/fj.12-212118

Huebbe, P., Wagner, A. E., Boesch-Saadatmandi, C., Sellmer, F., Wolffram, S., & Rimbach, G. (2010). Effect of dietary quercetin on brain quercetin levels and the expression of antioxidant and Alzheimer's disease relevant genes in mice. *Pharmacological Research*, *61*(3), 242–246. https://doi.org/10.1016/j.phrs.2009.08.006

Ishisaka, A., Ichikawa, S., Sakakibara, H., Piskula, M. K., Nakamura, T., Kato, Y., . . . Terao, J. (2011). Accumulation of orally administered quercetin in brain tissue and its antioxidative effects in rats. *Free Radical Biology and Medicine*, *51*(7), 1329–1336. https://doi.org/10.1016/j.freeradbiomed.2011.06.017

Jablonski, M., Maciejewski, R., Januszewski, S., Ulamek, M., & Pluta, R. (2011). One year follow up in ischemic brain injury and the role of Alzheimer factors. *Physiological Research*, *60*(Suppl 1), S113–S119.

Jung, W. Y., Park, S. J., Park, D. H., Kim, J. M., Kim, D. H., & Ryu, J. H. (2010). Quercetin impairs learning and memory in normal mice via suppression of hippocampal phosphorylated cyclic AMP response element-binding protein expression. *Toxicology Letters*, *197*(2), 97–105. https://doi.org/10.1016/j.toxlet.2010.05.001

Kim, J. H., Lee, J., Lee, S., & Cho, E. J. (2016). Quercetin and quercetin-3-β-D-glucoside improve cognitive and memory function in Alzheimer's disease mouse. *Applied Biological Chemistry*, *59*(5), 721–728. https://doi.org/10.1007/s13765-016-0217-0

Li, Y. L., Guo, H., Zhao, Y. Q., Li, A. F., Ren, Y. Q., & Zhang, J. W. (2017). Quercetin protects neuronal cells from oxidative stress and cognitive degradation induced by amyloid β-peptide treatment. *Molecular Medicine Reports*, *16*(2), 1573–1577. https://doi.org/10.3892/mmr.2017.6704

Liu, P., Zou, D., Yi, L., Chen, M., Gao, Y., Zhou, R., . . . Mi, M. (2015). Quercetin ameliorates hypobaric hypoxia-induced memory impairment through mitochondrial and neuron function adaptation via the PGC-1α pathway. *Restorative Neurology and Neuroscience*, *33*(2), 143–157. https://doi.org/10.3233/RNN-140446

Liu, R., Zhang, T. T., Zhou, D., Bai, X. Y., Zhou, W. L., Huang, C., . . . Du, G. H. (2013). Quercetin protects against the Aβ(25–35)-induced amnesic injury: Involvement of inactivation of rage-mediated pathway and conservation of the NVU. *Neuropharmacology*, *67*, 419–431. https://doi.org/10.1016/j.neuropharm.2012.11.018

Maciel, R. M., Carvalho, F. B., Olabiyi, A. A., Schmatz, R., Gutierres, J. M., Stefanello, N., . . . Lopes, S. T. (2016). Neuroprotective effects of quercetin on memory and anxiogenic-like behavior in diabetic rats: Role of ectonucleotidases and acetylcholinesterase activities. *Biomedicine and Pharmacotherapy*, *84*, 559–568. https://doi.org/10.1016/j.biopha.2016.09.069

Manach, C., Williamson, G., Morand, C., Scalbert, A., & Rémésy, C. (2005). Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *The American Journal of Clinical Nutrition*, *81*(1 Suppl), 230S–242S.

Martínez de Morentin, P. B., González, C. R., & López, M. (2010). AMP-activated protein kinase: 'a cup of tea' against cholesterol-induced neurotoxicity. *The Journal of Pathology*, *222*(4), 329–334. https://doi.org/10.1002/path.2778

Mehta, V., Parashar, A., Sharma, A., Singh, T. R., & Udayabanu, M. (2017a). Quercetin ameliorates chronic unpredicted stress-mediated memory dysfunction in male Swiss albino mice by attenuating insulin resistance and elevating hippocampal GLUT4 levels independent of insulin receptor expression. *Hormones & Behavior*, *89*, 13–22. https://doi.org/10.1016/j.yhbeh.2016.12.012

Mehta, V., Parashar, A., & Udayabanu, M. (2017b). Quercetin prevents chronic unpredictable stress induced behavioral dysfunction in mice by alleviating hippocampal oxidative and inflammatory stress. *Physiology and Behavior*, *171*, 69–78. https://doi.org/10.1016/j.physbeh.2017.01.006

Mohammadi, H. S., Goudarzi, I., Lashkarbolouki, T., Abrari, K., & Elahdadi Salmani, M. (2014). Chronic administration of quercetin prevent spatial learning and memory deficits provoked by chronic stress in rats. *Behavioural Brain Research*, *270*, 196–205. https://doi.org/10.1016/j.bbr.2014.05.015

Moreno, L. C. G.EI., Puerta, E., Suárez-Santiago, J. E., Santos-Magalhães, N. S., Ramirez, M. J., & Irache, J. M. (2017). Effect of the oral administration of nanoencapsulated quercetin on a mouse model of Alzheimer's disease. *International Journal of Pharmaceutics*, *517*(1–2), 50–57. https://doi.org/10.1016/j.ijpharm.2016.11.061

Mullen, W., Rouanet, J. M., Auger, C., Teissèdre, P. L., Caldwell, S. T., Hartley, R. C., . . . Crozier, A. (2008). Bioavailability of [2-(14)C]quercetin-4′-glucoside in rats. *Journal of Agricultural and Food Chemistry*, *56*(24), 12127–12137. https://doi.org/10.1021/jf802754s

Nakagawa, T., Itoh, M., Ohta, K., Hayashi, Y., Hayakawa, M., Yamada, Y., . . . Inuzuka, T. (2016). Improvement of memory recall by quercetin in rodent contextual fear conditioning and human early stage Alzheimer's disease patients. *Neuroreport*, *27*(9), 671–676. https://doi.org/10.1097/WNR.0000000000000594

Nassiri-Asl, M., Moghbelinejad, S., Abbasi, E., Yonesi, F., Haghighi, M. R., Lotfizadeh, M., & Bazahang, P. (2013). Effects of quercetin on oxidative stress and memory retrieval in kindled rats. *Epilepsy and Behavior*, *28*(2), 151–155. https://doi.org/10.1016/j.yebeh.2013.04.019

Nieoczym, D., Socała, K., Raszewski, G., & Wlaź, P. (2014). Effect of quercetin and rutin in some acute seizure models in mice. *Progress in Neuro-psychopharmacology and Biological Psychiatry*, *54*, 50–58. https://doi.org/10.1016/j.pnpbp.2014.05.007

Nouriziabari, B., Sarkar, S., Tanninen, S. E., Dayton, R. D., Klein, R. L., & Takehara-Nishiuchi, K. (2018). Aberrant cortical event-related potentials during associative learning in rat models for presymptomatic stages of Alzheimer's disease. *Journal of Alzheimer's Disease*, *63*(2), 725–740. https://doi.org/10.3233/JAD-171033

Pattanashetti, L. A., Taranalli, A. D., Parvatrao, V., Malabade, R. H., & Kumar, D. (2017). Evaluation of neuroprotective effect of quercetin with donepezil in scopolamine-induced amnesia in rats. *Indian Journal of Pharmacology*, *49*(1), 60–64. https://doi.org/10.4103/0253-7613.201016

Pei, B., Yang, M., Qi, X., Shen, X., Chen, X., & Zhang, F. (2016). Quercetin ameliorates ischemia/reperfusion-induced cognitive deficits by inhibiting ASK1/JNK3/caspase-3 by enhancing the Akt signaling pathway. *Biochemical and Biophysical Research Communications*, *478*(1), 199–205. https://doi.org/10.1016/j.bbrc.2016.07.068

Prasad, J., Baitharu, I., Sharma, A. K., Dutta, R., Prasad, D., & Singh, S. B. (2013). Quercetin reverses hypobaric hypoxia-induced hippocampal neurodegeneration and improves memory function in the rat. *High Altitude Medicine and Biology*, *14*(4), 383–394. https://doi.org/10.1089/ham.2013.1014

Prince, M., Wimo, A., Guerchet, M., Ali, G. C., Wu, Y. T., & Prina, M. (2015). World Alzheimer Report 2015. The global impact of dementia: An analysis of prevalence, incidence, cost and trends. *Alzheimer's Disease International*, Retrieved from https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf

Richetti, S. K., Blank, M., Capiotti, K. M., Piato, A. L., Bogo, M. R., Vianna, M. R., & Bonan, C. D. (2011). Quercetin and rutin prevent scopolamine-induced memory impairment in zebrafish. *Behavioural Brain Research*, *217*(1), 10–15. https://doi.org/10.1016/j.bbr.2010.09.027

Rinwa, P., & Kumar, A. (2017). Quercetin along with piperine prevents cognitive dysfunction, oxidative stress and neuro-inflammation associated with mouse model of chronic unpredictable stress. *Archives of Pharmacal Research*, *40*(10), 1166–1175. https://doi.org/10.1007/s12272-013-0205-4

Ross, J. A., & Kasum, C. M. (2002). Dietary flavonoids: Bioavailability, metabolic effects, and safety. *Annual Review of Nutrition*, *22*, 19–34. https://doi.org/10.1146/'annurev.nutr.22.111401.144957

Ruan, Q., Ruan, J., Zhang, W., Qian, F., & Yu, Z. (2018). Targeting NAD+ degradation: The therapeutic potential of flavonoids for Alzheimer's disease and cognitive frailty. *Pharmacological Research*, *128*, 345–358. https://doi.org/10.1016/j.phrs.2017.08.010

Russo, M., Spagnuolo, C., Tedesco, I., Bilotto, S., & Russo, G. L. (2012). The flavonoid quercetin in disease prevention and therapy: Facts and fancies. *Biochemical Pharmacology*, *83*(1), 6–15. https://doi.org/10.1016/j.bcp.2011.08.010

Sabogal-Guáqueta, A. M., Muñoz-Manco, J. I., Ramírez-Pineda, J. R., Lamprea-Rodriguez, M., Osorio, E., & Cardona-Gómez, G. P. (2015). The flavonoid quercetin ameliorates Alzheimer's disease pathology and protects cognitive and emotional function in aged triple transgenic Alzheimer's disease model mice. *Neuropharmacology*, *93*, 134–145. https://doi.org/10.1016/j.neuropharm.2015.01.027

Sachdeva, A., Chandra, M., Choudhary, M., Dayal, P., & Anand, K. S. (2016). Alcohol-related dementia and neurocognitive impairment: A review study. *International Journal of High Risk Behaviors and Addiction*, *5*(3), e27976. https://doi.org/10.5812/ijhrba.27976

Sarubbo, F., Ramis, M. R., Kienzer, C., Aparicio, S., Esteban, S., Miralles, A., & Moranta, D. (2018). Chronic silymarin, quercetin and naringenin treatments increase monoamines synthesis and hippocampal Sirt1 levels improving cognition in aged rats. *Journal of Neuroimmune Pharmacology*, *13*(1), 24–38. https://doi.org/10.1007/s11481-017-9759-0

Selvakumar, K., Bavithra, S., Ganesh, L., Krishnamoorthy, G., Venkataraman, P., & Arunakaran, J. (2013). Polychlorinated biphenyls induced oxidative stress mediated neurodegeneration in hippocampus and behavioral changes of adult rats: Anxiolytic-like effects of quercetin. *Toxicology Letters*, *222*(1), 45–54. https://doi.org/10.1016/j.toxlet.201q3.06.237

Sorbi, S., Hort, J., Erkinjuntti, T., Fladby, T., Gainotti, G., Gurvit, H., . . . Scheltens, P. (2012). EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. *European Journal of Neurology*, *19*(9), 1159–1179. https://doi.org/10.1111/j.1468-1331.2012.03784.x

Sriraksa, N., Wattanathorn, J., Muchimapura, S., Tiamkao, S., Brown, K., & Chaisiwamongkol, K. (2012). Cognitive-enhancing effect of quercetin in a rat model of Parkinson's disease induced by 6-hydroxydopamine. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 823206. https://doi.org/10.1155/2012/823206

Suganthy, N., Devi, K. P., Nabavi, S. F., Braidy, N., & Nabavi, S. M. (2016). Bioactive effects of quercetin in the central nervous system: Focusing on the mechanisms of actions. *Biomedicine and Pharmacotherapy*, *84*, 892–908. https://doi.org/10.1016/j.biopha.2016.10.011

Sun, D., Li, N., Zhang, W., Zhao, Z., Mou, Z., Huang, D., . . . Wang, W. (2016). Design of PLGA functionalized quercetin nanoparticles for potential use in Alzheimer's disease. *Colloids and Surfaces B Biointerfaces*, *148*, 116–129. https://doi.org/10.1016/j.colsurfb.2016.08.052

Sunada, H., Riaz, H., de Freitas, E., Lukowiak, K., Swinton, C., Swinton, E., . . . Lukowiak, K. (2016). Heat stress enhances LTM formation in *Lymnaea*: Role of HSPs and DNA methylation. *The Journal of Experimental Biology*, *219*(Pt 9), 1337–1345. https://doi.org/10.1242/jeb.134296

Sureda, A., Xavier, C., & Tejada, S. (2017). Neuroprotective effects of flavonoid compounds on neuronal death associated to Alzheimer's disease. *Current Medicinal Chemistry*, in press. https://doi.org/10.2174/0929867325666171226103237

Thilakarathna, S. H., & Rupasinghe, H. P. V. (2013). Flavonoid bioavailability and attempts for bioavailability enhancement. *Nutrients*, *5*(9), 3367–3387. https://doi.org/10.3390/nu5093367

Tongjaroenbuangam, W., Ruksee, N., Chantiratikul, P., Pakdeenarong, N., Kongbuntad, W., & Govitrapong, P. (2011). Neuroprotective effects of quercetin, rutin and okra (*Abelmoschus esculentus* Linn.) in dexamethasone-treated mice. *Neurochemistry International*, *59*(5), 677–685. https://doi.org/10.1016/j.neuint.2011.06.014

Tong-un, T., Wannanon, P., Wattanathorn, J., & Phachonpai, W. (2010). Cognitive-enhancing and antioxidant activities of quercetin liposomes in animal model of Alzheimer's disease. *OnLine Journal of Biological Sciences*, *10*(2), 84–91. https://doi.org/10.3844/ojbsci.2010.84.91

Tota, S., Awasthi, H., Kamat, P. K., Nath, C., & Hanif, K. (2010). Protective effect of quercetin against intracerebral streptozotocin induced reduction in cerebral blood flow and impairment of memory in mice. *Behavioural Brain Research*, *209*(1), 73–79. https://doi.org/10.1016/j.bbr.2010.01.017

Uriarte-Pueyo, I., & Calvo, M. (2011). Flavonoids as acetylcholinesterase inhibitors. *Current Medicinal Chemistry*, *18*(34), 5289–5302.

Viswanatha, G., Shylaja, H., & Mohan, C. G. (2013). Alleviation of transient global ischemia/reperfusion-induced brain injury in rats with 1,2,3,4,6-penta-O-galloyl-β-d-glucopyranose isolated from *Mangifera indica*. *European Journal of Pharmacology*, *720*(1–3), 286–293. https://doi.org/10.1016/j.ejphar.2013.10.016

Viswanatha, G. L., Kumar, L. M., Rafiq, M., Kavya, K. J., Thippeswamy, A. H., Yuvaraj, H. C., . . . Ramakrishnan, S. (2015). LC-MS/MS profiling and neuroprotective effects of Mentat® against transient global ischemia and reperfusion–induced brain injury in rats. *Nutrition*, *31*(7–8), 1008–1017. https://doi.org/10.1016/j.nut.2015.02.009

Wang, D. M., Li, S. Q., Wu, W. L., Zhu, X. Y., Wang, Y., & Yuan, H. Y. (2014). Effects of long-term treatment with quercetin on cognition and mitochondrial function in a mouse model of Alzheimer's disease. *Neurochemical Research*, *39*(8), 1533–1543. https://doi.org/10.1007/s11064-014-1343-x

Wang, W., Sun, C., Mao, L., Ma, P., Liu, F., Yang, J., & Gao, Y. (2016). The biological activities, chemical stability, metabolism and delivery systems of quercetin: A review. *Trends in Food Science and Technology*, *56*, 21–38. https://doi.org/10.1016/j.tifs.2016.07.004.

Wang, Y., Wang, M., Fan, K., Li, T., Yan, T., Wu, B., . . . Jia, Y. (2018). Protective effects of Alpinae Oxyphyllae Fructus extracts on lipopolysaccharide-induced animal model of Alzheimer's disease. *Journal of Ethnopharmacology*, *217*, 98–106. https://doi.org/10.1016/j.jep.2018.02.015

Wilson, D. L., Barnes, M., Ellett, L., Permezel, M., Jackson, M., & Crowe, S. F. (2011). Compromised verbal episodic memory with intact visual and procedural memory during pregnancy. *Journal of Clinical and Experimental Neuropsychology*, *33*(6), 680–691. https://doi.org/10.1080/13803395.2010.550604

Wu, Y. T., Beiser, A. S., Breteler, M. M. B., Fratiglioni, L., Helmer, C., Hendrie, H. C., . . . Brayne, C. (2017). The changing prevalence and incidence of dementia over time—Current evidence. *Nature Review Neurology*, *13*(6), 327–339. https://doi.org/10.1038/nrneurol.2017.63

Xia, S. F., Xie, Z. X., Qiao, Y., Li, L. R., Cheng, X. R., Tang, X., . . . Le, G. W. (2015). Differential effects of quercetin on hippocampus-dependent learning and memory in mice fed with different diets related with oxidative stress. *Physiology and Behavior*, *138*, 325–331. https://doi.org/10.1016/j.physbeh.2014.09.008

Yao, Y., Han, D. D., Zhang, T., & Yang, Z. (2010). Quercetin improves cognitive deficits in rats with chronic cerebral ischemia and inhibits voltage-dependent sodium channels in hippocampal CA1 pyramidal neurons. *Phytotherapy Research*, *24*(1), 136–140. https://doi.org/10.1002/ptr.2902

Zhao, W., Wang, J., Bi, W., Ferruzzi, M., Yemul, S., Freire, D., . . . Pasinetti, G. M. (2015). Novel application of brain-targeting polyphenol compounds in sleep deprivation-induced cognitive dysfunction. *Neurochemistry International*, *89*, 191–197. https://doi.org/10.1016/j.neuint.2015.07.023