Life Sciences 224 (2019) 109–119

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Molecular mechanisms underlying protective role of quercetin in attenuating Alzheimer's disease

Elizabeta Zaplatic[a], Muhammed Bule[b], Syed Zahid Ali Shah[c], Md. Sahab Uddin[d], Kamal Niaz[e,*]

[a] Faculty of Bioscience and Agri-Food and Environmental Technology, University of Teramo, 64100, Italy
[b] Department of Pharmacy, College of Medicine and Health Sciences, Ambo University, Ambo, Ethiopia
[c] Department of Pathology, Faculty of Veterinary Science, Cholistan University of Veterinary and Animal Sciences (CUVAS), Bahawalpur 63100, Pakistan
[d] Department of Pharmacy, Southeast University Dhaka, Bangladesh
[e] Department of Pharmacology and Toxicology, Faculty of Bio-Sciences, Cholistan University of Veterinary and Animal Sciences (CUVAS), Bahawalpur 63100, Pakistan

ARTICLE INFO

Keywords:
Quercetin
Alzheimer's disease
Reactive oxygen species
Oxidative stress

ABSTRACT

Quercetin belongs to the flavonoids family, which is present in most of the plants including fruits, vegetables, green tea and even in red wine having antioxidant activities. It is available as a food supplement in the market and has physiological health effects. Quercetin has anti-inflammatory, anticancer and anti-prostate activities along with its beneficial effects on high cholesterol, kidney transplantation, asthma, diabetes, viral infections, pulmonary, schizophrenia and cardiovascular diseases. Quercetin possesses scavenging potential of hydroxyl radical (OH^-), hydrogen peroxide (H_2O_2), and superoxide anion (O_2^-). These reactive oxygen species (ROS) hampers lipid, protein, amino acids and deoxyribonucleic acid (DNA) processing leading to epigenetic alterations. Quercetin has the ability to combat these harmful effects. ROS plays a vital role in the progression of Alzheimer's disease (AD), and we propose that quercetin would be the best choice to overcome cellular and molecular signals in regulating normal physiological functions. However, data are not well documented regarding exact cellular mechanisms of quercetin. The neuroprotective effects of quercetin are mainly due to potential up- and/or down-regulation of cytokines via nuclear factor (erythroid-derived 2)-like 2 (Nrf2), Paraoxonase-2, c-Jun N-terminal kinase (JNK), Protein kinase C, Mitogen-activated protein kinase (MAPK) signalling cascades, and PI3K/Akt pathways. Therefore, the aim of the present review was to elaborate on the cellular and molecular mechanisms of the quercetin involved in the protection against AD.

1. Introduction

Quercetin is a polar inhibitor of auxin transport, and named after quercetum (oak forest, Quercus) since 1857. Quercetin is a member of the flavonols, compounds belonging to the class of flavonoids with 3-hydroxyflavone backbone [1]. A number of beneficial health effects of quercetin acting via modulating signalling pathways and gene expressions have been demonstrated in cell and animal models [2]. In particular, the antioxidant potential of quercetin studied both in in vitro (muscle progenitor cells) and in vivo models (rodent models) showed the effect of increasing the mitochondrial activity along with suppressing atrophic factors (transcript levels of adipogenic markers, such as peroxisome proliferator-activated receptor-γ and fatty acid binding protein-4) [3]. Structurally, the antioxidant and strong chelating actions of quercetin are the result of catechol groups in the ring B and free hydroxyl group (OH^-) of the A and/or ring [4]. Moreover, quercetin has different health or pharmacological actions including anti-inflammatory, anticancer, anti-diabetic, neuroprotective, cardioprotective, prophylaxis of osteoporosis and anti-allergic [5].

Scientific community developed a strong interest in studying quercetin mainly due to the fact of its widespread availability amongst dietary sources and its contribution in about 75% of the total flavonols intake. Quercetin is mainly found in barks and rinds and is known for providing characteristic colors to fruits and vegetables [4]. Vegetables, fruits, and nuts mainly contain quercetin glycosides (quercetin aglycone conjugated to sugar) [6]. In plants, it exists in various glycosidic forms, where rutin or quercetin- 3-rutinoside (quercetin-3-rhamnoglucoside) is the most abundant. Onions contain a good quantity of flavonols, which is estimated up to 1.3 g/kg d.m [7]. Dietary quercetin is mostly bound to glucose molecules. For instance, in onions it is found as quercetin-4V-glucoside and quercetin-3,4V-glucoside, as well as quercetin galactosides and arabinosides in apple and in berries respectively. In addition, other flavonols are also available such as kaempferol, myricetin and isorhamnetin in broccoli, berries, and onions respectively [8]. Being a

* Corresponding author.
E-mail addresses: kniaz@unite.it, kamalniaz1989@gmail.com (K. Niaz).

https://doi.org/10.1016/j.lfs.2019.03.055
Received 22 January 2019; Received in revised form 22 March 2019; Accepted 22 March 2019
Available online 23 March 2019

good source of quercetin, apple and apple pomace comprises of 3-glycosylated derivatives containing glucose, galactose, rhamnose, xylose and arabinose at the 3-position of quercetin [9]. Different studies recommended various daily intakes, however, as a dietary supplement, commonly quercetin is taken at 200–1200 mg of the daily recommended dose. In dietary supplements, recommended daily doses of quercetin in the form of aglycone is 500 mg commonly, however exceeding up to 1000 mg, while in functional foods its amount is between 10 and 25 mg per serving. Data on the safety of quercetin highly supports its inclusion in food items and dietary supplements [2].

Understanding the fate of quercetin in the organism is a major step towards unraveling the underlying mechanisms of its biological activities. In this regard, studying the bioavailability, metabolism and measuring the exposure of the organism to quercetin is important in determining its physiological functions [10]. Earlier studies suggested poor oral bioavailability of quercetin after oral administration (~2%), however, recent studies using radiolabeled quercetin aglycone administered to measure the absolute bioavailability estimated it to be about 44.8% [1]. It has also been reported that conjugation with glycosides considerably facilitates quercetin absorption. Thus, it can be concluded that increased quercetin glycosides absorption is related to deglycosylation and/or carrier-mediated transport [11]. Furthermore, cell-based analysis (Caco-2 cell line) showed that direct absorption of quercetin glycosides is low because of their hydrophilic nature and high molecular weight. Iso-quercetin (quercetin 3-O-glucoside) and quercetin-4′-glucoside are mainly hydrolyzed in the small intestine by intestinal β-glucosidases [14]. While other derivatives such as quercetin rutinosides, rhamnosides, and galactosides, which cannot be hydrolyzed in the small intestine, are metabolized by Enterobacteriaceae in the large intestine. In the small intestine, the free aglycone should be kept soluble until it passes via enterocytes by passive transport. Its absorption in the small intestine is influenced by multiple factors, such as food processing, food matrix, macro-constituents and/or micro-constituents influence the free aglycone [12,13]. In contrary to this dietary fats improves quercetin bioavailability probably due to intestinal micellization. Generally, as a result of their solubility dietary quercetin glycosides are much more absorbable than aglycone available in oral formulations [14].

Since quercetin is a dietary xenobiotic, it undergoes xenobiotic metabolism, which comprises three phases acting additively and/or independently to minimize the absorption together with the accumulation of xenobiotic via phase-I (modification), phase-II (conjugation) and phase-III (elimination) [6]. After absorption, quercetin undergoes various types of metabolism and produces metabolites, where quercetin-3-O-β-D-glucuronide (Q3GA) is a major metabolite [15]. Phase-II metabolisms of quercetin aglycone occur in the enterocytes and are subjected to reactions such as methylation, sulfation and glucuronidation, before entering the portal circulation. Although a small amount is trapped in the gastrointestinal tract (GIT), quercetin and its metabolites are subjected to phase-I metabolism in the liver. Mainly, quercetin can be subjected to reactions like oxidation, reduction, and hydrolysis in order to produce these metabolites for phase-II metabolism [14]. The serum albumin bound conjugated quercetin metabolites; total plasma level is mostly in the nanomolar range, whereas free aglycone and glycosides of quercetin are rarely available or are below the detection limit [12]. Yet, brain concentration of alone quercetin is low. In a study on mice model, it was demonstrated that quercetin-enriched diet significantly improved the quercetin and isorhamnetin, its methylated metabolite level in the brain. Blood-brain barrier (BBB) efflux transporters like P-glycoprotein have quercetin as their substrate, which is the major factor for its low concentration in the brain [16]. It is also revealed that quercetin has the potential to cross BBB significantly and restrain the proliferation of U251 cells and trigger apoptosis. The use of quercetin conjugated with α-tocopherol may promote to cross BBB which increase their concentration in the brain to protect brain microvascular endothelial cells from β-amyloid$_{1-40}$-induced toxicity [17–19].

A wide range of biological activities of quercetin has been mentioned in different studies and most of these activities are attributed to antioxidant property, which plays a major role from a mechanistic point of view. Despite large number of studies on the biological activity of quercetin and its derivatives, the mechanisms of its action are not well understood. Studies have suggested that quercetin in food products has a potential protective effect against neurodegenerative diseases. In relation to this, a great number of in vitro and in vivo studies has evaluated and reported the potential biological activities of the compound against neurodegenerative diseases especially Alzheimer's disease (AD). In this review, we have covered the anti-Alzheimer antioxidant and molecular mechanisms of quercetin to ameliorate AD.

2. Oxidative stress and the protective role of quercetin

Oxidative stress is a state of disturbed balance between reactive oxygen species (ROS) production and biological system's antioxidant defense mechanisms which act by detoxifying the reactive intermediates or thereby repairing the damage caused [20–22]. ROS, also referred as free radicals production, causes an imbalance of the normal cell reduction-oxidation (redox) state by damaging DNA, proteins, lipids, and all the other cell components as well as disrupting normal cellular signalling. Oxidative stress is reported to play a central role in the onset of numerous human chronic diseases such as diabetes, atherosclerosis, cardiovascular diseases, myocardial infarction, rheumatoid arthritis, chronic inflammation as well as aging and a number of other neurodegenerative diseases [23,24]. ROS affects the neurotransmitters and excitatory amino acids present in the brain. In addition to that, the brain itself represents a substantial source of oxidative stress, as brain metabolism serves as a “factory” of ROS which attacks glial cells and neurons, resulting in neuronal damage which may lead to oxidative injury and programmed cell death by apoptosis [24–26]. Antioxidants are compounds that scavenge and neutralize free radicals through either implication of defense enzymes copper/zinc superoxide dismutase and glutathione peroxidase, or by direct non-enzymatic modes of action. Quercetin is a bioflavonoid present in many foods and vegetables including peanuts, soybeans, capers, lovage, apples, mulberries, carob, radish, broccoli, onion, and potatoes, etc. In foods, quercetin is present in a form of glycoside (with sugar groups attached) and is being deglycosylated to quercetin aglycone prior to absorption into the small intestine [6]. Quercetin is effective in preventing oxidants-caused endothelial apoptosis and it is more potent compared to other antioxidant nutrients, such as β-carotene, glutathione and vitamins C and E [28,29]. This property might be a consequence of two antioxidant pharmacophores within the quercetin molecule whose configuration is optimal for free radical scavenging [30]. Moreover, its ability to chelate iron and other transition metal ions enables it also to prevent iron-catalyzed Fenton reaction [26,29]. Additionally, it protects against liver damage by reducing overexpression of the nitric oxide synthase induced by different stimuli [31].

3. Antioxidant activities and modulation of pathways

3.1. α-Nuclear factor (erythroid-derived 2)-like 2 pathway

The nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is a member of the Cap'n'collar (CNc) subfamily of basic region leucine zipper (bZip) transcription factors [32]. It regulates anti-oxidative stress enzymes and drug-metabolizing enzymes (DMEs), such as glutathione S-transferase (GST) and NAD (P) H: quinone oxidoreductase 1 (NQO1). Its activity is induced by binding to an NFE2-binding motif within *cis*-acting enhancer termed antioxidant response element (ARE) in the promoter region of antioxidant enzymes encoding genes [33,34]. Moreover, the Nrf2 gene contains two ARE-like sequences, allowing for Nrf2 autoregulation and potential sustention of ARE-mediated gene expression

[35]. Nrf2 pathway plays regulatory roles in energy metabolism, mitochondrial function, and control of cellular redox balance as Nrf2 is a master regulator of inducible antioxidant responses [32,34]. Saw et al. [36] studied the role of quercetin and two other flavonoids (kaempferol, and pterostilbene) abundant in berries and its cancer prevention potential due to their oxidative properties. In the DPPH assay, all three assessed compounds demonstrated strong activity against free radical scavenging, while the DCFH-DA assay and consequent calculation of combination index suggested attenuation of intracellular ROS levels with the synergistic effect upon combined treatment of all the three flavonoids. Furthermore, combination treatment also resulted in upregulation of micro ribonucleic acid (miRNA) levels and increased protein expression of protein corresponding to Nrf2-regulated genes. Last but not the least, quercetin, pterostilbene and kaempferol induced ARE-luciferase activity in vitro when applied both individually and in combination. Lee et al. [37] investigated the anti-oxidative role of quercetin with respect to oxidative damage induced by the chemotherapeutic drug, cisplatin in malignant mesothelioma (MM) MSTO-211H and H2452 cancer cells. Treatment with quercetin inhibited cell growth and increased Nrf2 expression at the level of both mRNA and protein. In support, analysis of nuclear Nrf2 levels, Nrf2 ARE-binding assay, Nrf2 promoter-luciferase assay and real-time PCR on Nrf2-regulated genes, heme oxygenase-1 demonstrated induced Nrf2 to be transcriptionally active. On the other hand, small interfering-RNA (siRNA)-mediated Nrf2 knockdown exhibited higher cytotoxicity upon induction of apoptosis, evidenced, inter alia, by an increased level of pro-apoptotic Bax and reduced levels of anti-apoptotic Bcl-2 with enhanced cleavage of caspase-3 and PARP proteins. In addition to that, Nrf2 knockdown MM cells showed enhanced sensitivity to cisplatin, presumably by potentiating the cisplatin-induced oxidative stress, as demonstrated by the increase in generated cellular ROS. A recent study by Xu et al. [38] demonstrated that phospholipid complex of quercetin (quercetin-PC), a pharmaceutical formulation of quercetin with improved solubility and enhanced bioavailability, has greater protective effects against oxidative stress-induced insults in ARPE-19 cells. With the use of 200 μM of quercetin-PC induced Nrf2 nuclear translocation and increased the expression of targeted genes involved in antioxidant defense (HO-1, NQO-1, and GCL), as demonstrated at the level of both mRNA and protein. Another study by Ramyaa et al. [39] demonstrated cytoprotective effects of quercetin against ochratoxin-A (OTA)-induced oxidative stress and redox-signalling. It has been shown that OTA-induced ROS generation, NF-κB activation and expression together with calcium release have been ameliorated in HepG2 cells pretreated with quercetin. Moreover, quercetin-induced Nrf-2 translocation from the cytoplasm to the nucleus upon oxidative stress stimulus and its subsequent expression are shown in Fig. 1.

On the other hands, in murine Nrf2, NLS1, NLS2, and NLS3 contain residues 42–53 (RQKDYELEKQKK) in the Neh2 domain, 494–511 (RRRGKQKVAANQCRKRK) in the Neh6 domain and 587–593 (PKSKKPD) in the Neh3 domain respectively [40,41].

3.2. b-Paraoxonase-2 pathway

Paraoxonase 2 (PON2), together with PON1 and PON3, belongs to the paraoxonase family of genes that encode mammalian calcium-dependent lactone-hydrolyzing enzymes [42]. PON2 is a ubiquitously expressed enzyme localized primarily in the astrocytes of dopaminergic regions, while subcellular distribution is mainly restricted to mitochondria [43], which supports its antioxidative role, as mitochondria are the dominant source of O_2^-. Antioxidant effects of PON2 have also been supported by findings in HeLa cells that binding to coenzyme Q10 was associated with mitochondrial complex III and by induction of superoxide release from the inner membrane of mitochondria, without any effect on other radicals, such as hydrogen peroxide and peroxynitrite [44,45]. Costa et al. [46] demonstrated that the region of the mouse brain with the highest mRNA and protein levels of PON2 is the striatum. Quercetin pre-treatment significantly mitigated ROS production ($PON2^{+/+}$ and $PON2^{-/-}$ in striatal neurons and striatal astrocytes were 180% and 600%, and 130% and 500% respectively) induced by both H_2O_2 and DMNQ, utilized as oxidants to induce oxidative stress. Upon the previously published study on polyphenols from pomegranate juice in relation to PON2 [47], the proposed mechanism of quercetin action involves activation of the c-Jun N-terminal kinase (JNK)/activator protein-1 (AP-1) pathway. Furthermore, the neuroprotective effect of quercetin was significantly lower in cells derived from knockout mice model of PNO2, as assessed by cytotoxicity assay. Another study by the same authors showed that the lack of PON2, as in the knockout mice model or sex-specific lower levels of PON2 increases susceptibility to toxicity induced by oxidative stress. Interestingly, male mice have been shown to have higher PON2 levels and its lactonase activity than the female counterparts, which has been attributed to the positive modulatory effect of estrogen [43].

3.3. c-JNK-mediated pathways

The JNK pathway is one of the major signallings within mitogen-activated protein kinase (MAPK) signalling pathway. JNKs are family of threonine protein kinases consisting of three genes JNK1, JNK2 and JNK3 that altogether encodes ten splice variants [48]. JNK1 and JNK2 are widely expressed throughout various tissues and have been shown to play a key role in the development of obesity-induced insulin resistance [49–51], while JNK3 is specifically expressed in the central nervous system and therefore shows therapeutic potential in neurodegenerative diseases such as Parkinson's disease, AD and other CNS disorders (Fig. 1) [52,53]. Activation of JNKs is achieved by phosphorylation on threonine and tyrosine residues, while the inactivation of the JNKs occurs through a negative feedback loop, induced by MAPK phosphatases [54]. Protective features of quercetin against oxidative stress have been explored related to type 2 diabetes [55]. Upon H_2O_2-induced oxidative stress in INS-1 insulin-secreting β-cells, p38 MAPK phosphorylation was found to be regulated positively by extracellular signal-regulated kinase1/2 (ERK1/2) and negatively by JNK, together with JNK pathway inhibitory effects on ERK1/2 activation and insulin secretion. The oxidative stress-protecting effects of quercetin, therefore, appear to be consequent to ERK1/2 hyperactivation and dependent on the balance between ERK1/2 and JNK activation (Fig. 1). Abdominal aortic aneurysms (AAAs) are another condition in which the antioxidant activity of quercetin has been studied [56]. In CaCl2-induced AAA mouse model, quercetin treatment has been shown to inhibit generation of ROS, and it attenuates the expression of JNK and its phosphorylated form as well as diminished activation of the activator protein (AP)-1 transcription factor. Furthermore, Ishikawa and Kitamura [57] reported that quercetin inhibited apoptosis induced by H_2O_2 in mesangial cells via mediation of the AP-1 pathway. Moreover, they showed that H_2O_2 activated ERKs and JNK kinase by their rapid phosphorylation, which was attenuated by pretreatment with quercetin. In addition, in many cell types, JNK and its substrate c-Jun have been referred to as mediators of apoptotic cell death [58]. Quercetin was also shown to attenuate the activation of JNK induced by 4-hydroxy-2-noneal, the end product of lipid peroxidation, in RL34 cells. Inhibition of enzymes involved in the HNE-triggered stress signalling pathways, particularly protein kinase-C (PKC) has been proposed as the possible mechanism responsible for the inhibitory effects of quercetin [59]. Furthermore, the implication of quercetin in the JNK signalling pathway has also been demonstrated in macrophages, in relation to its anti-inflammatory activity. Currently, Park et al. [60] demonstrated anti-inflammatory properties of a glycoside derivative of quercetin, quercetin n-3-O-β-D-glucuronide (QG), in LPS-challenged RAW264.7 macrophage cells, by attenuating JNK phosphorylation in a concentration-dependent manner.

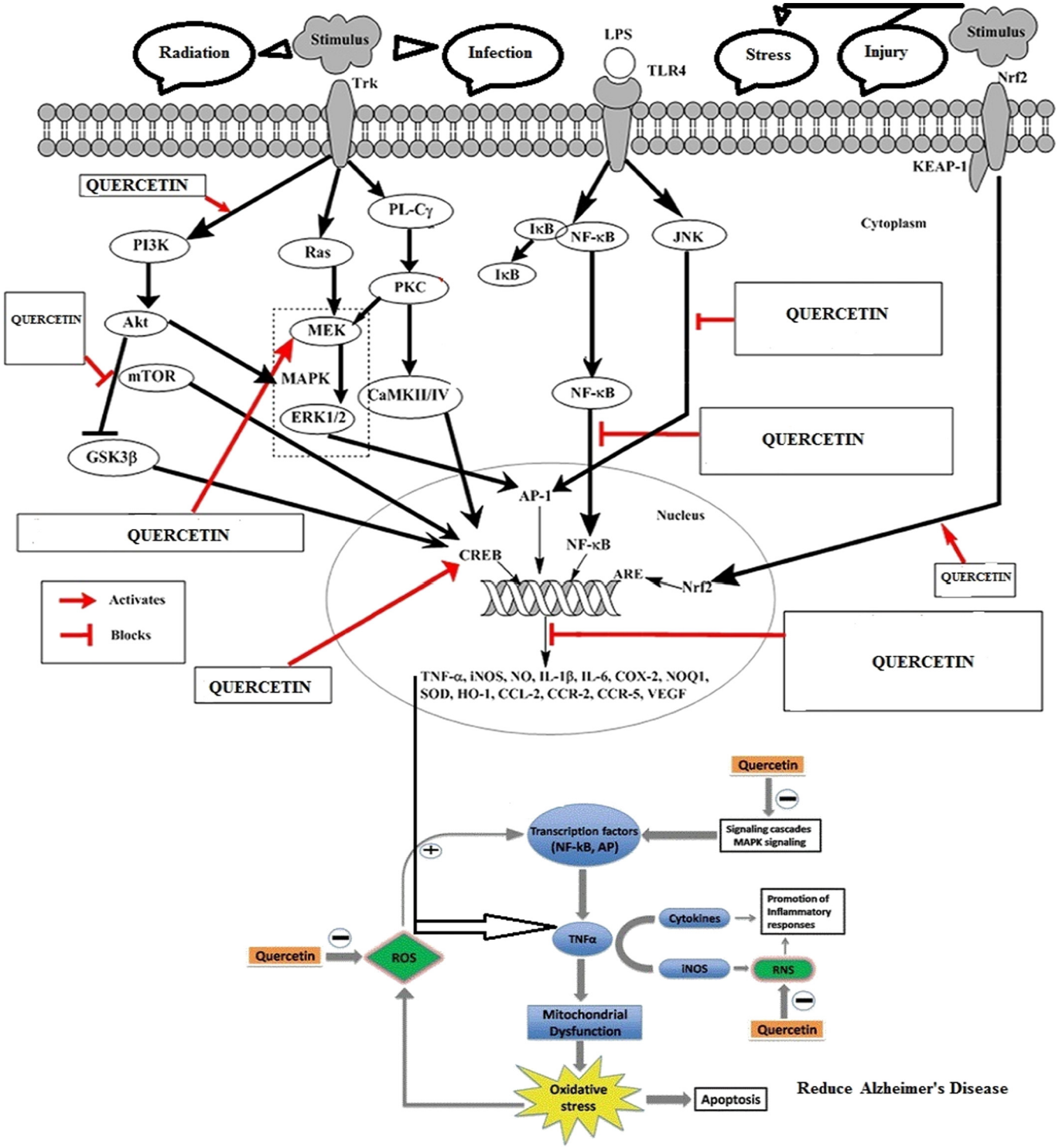

Fig. 1. Role of quercetin to up-regulate and down-regulate cellular cytokines helping in ameliorating AD.

3.4. d-PKC pathway

PKC is a family of serine-threonine kinases comprised of 11 isozymes that are subgrouped into three classes based on their structure and cofactor of their regulation, amongst which the best characterized are α and two alternatively spliced variants β-I and β-II [61]. They regulate a number of cellular responses including gene expression, cell proliferation, protein secretion and inflammatory response [62]. ROS have been demonstrated to trigger PKC through redox signalling, where PKC is activated by oxidation of their cysteine residues [63]. Several studies demonstrated the relationship between PKC family members and oxidative stress in cardiovascular diseases, such as the increase of intracellular ROS leads to PKC-δ activation [64] and loss of ROS formation in PKC-δ knockout mice are resistant to H_2O_2 induced cell death [65]. Additionally, obesity induces oxidative stress and increase ROS production in adipocytes, as evident by PKCβ activation upon intracellular ROS increase due to high glucose levels [66]. Effect of quercetin on ROS and PKC activity has also been investigated in cancer cells, as PKC contributes to cancer progression, while the prevention of cancer could be mediated by antioxidants as shown in (Fig. 1) [67].

Recent studies on ascites cells of Dalton's lymphoma-bearing mice showed that quercetin modulated the expression of almost all PKC isozymes (classical, atypical and novel) and down-regulated the expression levels of PKCα. In addition to the reduction of oxidative stress, quercetin has been demonstrated to facilitate differential localization of the TNFR1 level in ascites cells and subsequently induce apoptosis mediated by death receptors. The antioxidant effect of Quercetin has also been investigated related to mania since antimanic drugs possess antioxidant activity or PKC inhibitory effects. In those terms, quercetin resembles the effects of lithium, which is most commonly used for the treatment of mania in bipolar disorder. In the animal model of mania, chronic treatment with quercetin in 10 and 40 mg/kg body weight doses has been shown to block methylphenidate-induced hyperlocomotion as well as attenuate the increase in the methylphenidate-induced oxidative stress indices [68]. These results confirm antimanic-like effects of quercetin, similar to the ones of lithium.

3.5. e-MAPK signalling cascades

MAPKs are a family of highly conserved protein kinases with serine/threonine activity, that can be classified into conventional MAPKs and lesser-studied, atypical kinases. Conventional include the ERK1/2 or p44/42, the JNK1-3/stress-activated protein kinases (SAPK1A, 1B, 1C), the p38 isoforms (p38α, β, γ, and δ), and ERK5, while atypical are Nemo-like kinase (NLK), ERK3/4, and ERK7/8 [69]. Briefly, the MAPK cascade includes the chain of proteins to amplify the signal and starts with the activation of MAPKK kinases (MAPKKKs) by a broad range of extracellular stimuli. These kinases further impose downstream effects by phosphorylation and activation of MAPK kinase (MAPKK), leading to the activation of MAPKs. Subsequently, they phosphorylate and activate specific MAPK-activated protein kinases that mediate numerous fundamental cellular processes such as proliferation, differentiation, motility, stress response, apoptosis and survival (Fig. 1) [70]. Several studies investigated the antioxidant properties of quercetin in relation to MAPK pathway with confounding results on the pathway activation. Most of the studies reported MAPK pathway activation upon quercetin treatment, e.g. in HepG2 cells quercetin has been shown to activate phosphorylation of JNK, p38 and phosphoinositide 3-kinase (PI3K)/Akt and enhance Nrf2 DNA-binding activity, resulting in the expression of metallothionein (MT) proteins that protect against metal toxicity in the liver [71]. Another study that supports these findings revealed quercetin-mediated protection of human hepatocytes from oxidative stress induced by activation of HO-1 via MAPK signalling pathways through p38 and Nrf2 translocation into nuclei mediated by ERK [72]. Moreover, in BV-2 microglial cells challenged with oxidative stress by LPS treatment, quercetin treatment has been shown to increase phospho-p38 MAPK expression and subsequently inhibit NO (nitric oxide) production [73]. On the contrary, another study reported that quercetin inhibits MAPK signalling pathways resulting in down-regulation of anti-apoptotic factor Mcl-1 in cell lines of leukemia and B-cells isolated from chronic lymphocytic leukemia [74]. To conclude, quercetin may exert both positive and negative effects on MAPK pathway activation, which, if occur in a wrong cell or inappropriate space-time window, may lead to proliferative stimulus and malignant transformation of cells [75–77].

3.6. e-PI3K/Akt pathway

PI3K/Akt pathway is a signalling cascade centering on serine/threonine kinase Akt [also known as protein kinase B (PKB)]. Its activation is achieved by either B and T cell receptors, receptor tyrosine kinases, cytokine and G-protein-coupled receptors, integrins and other stimuli that induce production of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) [78]. This leads to phosphorylation of Akt, which can act as downstream on a number of target proteins, activating or suppressing their activity. Thus, it regulates numerous different cell functions, amongst which processes of cell apoptosis and survival, protein synthesis, cell growth, cell cycle, proliferation, and metabolism are the most prominent events [79,80]. One of the best known Akt-acting downstream effectors is the mammalian target of the rapamycin (mTOR), which plays an evolutionarily conserved role in the control of cell growth as the critical regulator of translation initiation and ribosome biogenesis. It is altered in many cancer types, leading to hyperactive signalling cascades correlated with excessive cellular growth, proliferation, and survival, by acting on a wide range of downstream effectors, including murine double minutes2 (Mdm2), FOXO and SK-3 [81]. In relation to protection against oxidative stress in neurodegenerative diseases, Xia et al. [82] explored compromised hippocampus-dependent learning and memory in high-fat diet fed mice that have been closely associated with oxidative stress. They have shown that diet high in saturated fat as well as the presence of ROS and carbonyls, down-regulated levels of hippocampal genes implicated in the latter processes, amongst which PI3K and downstream Akt, GSK-3β, and Nrf2 are crucial. However, quercetin supplemented to HFD improved antioxidant capacity and reversed learning and memory impairment, whereas, in a balanced redox situation, it surprisingly exerted pro-oxidant effects worsening the cognitive impairment. In the brain of ischemic rats, quercetin treatment is demonstrated to significantly reduce oxidative stress and promote antioxidative and anti-apoptotic signalling, as evidenced by the expression of cytochrome *c* and GSH, GPx, GRx and LP in striatum and cortex brain regions, which was further enhanced combined with exercise training [83]. Furthermore, PI3K/Akt inhibitor such as LY294002 eliminated the effects of both quercetin and exercise co-treatment, indicating that antioxidative properties of both treatments are mediated through PI3K/Akt pathway, resulting in neuroprotection and motor function improvement. Effects of quercetin on PI3K/Akt/GSK3β signalling pathway were investigated by co-treatment with the same inhibitor in HT22 hippocampal neurons as well, where quercetin led to down-regulation of GSK3β activity via promotion of PI3K/Akt [84] as shown in Fig. 1. Moreover, oxidative stress-induced phosphorylation of tau protein, one of the foremost downstream targets of PI3K/Akt pathway was suppressed by quercetin treatment suggesting that its neuroprotective effects are exerted by tau anti-hyperphosphorylation especially in neurodegenerative disorders such as AD and Parkinson's disease. Another study reports similar findings in PC12 phaeochromocytoma cells, where quercetin showed a protective effect against H_2O_2-induced apoptosis by reducing LDH release, ROS concentration, and MDA level and regaining activities of GSH-Px and superoxide dismutase (SOD) [85]. Co-treatment with LY294002 inhibitor has again revealed the underlying mechanism by activation of PI3K/Akt signalling pathway and subsequent increase in Bax/Bcl-2 ratio, accounting for neuroprotective properties of quercetin.

4. Mechanisms linking quercetin role in AD

AD is a chronic neurodegenerative disease that usually starts slowly and worsens over time with increasing age. AD is the cause of 60–80% dementia cases [86,87]. On the other hand, pathological studies of AD have revealed extracellular aggregation of senile plaques (SPs); development of intracellular neurofibrillary tangles (NFTs); and lesions of cholinergic neurons [88,89]. In the central cholinergic system, numerous neurotransmitters and neuronal pathways function together in learning and memory. Thus, cognitive impairment in AD is related to functional loss in the central cholinergic system [90]. Moreover, the aggregation of amyloid-β (Aβ) peptide, which is referred to as amyloid hypothesis is the cause of synaptic dysfunction and neurodegeneration [91]. Other pathological processes are also reported in relation to AD such as neuroinflammation, impairment of cerebral circulation, altered synaptic function and cerebral amyloid angiopathy. Hence, these pathological anomalies that are identified to cause AD are considered important drug targets towards AD drug search [92]. A considerable number of evidence indicates that dietary control can minimize the risk of developing AD. Animal model studies have also shown a decreasing

Table 1
Auspicious studies reported anti-Alzheimer's and neuroprotective effects of quercetin.

Doses of quercetin	Duration and route of administration	Species/studied material	Experimental model	Effects	References
50 mg/kg body weight	2 times a week orally for 4 weeks	Homozygotic transgenic mouse line B6.129S7-Sod2tm1Leb/J	Hydrogen peroxide- and Aβ-induced neurotoxicity	▪ Decreased ROS levels ▪ Improved the typical morphology of mitochondria ▪ Prevented mitochondrial dysfunction	[122]
50 mg/kg body weight	Every day orally for 10 weeks	Male C57BL/6J mice	AMP-activated protein kinase activity on hyperphosphorylation of tau	▪ Enhances AMP-activated protein kinase activity ▪ Reduces tau hyperphosphorylation ▪ Improves cognitive deficit	[123]
25 mg/kg body weight	Every 2 days orally for 2 months	Male SAMP8 mice	Mouse model of AD	▪ Improves the cognition deficit ▪ Enhances the memory impairments ▪ Reduces the astrogliosis	[124]
30 mg/kg body weight	Every day intraperitoneally for 8 days	Male Albino Wistar rats	Scopolamine induced Cognitive dysfunction and neurodegeneration	▪ Abridges the transfer latency ▪ Reduces avoidance response ▪ Decrease in 3,4-methylene dioxy amphetamine, acetylcholinesterase levels ▪ Increases the brain catalase and glutathione levels	[90]
10 mg/kg body weight	Every day orally for 12 weeks	Male Albino Wistar rats	Aluminum-induced neurodegeneration	▪ Decreases ROS production ▪ Amplified mitochondrial superoxide dismutase activity	[125]
25 mg/kg body weight	Every day intraperitoneally for 3 months	Homozygous transgenic mice	Triple transgenic mouse model of AD	▪ Reduces Alzheimer's pathology ▪ Protects cognitive deficit ▪ Improves emotional function	[98]
500 mg/kg body weight	Every day orally for 10 days	Transgenic male and female mice	Five-familial transgenic mouse model of AD	▪ Increases brain apolipoprotein E ▪ Reduces insoluble Aβ levels	[126]
1% in mouse chow	Orally for from 3 to 13 months	Double transgenic female mice	Mouse model of AD	▪ Decreases neuroinflammation ▪ Reduces neurodegeneration	[127]
		Cultured neurons	Aβ42-induced oxidative cell toxicity	▪ Decreases oxidative stress ▪ Reduces neurotoxicity	[95]
10 and 50 mg/kg body weight	Intraperitoneally at 30 min, 12 h, and 24 h after subarachnoid hemorrhage	Adult male Sprague-Dawley rats	Rat model of subarachnoid hemorrhage	▪ Improves brain damage ▪ Provides neuroprotection	[21]
0.5% in AIN93G diet	Orally for 5 weeks	Aβ precursor protein 23 mice	Murine model of AD	▪ Reduces memory dysfunction ▪ Decreases oxidative stress	[130]
		Cell culture (PC12)	Hydroxy peroxide-induced neurodegeneration	▪ Reduces oxidative stress ▪ Abates neurotoxicity	[131]

high-calorie diet to be neuroprotective by reducing Aβ accumulation [93]. The flavonol quercetin, which is found in various vegetables and fruits, has captured a significant attention for its potential biological activities including preventing oxidative stress [94]. Generally, flavonoids and in particular quercetin is an important compound for the development of AD therapeutics since it can protect the neurons against oxidative agents and excitotoxicity through regulating cell death mechanisms [95]. In addition, quercetin is capable of improving cholinergic functions and acts as a neuroprotective agent in AD [96]. A number of epidemiological studies have shown that coffee has a neuroprotective effect. Moreover, Lee et al. [97] found that quercetin is the main ingredient in coffee that has a neuroprotective action against AD after comparing the neuroprotective properties of quercetin, flavones, chlorogenic acid, and caffeine. Various mechanisms have been suggested for the neuroprotective actions of quercetin including inhibition of Aβ aggregation, inhibition of NFTs formation, amyloid precursor protein (APP) cleaving enzyme (BACE1) inhibition, acetylcholinesterase (AChE) inhibition and others attenuating the oxidative stress in AD (Table 1).

4.1. Aβ aggregation inhibitive effect of quercetin

Extracellular deposition of SPs, intraneuronal NFTs and vascular amyloid are the hallmarks of AD. The major components of SPs are the Aβ peptides, which are caused by the proteolysis of APP. Quercetin and its bioactive molecules are helpful to ameliorate neurogenesis and neurol longevity modulating signalling pathway such as P13 kinase, AKT/PKB tyrosine kinase and protein kinase C in AD [98,99]. Since, amyloid hypothesis focuses on the assembly of Aβ peptide into neurotoxic oligomers and its aggregation into fibrils proposes which is a vital feature of AD [86]. The APP is cleaved in a series of distinct steps producing 39–42 amino acid peptides of Aβ. The aggregation of the resulting Aβ gives rise to toxic dimers, oligomers and fibrils, which mainly accumulates in the postsynaptic compartments [100]. The most prominent theory to elucidate AD pathogenesis is the amyloid cascade hypothesis (ACH). The initiation of AD pathogenesis starts with deposition of Aβ which trigger SPs formation and then NFTs death of neurons and dementia [101]. The ACH is the result of two major observations: 1. identifying Aβ as a major SP constituent and 2. Mutations in the *PSEN1*, *PSEN2* and *APP* genes, which are mostly detected at the onset of AD. Consequently, the appearance of Aβ within SPs is considered as the result of these mutations that lead to neuronal cell death and dementia [102]. In vitro studies revealed that quercetin inhibits the fibrils aggregation of Aβ and disrupt the mature fibrils by forming hydrophobic interactions and hydrogen bonds with the β-sheet structure of Aβ. The OH^- functional groups of the B-ring of quercetin have an important role in inhibiting the aggregation of Aβ [99]. Additionally, other studies have shown the administration of quercetin to neuronal culture in vitro increased their survival [12]. Jiménez-Aliaga et al. [103] demonstrated the anti-amyloidogenic action of quercetin and rutin by incubating Aβ 25–35 alone, which resulted in robust fibrils and a decrease in the number of fibrils after co-incubating Aβ 25–35 with 10 μM quercetin or 10 μM rutin. Structurally, quercetin catechol moiety plays a dual role by acting as a metal chelator and interacting with Aβ peptides to inhibit their aggregation. The metal chelating effect of quercetin allows binding competitively on the metal binding site of Aβ and thus their ketoenolate group contributes to the reduction of oxidative stress induced by Ab-Cu^{2+} [99].

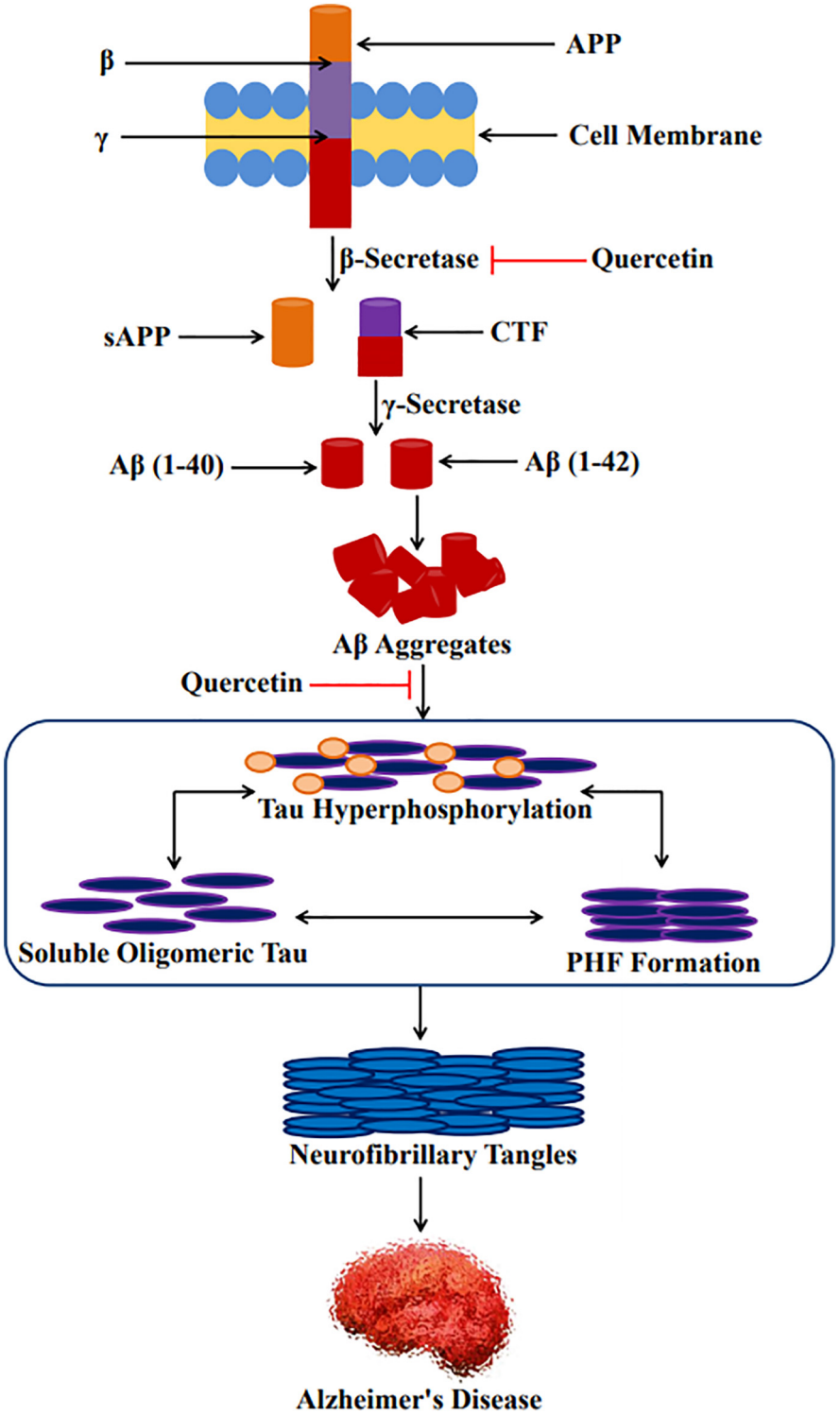

Fig. 2. The formation of Aβ and tau pathology and the role of quercetin in blocking AD. APP, amyloid precursor protein; Aβ, Amyloid beta; sAPP, soluble amyloid precursor protein; CTF, C-terminal fragment; PHF, Paired helical filament.

4.2. β-site APP cleaving enzyme 1 (BACE) inhibitory activity of quercetin

The formation of Aβ peptide, which is the main component of SPs, is the result of two-step APP proteolytic cleavage by β- and ɤ-secretase enzymes [104]. Particularly, the proteolytic action of β-secretase on APP produces secreted APP- (sAPP) and C-terminal fragment (CTF), which will undergo further proteolysis by ɤ-secretase to generate Aβ (Fig. 2) [105]. Consequently, an insoluble and neurotoxic plaque will be formed by the miss-folded Aβ peptide aggregation and accumulation [16]. BACE1 is related to the pepsin family and it is a type I aspartic protease trans-membrane protein composed of 501 amino acids, which is highly expressed in the brain [106,107]. The β-secretase demonstrated efficient action against the membrane-bound substrates since the β-secretase itself is probably a membrane-bound or it is a membrane protein related structure [108]. As an important therapeutic target regulating BACE1 activity has a great significance to control the

formation of Aβ peptide and plaque accumulation in AD [109]. BACE1 selective inhibition at subcellular compartment level, where APP cleavage occurs is an effective therapeutic means to prevent Aβ formation [110]. Natural product derived compounds like curcumin and flavonoids have inhibitory actions against BACE1 in both cell-free and neuronal cell systems. Flavonols such as myricetin, quercetin, kaempferol, and morin along with another flavone compound such as apigenin have direct inhibitory activity against BACE-1 in a dose-dependent manner (Fig. 2) [109]. A study revealed that quercetin and rutin at a concentration of 100 μM displayed a considerable inhibition of BACE1 in vitro in a cell-free system by 11.85% and 50.67% respectively [103]. Another study also reported that quercetin inhibits Aβ peptide aggregation and the related paralysis through macro-autophagy activation and proteasomal degradation pathways. In addition to its direct Aβ peptide aggregation inhibitory activity, it acts by inhibiting BACE1 induced APP cleavage at β-site to prevent Aβ (1-42) formation [99].

4.3. Quercetin inhibiting NFTs formation

The other pathological implication of AD is the appearance of NFTs with the core protein being tau and its accumulation into tangles involves phosphorylation [111]. Various studies have attempted to define the mechanism through which Aβ deposition induces the formation of NFTs [112]. Yet, other studies argue that Aβ peptide can facilitate the formation of intracellular tau, however, Aβ deposition is not associated with NFTs formation, cell loss or dementia [101,113]. Tau protein has about 84 putative phosphorylation sites, in which serine, threonine, and tyrosine are 45, 35 and 4 respectively. Although, poorly understood phosphorylation of tau negatively influences the binding of tau to microtubules. Especially, neuronal functions are affected most with hyperphosphorylated tau including as mitochondrial respiration and axonal transport [100]. Tau hyperphosphorylation leads to detachment, self-aggregation and depolymerization of microtubules causing the neuronal cell death [99]. Recently, it was revealed that quercetin efficiently inhibited okadaic acid-induced tau pathology (Fig. 2) via considerably reducing hyperphosphorylation of tau protein and retrogressive action on the hyperphosphorylation process [103]. In addition, quercetin showed GSK3b inhibitory activity and consequently inhibited hyperphosphorylation of tau protein. Furthermore, quercetin has anti-HSP 70 activity and thus reduces tau pathology via attenuating hyperphosphorylated tau level [99].

4.4. AChE inhibitory activity of quercetin

Loss of cholinergic neurons is another important trademark of AD and one of the most consistent neurotransmitter alterations marked in the brain of the patients. Loss of the cholinergic neurons and the correlation of decrease in mental status score and loss of choline acetyltransferase (ChAT) resulted in the cholinergic hypothesis of cognitive impairment in AD [114]. The cholinergic hypothesis states that shortage of the neurotransmitter, such as acetylcholine in the brain can be because of a decline in the neurotransmitter production or increase in the AChE activity [115]. Basically, the role of AChE is to terminate the cholinergic transmission via hydrolyzing the acetylcholine [116,117]. Since the decline in cholinergic neurotransmission is a consistent and early symptom in AD, AChE is a noteworthy therapeutic target for symptomatic improvement in AD [118]. Recent studies indicated that AChE inhibition improved cognitive memory in AD patients through up-regulating the expression of nicotinic acetylcholine receptors. In vitro AChE inhibitory activity evaluation revealed that quercetin competitively inhibits AChE. Similarly, a Parkinson's disease animal model showed that high doses of quercetin considerably diminished AChE activity in the hippocampal region [99]. In one study, quercetin at a dose of 50 mg/kg body weight stopped the rise of AChE activity due to diabetes in the cerebral cortex and hippocampus. In relation to this through restoring the function of acetylcholine (ACh) quercetin mitigated the cholinergic signalling and facilitated regaining lost memory in diabetic rats [119]. In another study, it was demonstrated that a single dose of quercetin or rutin acute pre-treatment 1 h before administering scopolamine avoided the memory impairment caused by scopolamine [120]. Moreover, a molecular docking study predicted that quercetin is superior to conventional AchE inhibitor drugs and recommended further study on the compound [121].

5. Conclusion

The flavonol quercetin and its glycosides possess a range of biological activities to combat neurodegeneration. Although, the above mentioned underlying mechanisms of actions (ERK1/2, Nrf2, PI3K/Akt, JNK, MAPK, NFTs, BACE and NFTs pathways) for quercetin is its antioxidant potential, which has a direct role in suppression of AD. In particular, quercetin anti-Alzheimer activity has witnessed various mechanisms of action both direct and indirect in cellular and molecular level. However, quercetin bioavailability is enhanced as its use as a CNS drug that can cross the BBB. Yet quercetin compound is not studied on molecular and cellular level as it is used as a dietary supplement and nutraceutical. Being a potent lead compound as anti-AD, structural manipulations on quercetin can provide a drug candidate/a drug that limits the progression of the disease. Therefore, further preclinical and clinical studies need to be done so as to improve quercetin molecular and pharmacological properties.

Conflict of interest

There is no conflict of interest amongst the author's or their institutes.

Acknowledgments

All the authors of the manuscript thank and acknowledge their respective universities and institutes.

Authors' contribution

KN gave the idea, prepared the outlines, wrote abstract, conclusion and designed the figures. EZ and MB contributed equally to the writing of the manuscript draft, while ZAS, MSU and KN did critical editing and reviewing of the whole manuscript. The final version of the manuscript has been approved by all authors.

References

[1] G. D'Andrea, Quercetin: a flavonol with multifaceted therapeutic applications? Fitoterapia 106 (2015) 256–271.
[2] Lesjak M, Beara I, Simin N, et al. (2018) Antioxidant and anti-inflammatory activities of quercetin and its derivatives. J. Funct. Foods 40:68–75 doi:https://doi.org/10.1016/j.jff.2017.10.047.
[3] T. Funakoshi, N. Kanzaki, Y. Otsuka, T. Izumo, H. Shibata, S. Machida, Quercetin inhibits adipogenesis of muscle progenitor cells in vitro, Biochemistry and Biophysics Reports 13 (2018) 39–44, https://doi.org/10.1016/j.bbrep.2017.12.003.
[4] L. Xiao, G. Luo, Y. Tang, P. Yao, Quercetin and iron metabolism: what we know and what we need to know, Food Chem. Toxicol. 114 (2018) 190–203, https://doi.org/10.1016/j.fct.2018.02.022.
[5] J.-Q. Xu, N. Fan, B.-Y. Yu, Q.-Q. Wang, J. Zhang, Biotransformation of quercetin by Gliocladium deliquescens NRRL 1086, Chin. J. Nat. Med. 15 (8) (2017) 615–624, https://doi.org/10.1016/S1875-5364(17)30089-4.
[6] Y. Guo, R.S. Bruno, Endogenous and exogenous mediators of quercetin bioavailability, J. Nutr. Biochem. 26 (3) (2015) 201–210, https://doi.org/10.1016/j.jnutbio.2014.10.008.
[7] Grzelak-Błaszczyk K, Milala J, Kosmala M, et al. (2018) Onion quercetin monoglycosides alter microbial activity and increase antioxidant capacity. J. Nutr. Biochem. 56:81–88 doi:https://doi.org/10.1016/j.jnutbio.2018.02.002.
[8] I. Erlund, Review of the flavonoids quercetin, hesperetin, and naringenin. Dietary sources, bioactivities, bioavailability, and epidemiology, Nutr. Res. 24 (10) (2004) 851–874, https://doi.org/10.1016/j.nutres.2004.07.005.
[9] Petersen B, Egert S, Bosy-Westphal A, et al. (2016) Bioavailability of quercetin in

humans and the influence of food matrix comparing quercetin capsules and different apple sources. Food Res. Int. 88:159–165.
[10] W. Wiczkowski, D. Szawara-Nowak, J. Topolska, K. Olejarz, H. Zieliński, M.K. Piskuła, Metabolites of dietary quercetin: profile, isolation, identification, and antioxidant capacity, J. Funct. Foods 11 (2014) 121–129, https://doi.org/10.1016/j.jff.2014.09.013.
[11] S.F. Nabavi, G.L. Russo, M. Daglia, S.M. Nabavi, Role of quercetin as an alternative for obesity treatment: you are what you eat!, Food Chem. 179 (2015) 305–310.
[12] F. Dajas, Life or death: neuroprotective and anticancer effects of quercetin, J. Ethnopharmacol. 143 (2) (2012) 383–396, https://doi.org/10.1016/j.jep.2012.07.005.
[13] J. Terao, Factors modulating bioavailability of quercetin-related flavonoids and the consequences of their vascular function, Biochem. Pharmacol. 139 (2017) 15–23.
[14] M.R. De Oliveira, S.M. Nabavi, N. Braidy, W.N. Setzer, T. Ahmed, S.F. Nabavi, Quercetin and the mitochondria: a mechanistic view, Biotechnol. Adv. 34 (5) (2016) 532–549, https://doi.org/10.1016/j.biotechadv.2015.12.014.
[15] M. Herranz-López, I. Borrás-Linares, M. Olivares-Vicente, J. Gálvez, A. Segura-Carretero, V. Micol, Correlation between the cellular metabolism of quercetin and its glucuronide metabolite and oxidative stress in hypertrophied 3T3-L1 adipocytes, Phytomedicine 25 (2017) 25–28, https://doi.org/10.1016/j.phymed.2016.12.008.
[16] P. Huebbe, A.E. Wagner, C. Boesch-Saadatmandi, F. Sellmer, S. Wolffram, G. Rimbach, Effect of dietary quercetin on brain quercetin levels and the expression of antioxidant and Alzheimer's disease relevant genes in mice, Pharmacol. Res. 61 (3) (2010) 242–246.
[17] Ferri P, Angelino D, Gennari L et al. (2015) Enhancemnt of flavonoid ability to cross the blood-brain barrier of rats by co-administration with α-tocopherol. Food Funct.. 6(2): 394–400.
[18] Ren SC, Suo QF, Du WT, Pan H et al. (2010) Quercetin permeability across blood-brain barrier and its effect on the viability of U251 cells. J Sichuan Uni Med Sci 41(5):751–4, 759.
[19] Yongjie Li, Sibai Z, Jinze L et al (2015) Quercetin protects human brain microvascular endothelial cells from fibrillar β-amyloid$_{1-40}$-induced toxicity. Acta Pharm. Sin. B. 5(1): 47–54.
[20] D.J. Betteridge, What is oxidative stress? Metab. Clin. Exp. 49 (2 Suppl 1) (2000) 3–8.
[21] Dong YS, Wang JL, Feng DY, et al. (2014b) Protective effect of quercetin against oxidative stress and brain edema in an experimental rat model of subarachnoid hemorrhage. Int. J. Med. Sci. 11(3):282–90 doi:https://doi.org/10.7150/ijms.7634.
[22] M.S. Uddin, G.M.S. Uddin, M.M. Begum, Y. Begum, O. Herrera-Calderon, M.M. Islam, M.M. Abdel-Daim, Inspection of phytochemical content and in vitro antioxidant profile of *Gnaphalium luteoalbum* L.: an unexplored phytomedicine, Journal of Pharmacy and Nutrition Sciences 7 (3) (2017) 136–146, https://doi.org/10.6000/1927-5951.2017.07.03.10.
[23] I. Fridovich, Fundamental aspects of reactive oxygen species, or what's the matter with oxygen? Ann. N. Y. Acad. Sci. 893 (1999) (13-8).
[24] B. Uttara, A.V. Singh, P. Zamboni, R.T. Mahajan, Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options, Curr. Neuropharmacol. 7 (1) (2009) 65–74, https://doi.org/10.2174/157015909787602823.
[25] Y. Gilgun-Sherki, E. Melamed, D. Offen, Oxidative stress induced-neurodegenerative diseases: the need for antioxidants that penetrate the blood brain barrier, Neuropharmacology 40 (8) (2001) 959–975.
[26] R.I. Salganik, The benefits and hazards of antioxidants: controlling apoptosis and other protective mechanisms in cancer patients and the human population, J. Am. Coll. Nutr. 20 (5 Suppl) (2001) 464S–472S (discussion 473S-475S).
[28] Y.J. Choi, J.S. Kang, J.H. Park, Y.J. Lee, J.S. Choi, Y.H. Kang, Polyphenolic flavonoids differ in their antiapoptotic efficacy in hydrogen peroxide-treated human vascular endothelial cells, J. Nutr. 133 (4) (2003) 985–991, https://doi.org/10.1093/jn/133.4.985.
[29] C.A. Rice-Evans, N.J. Miller, P.G. Bolwell, P.M. Bramley, J.B. Pridham, The relative antioxidant activities of plant-derived polyphenolic flavonoids, Free Radic. Res. 22 (4) (1995) 375–383.
[30] C.G. Heijnen, G.R. Haenen, R.M. Oostveen, E.M. Stalpers, A. Bast, Protection of flavonoids against lipid peroxidation: the structure activity relationship revisited, Free Radic. Res. 36 (5) (2002) 575–581.
[31] Pavanato A, Tunon MJ, Sanchez-Campos S, et al. (2003) Effects of quercetin on liver damage in rats with carbon tetrachloride-induced cirrhosis. Dig. Dis. Sci. 48(4):824–9.
[32] Q. Ma, Role of nrf2 in oxidative stress and toxicity, Annu. Rev. Pharmacol. Toxicol. 53 (2013) 401–426, https://doi.org/10.1146/annurev-pharmtox-011112-140320.
[33] S. Petri, S. Korner, M. Kiaei, Nrf2/ARE signaling pathway: key mediator in oxidative stress and potential therapeutic target in ALS, Neurology research international 2012 (2012) 878030, , https://doi.org/10.1155/2012/878030.
[34] E.E. Vomhof-Dekrey, M.J. Picklo Sr., The Nrf2-antioxidant response element pathway: a target for regulating energy metabolism, J. Nutr. Biochem. 23 (10) (2012) 1201–1206, https://doi.org/10.1016/j.jnutbio.2012.03.005.
[35] T.W. Kensler, N. Wakabayashi, S. Biswal, Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway, Annu. Rev. Pharmacol. Toxicol. 47 (2007) 89–116, https://doi.org/10.1146/annurev.pharmtox.46.120604.141046.
[36] Saw CL, Guo Y, Yang AY, et al. (2014) The berry constituents quercetin, kaempferol, and pterostilbene synergistically attenuate reactive oxygen species: involvement of the Nrf2-ARE signaling pathway. Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association 72:303–11 doi:https://doi.org/10.1016/j.fct.2014.07.038.
[37] Y.J. Lee, D.M. Lee, S.H. Lee, Nrf2 expression and apoptosis in quercetin-treated malignant mesothelioma cells, Molecules and cells 38 (5) (2015) 416–425, https://doi.org/10.14348/molcells.2015.2268.
[38] X.R. Xu, H.T. Yu, Y. Yang, L. Hang, X.W. Yang, S.H. Ding, Quercetin phospholipid complex significantly protects against oxidative injury in ARPE-19 cells associated with activation of Nrf2 pathway, Eur. J. Pharmacol. 770 (2016) 1–8, https://doi.org/10.1016/j.ejphar.2015.11.050.
[39] P. Ramyaa, R. Krishnaswamy, V.V. Padma, Quercetin modulates OTA-induced oxidative stress and redox signalling in HepG2 cells - up regulation of Nrf2 expression and down regulation of NF-kappaB and COX-2, Biochim. Biophys. Acta 1840 (1) (2014) 681–692, https://doi.org/10.1016/j.bbagen.2013.10.024.
[40] Jain AK, Bloom DA, Jaiswal AK. (2017) Nuclear import and export signals in control of Nrf2. J. Biol. Chem.. 3;292(5):2052.
[41] M. Theodore, Y. Kawai, J. Yang, Y. Kleshchenko, S.P. Reddy, F. Villalta, I.J. Arinze, Multiple nuclear localization signals function in the nuclear import of the transcription factor Nrf2, J. Biol. Chem. 4 (283) (2008) 8984–8994 14.
[42] L.G. Costa, J.M. Garrick, P.J. Roque, C. Pellacani, Mechanisms of neuroprotection by quercetin: counteracting oxidative stress and more, Oxidative Med. Cell. Longev. 2016:2986796 (2016), https://doi.org/10.1155/2016/2986796.
[43] G. Giordano, T.B. Cole, C.E. Furlong, L.G. Costa, Paraoxonase 2 (PON2) in the mouse central nervous system: a neuroprotective role? Toxicol. Appl. Pharmacol. 256 (3) (2011) 369–378, https://doi.org/10.1016/j.taap.2011.02.014.
[44] Altenhofer S, Witte I, Teiber JF, et al. (2010) One enzyme, two functions: PON2 prevents mitochondrial superoxide formation and apoptosis independent from its lactonase activity. J. Biol. Chem. 285(32):24398–403 doi:https://doi.org/10.1074/jbc.M110.118604.
[45] Devarajan A, Bourquard N, Hama S, et al. (2011) Paraoxonase 2 deficiency alters mitochondrial function and exacerbates the development of atherosclerosis. Antioxid. Redox Signal. 14(3):341–51 doi:https://doi.org/10.1089/ars.2010.3430.
[46] Costa LG, Tait L, de Laat R, et al. (2013) Modulation of paraoxonase 2 (PON2) in mouse brain by the polyphenol quercetin: a mechanism of neuroprotection? Neurochem. Res. 38(9):1809–18 doi:https://doi.org/10.1007/s11064-013-1085-1.
[47] M. Shiner, B. Fuhrman, M. Aviram, Macrophage paraoxonase 2 (PON2) expression is up-regulated by pomegranate juice phenolic anti-oxidants via PPAR gamma and AP-1 pathway activation, Atherosclerosis 195 (2) (2007) 313–321, https://doi.org/10.1016/j.atherosclerosis.2007.01.007.
[48] K. Sabapathy, Role of the JNK pathway in human diseases, Prog. Mol. Biol. Transl. Sci. 106 (2012) 145–169, https://doi.org/10.1016/b978-0-12-396456-4.00013-4.
[49] B.F. Belgardt, J. Mauer, J.C. Bruning, Novel roles for JNK1 in metabolism, Aging 2 (9) (2010) 621–626, https://doi.org/10.18632/aging.100192.
[50] B.L. Bennett, Y. Satoh, A.J. Lewis, JNK: a new therapeutic target for diabetes, Curr. Opin. Pharmacol. 3 (4) (2003) 420–425.
[51] Kaneto H, Matsuoka TA, Nakatani Y, et al. (2005) Oxidative stress, ER stress, and the JNK pathway in type 2 diabetes. J. Mol. Med. (Berlin, Germany) 83(6):429–39 doi:https://doi.org/10.1007/s00109-005-0640-x.
[52] L. Resnick, M. Fennell, Targeting JNK3 for the treatment of neurodegenerative disorders, Drug Discov. Today 9 (21) (2004) 932–939, https://doi.org/10.1016/s1359-6446(04)03251-9.
[53] T. Yamasaki, H. Kawasaki, H. Nishina, Diverse roles of JNK and MKK pathways in the brain, Journal of signal transduction 2012 (2012) 459265, , https://doi.org/10.1155/2012/459265.
[54] Kumar A, Singh UK, Kini SG, et al. (2015) JNK pathway signaling: a novel and smarter therapeutic targets for various biological diseases. Future Med. Chem. 7(15):2065–86 doi:https://doi.org/10.4155/fmc.15.132.
[55] E. Youl, R. Magous, G. Cros, C. Oiry, MAP kinase cross talks in oxidative stress-induced impairment of insulin secretion. Involvement in the protective activity of quercetin, Fundamental & clinical pharmacology 28 (6) (2014) 608–615, https://doi.org/10.1111/fcp.12078.
[56] Wang L, Cheng X, Li H, et al. (2014) Quercetin reduces oxidative stress and inhibits activation of cJun Nterminal kinase/activator protein1 signaling in an experimental mouse model of abdominal aortic aneurysm. Mol. Med. Rep. 9(2):435–42 doi:https://doi.org/10.3892/mmr.2013.1846.
[57] Y. Ishikawa, M. Kitamura, Anti-apoptotic effect of quercetin: intervention in the JNK- and ERK-mediated apoptotic pathways, Kidney Int. 58 (3) (2000) 1078–1087, https://doi.org/10.1046/j.1523-1755.2000.00265.x.
[58] Verheij M, Bose R, Lin XH, et al. (1996) Requirement for ceramide-initiated SAPK/JNK signalling in stress-induced apoptosis. Nature 380(6569):75–9 doi:https://doi.org/10.1038/380075a0.
[59] K. Uchida, M. Shiraishi, Y. Naito, Y. Torii, Y. Nakamura, T. Osawa, Activation of stress signaling pathways by the end product of lipid peroxidation. 4-hydroxy-2-nonenal is a potential inducer of intracellular peroxide production, J. Biol. Chem. 274 (4) (1999) 2234–2242.
[60] Park JY, Lim MS, Kim SI, et al. (2016) Quercetin-3-O-beta-D-glucuronide suppresses lipopolysaccharide-induced JNK and ERK phosphorylation in LPS-challenged RAW264.7 cells. Biomol. Ther. 24(6):610–615 doi:https://doi.org/10.4062/biomolther.2016.026.
[61] A.C. Newton, Protein kinase C: structure, function, and regulation, J. Biol. Chem. 270 (48) (1995) 28495–28498.
[62] J.D. Violin, A.C. Newton, Pathway illuminated: visualizing protein kinase C signaling, IUBMB Life 55 (12) (2003) 653–660, https://doi.org/10.1080/15216540310001642216.
[63] E. De Marchi, F. Baldassari, A. Bononi, M.R. Wieckowski, P. Pinton, Oxidative stress in cardiovascular diseases and obesity: role of p66Shc and protein kinase C,

Oxidative Med. Cell. Longev. 2013:564961 (2013), https://doi.org/10.1155/2013/564961.
[64] Giorgi C, Agnoletto C, Baldini C, et al. (2010) Redox control of protein kinase C: cell- and disease-specific aspects. Antioxid. Redox Signal. 13(7):1051–85 doi:https://doi.org/10.1089/ars.2009.2825.
[65] Leitges M, Mayr M, Braun U, et al. (2001) Exacerbated vein graft arteriosclerosis in protein kinase Cdelta-null mice. J. Clin. Invest. 108(10):1505–12 doi:https://doi.org/10.1172/jci12902.
[66] Aguiari P, Leo S, Zavan B, et al. (2008) High glucose induces adipogenic differentiation of muscle-derived stem cells. Proc. Natl. Acad. Sci. U. S. A. 105(4):1226–31 doi:https://doi.org/10.1073/pnas.0711402105.
[67] A.K. Maurya, M. Vinayak, Modulation of PKC signaling and induction of apoptosis through suppression of reactive oxygen species and tumor necrosis factor receptor 1 (TNFR1): key role of quercetin in cancer prevention, Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine 36 (11) (2015) 8913–8924, https://doi.org/10.1007/s13277-015-3634-5.
[68] Kanazawa LK, Vecchia DD, Wendler EM, et al. (2017) Effects of acute and chronic quercetin administration on methylphenidate-induced hyperlocomotion and oxidative stress. Life Sci. 171:1–8 doi:https://doi.org/10.1016/j.lfs.2017.01.007.
[69] J.S. Arthur, S.C. Ley, Mitogen-activated protein kinases in innate immunity, Nat. Rev. Immunol. 13 (9) (2013) 679–692, https://doi.org/10.1038/nri3495.
[70] M. Cargnello, P.P. Roux, Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases, Microbiology and molecular biology reviews: MMBR 75 (1) (2011) 50–83, https://doi.org/10.1128/mmbr.00031-10.
[71] C.J. Weng, M.J. Chen, C.T. Yeh, G.C. Yen, Hepatoprotection of quercetin against oxidative stress by induction of metallothionein expression through activating MAPK and PI3K pathways and enhancing Nrf2 DNA-binding activity, New Biotechnol. 28 (6) (2011) 767–777, https://doi.org/10.1016/j.nbt.2011.05.003.
[72] Yao P, Nussler A, Liu L, et al. (2007) Quercetin protects human hepatocytes from ethanol-derived oxidative stress by inducing heme oxygenase-1 via the MAPK/Nrf2 pathways. J. Hepatol. 47(2):253–61 doi:https://doi.org/10.1016/j.jhep.2007.02.008.
[73] Sun GY, Chen Z, Jasmer KJ, et al. (2015) Quercetin attenuates inflammatory responses in BV-2 microglial cells: role of MAPKs on the Nrf2 pathway and induction of heme oxygenase-1. PLoS One 10(10):e0141509.
[74] C. Spagnuolo, C. Cerella, M. Russo, S. Chateauvieux, M. Diederich, G.L. Russo, Quercetin downregulates Mcl-1 by acting on mRNA stability and protein degradation, Br. J. Cancer 105 (2) (2011) 221.
[75] H. Liu, M. Zhou, Antitumor effect of quercetin on Y79 retinoblastoma cells via activation of JNK and p38 MAPK pathways, BMC Complement. Altern. Med. 17 (1) (2017) 531.
[76] Russo GL, Russo M, Spagnuolo C, et al. (2014) Quercetin: a pleiotropic kinase inhibitor against cancer Advances in Nutrition and Cancer. Springer, p 185–205.
[77] Y. Safdari, M. Khalili, M.A. Ebrahimzadeh, Y. Yazdani, S. Farajnia, Natural inhibitors of PI3K/AKT signaling in breast cancer: emphasis on newly-discovered molecular mechanisms of action, Pharmacol. Res. 93 (2015) 1–10.
[78] L. Bozulic, B.A. Hemmings, PIKKing on PKB: regulation of PKB activity by phosphorylation, Curr. Opin. Cell Biol. 21 (2) (2009) 256–261.
[79] S.A. Danielsen, P.W. Eide, A. Nesbakken, T. Guren, E. Leithe, R.A. Lothe, Portrait of the PI3K/AKT pathway in colorectal cancer, Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 1855 (1) (2015) 104–121.
[80] M. Martini, M.C. De Santis, L. Braccini, F. Gulluni, E. Hirsch, PI3K/AKT signaling pathway and cancer: an updated review, Ann. Med. 46 (6) (2014) 372–383.
[81] T. Ersahin, N. Tuncbag, R. Cetin-Atalay, The PI3K/AKT/mTOR interactive pathway, Mol. BioSyst. 11 (7) (2015) 1946–1954.
[82] Xia S-F, Xie Z-X, Qiao Y, et al. (2015) Differential effects of quercetin on hippocampus-dependent learning and memory in mice fed with different diets related with oxidative stress. Physiol. Behav. 138:325–331.
[83] H.-C. Chang, Y.-R. Yang, P.S. Wang, R.-Y. Wang, Quercetin enhances exercise-mediated neuroprotective effects in brain ischemic rats, Med. Sci. Sports Exerc. 46 (10) (2014) 1908–1916.
[84] Jiang W, Luo T, Li S, et al. (2016) Quercetin protects against Okadaic acid-induced injury via MAPK and PI3K/Akt/GSK3β signaling pathways in HT22 hippocampal neurons. PLoS One 11(4):e0152371.
[85] L. Chen, L. Sun, Z. Liu, H. Wang, C. Xu, Protection afforded by quercetin against H2O2-induced apoptosis on PC12 cells via activating PI3K/Akt signal pathway, Journal of Receptors and Signal Transduction 36 (1) (2016) 98–102.
[86] S.H. Omar, C.J. Scott, A.S. Hamlin, H.K. Obied, The protective role of plant biophenols in mechanisms of Alzheimer's disease, J. Nutr. Biochem. 47 (2017) 1–20, https://doi.org/10.1016/j.jnutbio.2017.02.016.
[87] M.S. Uddin, M.T. Kabir, A. Al Mamun, M.M. Abdel-Daim, G.E. Barreto, G.M. Ashraf, *APOE* and Alzheimer's disease: evidence mounts that targeting *APOE4* may combat Alzheimer's pathogenesis, Mol. Neurobiol. (2018) 1–20, https://doi.org/10.1007/s12035-018-1237-z In Press.
[88] M.S. Uddin, A.A. Mamun, S. Takeda, M.S. Sarwar, M.M. Begum, Analyzing the chance of dementia amid geriatric people: a cross-sectional pilot study in Bangladesh, Psychogeriatrics (2018) 1–8, https://doi.org/10.1111/psyg.12368 In Press.
[89] T.-Y. Wu, C.-P. Chen, T.-R. Jinn, Traditional Chinese medicines and Alzheimer's disease, Taiwanese Journal of Obstetrics and Gynecology 50 (2) (2011) 131–135, https://doi.org/10.1016/j.tjog.2011.04.004.
[90] S. Palle, P. Neerati, Quercetin nanoparticles attenuates scopolamine induced spatial memory deficits and pathological damages in rats, Bulletin of Faculty of Pharmacy, Cairo University 55 (1) (2017) 101–106.
[91] C.H. van Dyck, Anti-amyloid-β monoclonal antibodies for Alzheimer's disease: pitfalls and promise, Biol. Psychiatry 83 (4) (2018) 311–319, https://doi.org/10.1016/j.biopsych.2017.08.010.
[92] A. Ghanemi, Alzheimer's disease therapies: selected advances and future perspectives, Alexandria Journal of Medicine 51 (1) (2015) 1–3, https://doi.org/10.1016/j.ajme.2014.09.006.
[93] Hartman RE, Shah A, Fagan AM, et al. (2006) Pomegranate juice decreases amyloid load and improves behavior in a mouse model of Alzheimer's disease. Neurobiol. Dis. 24(3):506–515.
[94] E.L. Cooper, M.J. Ma, Alzheimer disease: clues from traditional and complementary medicine, Journal of traditional and complementary medicine 7 (4) (2017) 380–385.
[95] M.A. Ansari, H.M. Abdul, G. Joshi, W.O. Opii, D.A. Butterfield, Protective effect of quercetin in primary neurons against Aβ(1–42): relevance to Alzheimer's disease, J. Nutr. Biochem. 20 (4) (2009) 269–275, https://doi.org/10.1016/j.jnutbio.2008.03.002.
[96] A. Gupta, K. Birhman, I. Raheja, S.K. Sharma, H.K. Kar, Quercetin: a wonder bioflavonoid with therapeutic potential in disease management, Asian Pacific Journal of Tropical Disease 6 (3) (2016) 248–252, https://doi.org/10.1016/S2222-1808(15)61024-6.
[97] M. Lee, E.G. McGeer, P.L. McGeer, Quercetin, not caffeine, is a major neuroprotective component in coffee, Neurobiol. Aging 46 (2016) 113–123.
[98] A.M. Sabogal-Guáqueta, J.I. Munoz-Manco, J.R. Ramírez-Pineda, M. Lamprea-Rodriguez, E. Osorio, G.P. Cardona-Gómez, 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 (2015) 134–145.
[99] N. Suganthy, K.P. Devi, S.F. Nabavi, N. Braidy, S.M. Nabavi, Bioactive effects of quercetin in the central nervous system: focusing on the mechanisms of actions, Biomed. Pharmacother. 84 (2016) 892–908, https://doi.org/10.1016/j.biopha.2016.10.011.
[100] L.M. Ittner, J. Götz, Amyloid-β and tau — a toxic pas de deux in Alzheimer's disease, Nat. Rev. Neurosci. 12 (2010) 67, https://doi.org/10.1038/nrn2967.
[101] R.A. Armstrong, The pathogenesis of Alzheimer's disease: a reevaluation of the “amyloid cascade hypothesis”, Int. J. Alzheimers Dis. 7 (2011) 630865, , https://doi.org/10.4061/2011/630865.
[102] C. Reitz, Alzheimer's disease and the amyloid cascade hypothesis: a critical review, Int. J. Alzheimers Dis. 2012 (2012).
[103] K. Jiménez-Aliaga, P. Bermejo-Bescós, J. Benedí, S. Martín-Aragón, Quercetin and rutin exhibit antiamyloidogenic and fibril-disaggregating effects in vitro and potent antioxidant activity in APPswe cells, Life Sci. 89 (25) (2011) 939–945, https://doi.org/10.1016/j.lfs.2011.09.023.
[104] H.A. Jung, S.H. Oh, J.S. Choi, Molecular docking studies of phlorotannins from Eisenia bicyclis with BACE1 inhibitory activity, Bioorg. Med. Chem. Lett. 20 (11) (2010) 3211–3215, https://doi.org/10.1016/j.bmcl.2010.04.093.
[105] W. Araki, Post-translational regulation of the β-secretase BACE1, Brain Res. Bull. 126 (2016) 170–177, https://doi.org/10.1016/j.brainresbull.2016.04.009.
[106] M. Ohno, Alzheimer's therapy targeting the β-secretase enzyme BACE1: benefits and potential limitations from the perspective of animal model studies, Brain Res. Bull. 126 (2016) 183–198, https://doi.org/10.1016/j.brainresbull.2016.04.007.
[107] R. Vassar, BACE1 inhibition as a therapeutic strategy for Alzheimer's disease, J. Sport Health Sci. 5 (4) (2016) 388–390, https://doi.org/10.1016/j.jshs.2016.10.004.
[108] S.L. Cole, R. Vassar, The Alzheimer's disease β-secretase enzyme, BACE1, Mol. Neurodegener. 2 (1) (2007) 22, https://doi.org/10.1186/1750-1326-2-22.
[109] M. Sathya, P. Premkumar, C. Karthick, P. Moorthi, K. Jayachandran, M. Anusuyadevi, BACE1 in Alzheimer's disease, Clin. Chim. Acta 414 (2012) 171–178.
[110] Ben Halima S, Mishra S, Raja KMuruga P, et al. (2016) Specific inhibition of β-secretase processing of the Alzheimer disease amyloid precursor protein. Cell Rep. 14(9):2127–2141 doi:https://doi.org/10.1016/j.celrep.2016.01.076.
[111] P.L. McGeer, E.G. McGeer, The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy, Acta Neuropathol. 126 (4) (2013) 479–497, https://doi.org/10.1007/s00401-013-1177-7.
[112] E. Giacobini, G. Gold, Alzheimer disease therapy—moving from amyloid-β to tau, Nat. Rev. Neurol. 9 (12) (2013) 677–686, https://doi.org/10.1038/nrneurol.2013.223.
[113] E. Karran, M. Mercken, B.D. Strooper, The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics, Nat. Rev. Drug Discov. 10 (2011) 698, https://doi.org/10.1038/nrd3505.
[114] V.N. Talesa, Acetylcholinesterase in Alzheimer's disease, Mech. Ageing Dev. 122 (16) (2001) 1961–1969, https://doi.org/10.1016/S0047-6374(01)00309-8.
[115] M. Singh, M. Kaur, H. Kukreja, R. Chugh, O. Silakari, D. Singh, Acetylcholinesterase inhibitors as Alzheimer therapy: from nerve toxins to neuroprotection, Eur. J. Med. Chem. 70 (2013) 165–188, https://doi.org/10.1016/j.ejmech.2013.09.050.
[116] H. Dvir, I. Silman, M. Harel, T.L. Rosenberry, J.L. Sussman, Acetylcholinesterase: from 3D structure to function, Chem. Biol. Interact. 187 (1) (2010) 10–22, https://doi.org/10.1016/j.cbi.2010.01.042.
[117] T. Mohamed, P.P. Rao, Design, synthesis and evaluation of 2,4-disubstituted pyrimidines as cholinesterase inhibitors, Bioorg. Med. Chem. Lett. 20 (12) (2010) 3606–3609.
[118] R. Anand, K.D. Gill, A.A. Mahdi, Therapeutics of Alzheimer's disease: past, present and future, Neuropharmacology 76 (2014) 27–50, https://doi.org/10.1016/j.neuropharm.2013.07.004.
[119] Maciel RM, Carvalho FB, Olabiyi AA, et al. (2016) Neuroprotective effects of quercetin on memory and anxiogenic-like behavior in diabetic rats: role of

ectonucleotidases and acetylcholinesterase activities. Biomed. Pharmacother. 84:559–568 doi:https://doi.org/10.1016/j.biopha.2016.09.069.
[120] Richetti SK, Blank M, Capiotti KM, et al. (2011) Quercetin and rutin prevent scopolamine-induced memory impairment in zebrafish. Behav. Brain Res. 217(1):10–15 doi:https://doi.org/10.1016/j.bbr.2010.09.027.
[121] M.R. Islam, A. Zaman, I. Jahan, R. Chakravorty, S. Chakraborty, In silico QSAR analysis of quercetin reveals its potential as therapeutic drug for Alzheimer's disease, Journal of Young Pharmacists 5 (4) (2013) 173–179, https://doi.org/10.1016/j.jyp.2013.11.005.
[122] J.A. Godoy, C.B. Lindsay, R.A. Quintanilla, F.J. Carvajal, W. Cerpa, N.C. Inestrosa, Quercetin exerts differential neuroprotective effects against H_2O_2 and Aβ aggregates in hippocampal neurons: the role of mitochondria, Mol. Neurobiol. 54 (9) (2017) 7116–7128.
[123] Chen J, Deng X, Liu N, et al. (2016a) Quercetin attenuates tau hyperphosphorylation and improves cognitive disorder via suppression of ER stress in a manner dependent on AMPK pathway. J. Funct. Foods 22:463–476.
[124] E. Puerta, J.E. Suárez-Santiago, N.S. Santos-Magalhães, M.J. Ramirez, J.M. Irache, Effect of the oral administration of nanoencapsulated quercetin on a mouse model of Alzheimer's disease, Int. J. Pharm. 517 (1–2) (2017) 50–57.
[125] Sharma D, Wani W, Sunkaria A, et al. (2016) Quercetin attenuates neuronal death against aluminum-induced neurodegeneration in the rat hippocampus. Neuroscience 324:163–176.
[126] Zhang X, Hu J, Zhong L, et al. (2016) Quercetin stabilizes apolipoprotein E and reduces brain Aβ levels in amyloid model mice. Neuropharmacology 108:179–192.
[127] S.H. Jung, E.A. Murphy, J.L. McClellan, M.D. Carmichael, J.M. Davis, The Dietary Flavonoid Quercetin Decreases Neuroinflammation in a Mouse Model of Alzheimer's Disease, Federation of American Societies for Experimental Biology, 2010.
[130] Braidy N, Behzad S, Habtemariam S, et al. (2017) Neuroprotective effects of citrus fruit-derived flavonoids, nobiletin and tangeretin in Alzheimer's and Parkinson's disease. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders) 16(4):387–397.
[131] H.J. Heo, C.Y. Lee, Protective effects of quercetin and vitamin C against oxidative stress-induced neurodegeneration, J. Agric. Food Chem. 52 (25) (2004) 7514–7517.