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REVIEW
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Neuropharmacological Effects of Quercetin: A Literature-Based Review

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Quercetin (QUR) is a natural bioactive flavonoid that has been lately very studied for its beneficial properties in many pathologies. Its neuroprotective effects have been demonstrated in many *in vitro* studies, as well as *in vivo* animal experiments and human trials. QUR protects the organism against neurotoxic chemicals and also can prevent the evolution and development of neuronal injury and neurodegeneration. The present work aimed to summarize the literature about the neuroprotective effect of QUR using known database sources. Besides, this review focuses on the assessment of the potential utilization of QUR as a complementary or alternative medicine for preventing and treating neurodegenerative diseases. An up-to-date search was conducted in PubMed, Science Direct and Google Scholar for published work dealing with the neuroprotective effects of QUR against neurotoxic chemicals or in neuronal injury, and in the treatment of neurodegenerative diseases. Findings suggest that QUR possess neuropharmacological protective effects in neurodegenerative brain disorders such as Alzheimer's disease, Amyloid β peptide, Parkinson's disease, Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis. In summary, this review emphasizes the neuroprotective effects of QUR and its advantages in being used in complementary medicine for the prevention and treatment o of different neurodegenerative diseases.

Abbreviations: ↑, increased; ↓, decreased; 3-NP, 3-nitropropionic acid; 6-OHDA, 6-hydroxy dopamine; ADA, adenosine deaminase; AChE, acetylcholinesterase; AKT, protein kinase B; AMPK, AMP-activated protein kinase; ALP, alkaline phosphatase; BACE1, beta-secretase 1; Bax Bcl-2, associated X; Bcl-2B-cell lymphoma 2; COX-2, Cyclooxygenase-2; CREB, cAMP response element-binding protein; GABA, γ-aminobutyric acid; GSH, glutathione; GT, glutamyl transpeptidase; hBMECs, brain microvascular endothelial cells; HIF1α, hypoxia inducible factor 1α; IL, interleukin-1; iNOS, inducible nitric oxide synthase; MCAO, middle cerebral artery occlusion; MPP + 1-methyl-4- phenylpyridinium ion; MPTP 1-methyl-4- phenyl-1, 2,3,6-tetrahydropyridine; NF-κB, nuclear factor kappa B; NO, nitric oxide; NTPDase nucleotoidase nucleoside triphosphate diphosphohydrolase; PI3K, phosphatidylinositol 3 kinase; PTZ, pentylenetetrazole; QA, quinolinic acid; SOD, superoxide dismutase; ROS, reactive oxygen species; TNF-α tumor necrosis factor-alfa; VEGF, vascular endothelial growth factor.

Keywords: quercetin, neuropharmacological effects, neural damage, signaling pathways, mechanisms, neurodegenerative disorders

INTRODUCTION

Neuropharmacology is the investigation of what medications mean for cell work in the sensory system and the neural components with its mechanisms through which they impact behavior (Yeung et al., 2018). There is plethora of neurological conditions such as neuropathic pain, neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD), psychological disorders.

The use of medicinal plants for the prevention or treatment of neurological diseases has a long history (Salehi et al., 2021a). Due to their active compounds such as flavonoids, curcumin, lycopene, resveratrol, sesamol, etc. several natural products have been tested and showed their neuroprotective effects *in vitro* and *in vivo* studies (Hanganu et al., 2019; Burlec et al., 2020). Quercetin (QUR, $C_{15}H_{10}O_7$), also known as 3,3′,4′,5,7-pentahydroxyflavone (**Figure 1**), is a unique bioflavonoid, plentifully found in various leafy foods and fruits e.g. apples, berries, chokeberries cilantro, dill, escapades, lingonberries, lovage, onions (Yang et al., 2020; Sharifi-Rad et al., 2021b). It exhibits several biopharmacological activities (Kawabata et al., 2015), including antioxidant (Chaudhary et al., 2015) and anti-inflammatory (Kim and Park, 2016; Zheng et al., 2016) activities, neuroprotective properties against CNS disorders, including memory impairment (Nassiri-Asl et al., 2013; Abdalla et al., 2014; Zhang et al., 2016), seizure (Nieoczym et al., 2014; Nassiri-Asl et al., 2016), Huntington's disease (HD) (Chakraborty et al., 2014), and PD (Gomez del Rio et al., 2013). QUR also exhibits anticonvulsant activity (Nassiri-Asl et al., 2013; Nassiri-Asl et al., 2016). QUR is clearly a polar auxin transport antagonist (Fischer et al., 1997).

This review focuses on emerging comprehension information to the preventive and therapeutic ability of this natural flavonoid against neurological and neurodegenerative diseases, along with its mechanisms of action. Additionally, we have also summarized the biological sources and other pharmacological activities of QUR.

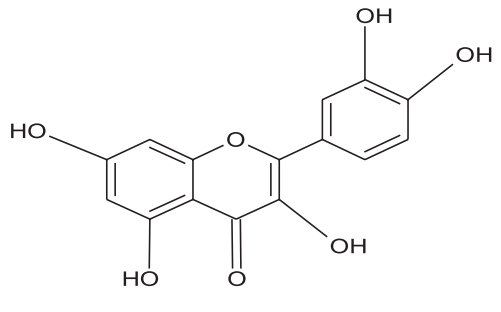

FIGURE 1 | Chemical structure of 2-(3,4-dihydroxy phenyl)-3,5,7-trihydroxychromen-4-one (Quercetin).

REVIEW METHODOLOGY

This updated review covers the neuroprotective effects and potential alternative therapeutic options of QUR in neurological disorders. Scientific data on the neuroprotective effects of QUR were collected from online databases such as PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Science Direct (http://www.sciencedirect.com/), and Google Scholar (https://scholar.google.com/).

Search keywords were: "Quercetin","biodisponibility" "neuroprotective", "neurodegenerative diseases", "oxidative stress", "neuroinflammation", "tau protein", "neurotrophic factors", "amyloid beta", "memory", "learning", "pharmaceutical formulations", "QUR encapsulation". The chemical structure was revised by consulting the open PubChem database (https://scholar.google.com/) and the scientific names of the plants were revised according to PlantList. For this updated review, were included: in extenso papers written in the English language, *in vitro* and *in vivo* experimental studies that showed the effective doses compared with control and studies hich highlighted the molecular mechanisms of the neuroprotective effects of QUR. Abstracts, communications, studies that included homoeopathic preparations or brain tumors associated with neurological/ neurodegenerative diseases were excluded.

BIOAVAILABILITY OF QUERCETIN

QUR is a flavonol known as a subcategory of flavonoids. These are plant pigments, known as phytonutrients with plenty of benefits for the body's health. This pigment can be found in many fruits, vegetables, plants and beverages such as berries, apples, cherries, red onions, tomatoes, broccoli and citrus, red wine and black (Suganthy et al., 2016). QUR can be assimilated by the daily consumption of fruits and vegetables (Khan et al., 2020). In vegetables, QUR is found in the highest amount in onions compared to other vegetables. One kilogram of onions contains around 300 mg of QUR (Khan et al., 2020; Kothari et al., 2020).

QUR has a bitter taste, low bioavailability due to poor solubility and absorption as well as rapid metabolism (Guo and Bruno, 2015; Khan et al., 2020). An *in vivo* study in pigs investigated the bioavailability and metabolism of QUR. An intravenous dose of 0.4 mg/kgc was initially administered and after seven days an oral dose of 50 mg/kgc. The results of this study showed that the apparent bioavailability of QUR was only 0.54 ± 0.19% when considering only free QUR, 8.6 ± 3.8% when measuring also the conjugated QUR in the intestinal wall and

17.0 ± 7.1% when considered also QUR metabolites (Ader et al., 2000).

QUR does not have the high efficiency of crossing the normal blood-brain barrier (Oliveira et al., 2021). Various methods have been tried to increase QUR's bioavailability such as the enzymatic modification or nanoencapsulation (Pateiro et al., 2021).

Enzymatically modified isoquercitrin (EMIQ) has an increased bioavailability and is prepared using a natural enzymatic process that attaches polysaccharides to convert QUR, which has poor bioavailability, into a water-soluble form (Alpha-Glycosyl Isoquercitrin) (Omi et al., 2019). This method has the advantage of high absorption and superior bioavailability. According to pharmacokinetic data, the absorption of Isoquercetin is up to 40 times higher (Cmax) than that of QUR and reaches maximum levels in the bloodstream in just 15 min (Omi et al., 2019). Therefore, Isoquercitrine is much more bioactive than QUR and has a broader spectrum of therapeutic activity.

Nanotechnologies and target carriers are the solution to overcome the disadvantage of low solubility and bioavailability, increased metabolism and low brain penetration of QUR (Naseri et al., 2015). Modern research has shown that there are many possibilities for the penetration of bioactive compounds into the brain such as blood-mediated receptor-mediated transcytosis (BBB) and coupling with transferrin receptors found on the luminal side of capillary endothelial cells of the brain. Therefore, the inclusion of QUR in transferrin-functionalized liposomes is a solution to facilitate QUR penetration into the brain (Pinheiro et al., 2020).

New nanoencapsulation pharmaceutical formulations such as phytosomes have been tried for increasing QUR bioavailability. Phytosomes are obtained from phospholipids, which are from the same material that makes up cell membranes. By encapsulation in phytosomes, QUR can cross the cell membrane and is delivered directly inside the cell, making it more bioavailable and easy to be absorbed and used by the tissues. This technology is similar to liposomal entanglement technology (Riva et al., 2019). In a randomized clinical trial, researchers compared two doses of QUR phytosomes administered orally (providing 100 and 200 mg of QUR), along with a single 500 mg dose of QUR (Riva et al., 2019). The results showed that, when administered in phytosomes, this compound could be administered at one-fifth of the dose of traditional QUR and at the same time to obtain a10 times higher exposure. This study showed that when encapsulated in phytosmes, QUR has a bioavailability of 50 times higher compared to QUR standard products.

QUERCETIN'S EFFECTS IN NEUROLOGICAL DISEASES: MOLECULAR MECHANISMS AND SIGNALING PATHWAYS

Quercetin Against Oxidative Stress

It is grounded by scientists that the human brain use 20% of the body's daily intake of O_2. The human brain has a significant amount of polyunsaturated fatty acids (Sharifi-Rad et al., 2021b). These along with transition metal ions and poor antioxidant enzymes makes the organ vulnerable in front of free radicals (Uttara et al., 2009; Buga et al., 2019; Aloizou et al., 2021). The neurotransmitters and excitatory amino acids act as a source of oxygen species like ROS, particularly present in the brain, promoting oxidative stress damage (Tsatsakis et al., 2019). ROS induce protein oxidation (Salehi et al., 2019a), lipid peroxidation (Salehi et al., 2019c), and neurons and glial cells leading to the death of neurons (Gilgun-Sherki et al., 2001). Moreover, aging established neuronal damage mediated by ROS cause neurodegeneration (Uttara et al., 2009; Alvarez-Arellano et al., 2020).

A series of studies have shown that the primary cause of neurodegenerative brain disease and vascular pathology is oxidative stress (Gandhi and Abramov, 2012; Sharifi-Rad et al., 2020d). Subsequently, the quest for a convincing instrument to counteract neuronal harm impacted by oxidative stress prompted the analysis of antioxidant molecules as a ROS scavenger (Feng and Wang, 2012; Salehi et al., 2020b).

Through scavenging oxygen radicals and metal chelating operations, QUR attenuates neuronal damage mediated by oxidative stress (Echeverry et al., 2010). The scavenging mechanism of QUR is followed by attenuating nitric oxide (NO) synthase and xanthine oxidase. Besides, QUR can activate the Nrf2-ARE signaling pathway and mitigate neuronal damage mediated by oxidative stress. γ-glutamyl-cysteine synthetase is elevated by Nrf2-ARE pathway for glutathione (GSH) synthesis (Arredondo et al., 2010) (**Figure 2**).

Several *in vitro* studies have shown that QUR, by its immediate and aberrant antioxidant action, enhances cell resistance to oxidative stress caused by hydrogen peroxide, β-amyloid peptide and 6-hydroxylamine (Ansari et al., 2009; Suematsu et al., 2011; Shokoohinia et al., 2015; Magalingam et al., 2016).

Omnipresently, a catalyst present in the human brain is paraoxonase 2 (PNO2), which protects the brain from neuroprotection by the reduction of injury caused by oxidation because they are located in mitochondria (Costa et al., 2014). QUR increases PNO2 expression in brain cells, macrophages, neurons, and striatal astrocytes, not only at the mRNA but also at the protein level (Boesch-Saadatmandi et al., 2009). The appropriate mechanism of expression of PNO2 by QUR can be associated with a high antioxidant effect or with the modification of JNK/AP-1 pathway. JNK/AP-1 pathway is known to enhance PNO2 expression (Granado-Serrano et al., 2010).

Quercetin Against Neuroinflammatory Responses

For neurodegenerative diseases, inflammation plays a key role (Alam et al., 2016; Sharifi-Rad et al., 2020b). Neuroinflammation tends to be a secondary reaction triggered by early brain injury (trauma, cancer, amyloid beta-peptide (Aβ) and hyperphosphorylated tau) that cause significant neuronal damage (Glass et al., 2010; Sharifi-Rad et al., 2021a). Therefore, in the creation of different neuropathologies,

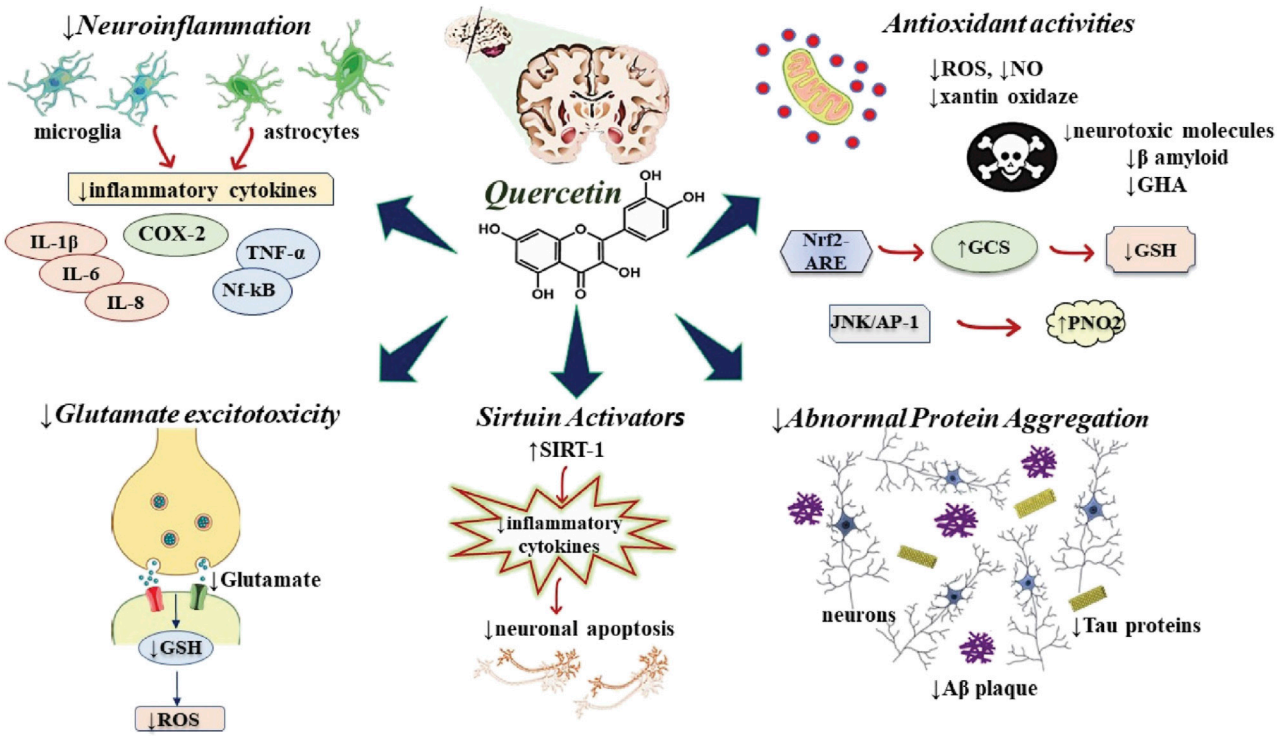

FIGURE 2 | Diagram with possible neuroprotective mechanisms of QUR. The figure highlights the neuronal neuroprotective action in various signaling pathways that lead to the release of proinflammatory cytokines, neurodegeneration and cellular apoptosis. *Abbreviations:* ↑, increase; ↓, decrease; Aβ, amyloid beta-peptide; GCS, γ-glutamyl-cysteine synthetase; GSH, glutathione; IL, interleukin; JNK, c-Jun N-terminal kinase; NO, nitric oxide; Nrf2-ARE, Nuclear factor erythroid-derived 2-like 2-antioxidant responsive element; PNO2, paraoxygenase 2; ROS, reactive oxygen species; SIRT1, sirtuin 1; TNF-α, tumor necrosis factor-alfa.

inflammation is now considered as a driving factor (Smith et al., 2012; Tsoukalas et al., 2021). Neuron-like activation of microglia and astrocytes induces pro-inflammatory mediator expression including such as cytokines (interleukin (IL)-1β, tumor necrosis factor (TNF)-α, complementary components, acute-phase protein (Smith et al., 2012), which can stimulate inducible nitric oxide synthase (iNOS) and NO production with abnormal phagocytic activity (Lyman et al., 2014) (**Figure 2**). All these phages contribute to neuronal degeneration and neurodegenerative disease development such as AD (Heneka et al., 2015), PD (Rocha et al., 2015), HD (Hsiao et al., 2013), multiple sclerosis (MS) (Naegele and Martin, 2014; Padureanu et al., 2019), and amyotrophic lateral sclerosis (ALS) (Hooten et al., 2015). CNS demonstrates extreme prevalence to inflammatory stimuli by increased development of cytokines and ROS with increased phagocytic potential during aging (Hickman et al., 2013).

Neuroinflammation can be suppressed by anti-inflammatory agents that can stimulate NO development, cascades of glial activation and inflammatory cytokines and prevent neuronal death (Lee et al., 2008). Several *in vitro* and *in vivo* experiments have demonstrated that QUR has significant anti-inflammatory activities (Assi and El Sayed, 1998). In PC12 cells and zebrafish models, QUR blocked inflammation induced by the toxicity of 6-hydroxydopamine (6-OHDA) via repressing overproduction of NO, iNOS enzyme, and other inflammatory genes (Zhang et al., 2011).

Similarly, QUR inhibited lipopolysaccharide (LPS)/Interferon γ induced inflammation by abrogating iNOS expression (Chen et al., 2006), downregulating the extracellular signal-regulated kinase, c-Jun, N-terminal kinase, Akt, Src, Janus kinase-1, activating protein-1 (AP-1) (Kim et al., 2005), and enhancing the expression of heme oxygenase (HO)-1 (Sun et al., 2015). Besides, in astrocytes, QUR decreases pro-inflammatory cytokines (e.g., TNF-α and IL-1α) (Sharma et al., 2007) and diminished microglial activated neuronal cell death in microglial N9-neuronal (PC12) co-culture (Bureau et al., 2008).

By downregulating TLR4 and COX2, QUR along with β-cyclodextrin-dodecylcarbonate nanoparticles illustrated strong anti-inflammatory activity. These nanoparticles demonstrated improved blood-brain cognitive pathways and pharmacokinetics to target cells (Testa et al., 2014). In brain tissue, QUR attenuates microglial activation and inflammation-induced neuron death evoked by 1-methyl-4-phenylpyridinium (Sternberg et al., 2008), and IL-1β and monocyte chemoattractant protein (MCP)-1 expression (Jung et al., 2010).

Furthermore, astrocytes liberate pro-inflammatory cytokines (e.g., TNF-α, IL-1, IL-6) and neurotoxic factors and cause neuronal damage (Niranjan, 2014). QUR exerts a defensive effect on tert-butyl hydroperoxide and H2O2 toxicity in astrocytes via modulating ROS generation, decreasing apoptosis and boosting HO-1 transcription. Moreover, expression of glutamate-cysteine ligase (GCL) and GSH

synthetase was increased dramatically by QUR, in astrocytes and attenuated inflammation by repression of IL-1β,6,8, monocyte chemoattractant protein-1 and ROS production release (Chen et al., 2006; Sharma et al., 2007). Therefore, QUR exhibits a potent anti neuroinflammatory activity, because QUR can repress TNF-α via amplifying the NFkB signaling pathway (Madhavan et al., 2009), with its antioxidant effect (Boesch-Saadatmandi et al., 2009).

Abrogation of Glutamate-Mediated Excitotoxicity

In CNS, L-glutamate is a stimulatory neurological substance that forms memory and learning by preserving synaptic plasticity and creating neural networks (Shigeri et al., 2004; Salehi et al., 2020c). In the postsynaptic terminal, ionotropic receptors and G protein-coupled receptors come into contact with glutamate discharged from the presynaptic terminal, mediating rapid excitatory transmission (Marshall, 2001). Glutamate uptake represses the molecular action of the stimulatory amino acid regulator in glia and astrocytes accompanying the synaptic connections (Dong et al., 2009).

Excitotoxicity is associated with prolonged and downregulated stimulation of glutamate receptors, which causes epilepsy, hypoxic-ischemic brain damage, neurotrauma, and neurological diseases such as AD, MS, ALS, etc (Akyuz et al., 2021). Moreover, excitotoxicity is found worldwide via NMDA receptors mostly by the uncontrolled accumulation of Ca2+ ions (Choi, 1992), AMPA receptors or voltage-gated Ca2+ channels which trigger proteases, phospholipases, and nucleases, that provoke apoptosis and damage to the brain (Choi, 1992). Cytosolic Ca2+ homeostasis modification contributes to mitochondrial dysfunction, ROS generated stress leading toward the death of neurotoxic cells (Rego and Oliveira, 2003; Szydlowska and Tymianski, 2010; Esposito et al., 2013).

QUR from the extract of onion peels and Hypericum perforatum L, by lessening ROS Production outcome, glutamate-induced Ca2+ upsurge, retention of mitochondrial membrane potentials, and downregulation a plethora of biochemical markers linked with cell death and autophagy, neuronal cells were protected against excitotoxicity insults (Silva et al., 2008; Yang et al., 2013) (**Figure 2**).

Inhibition of Cholinesterase Activity

The cholinergic hypothesis shows that the main cause of cognitive dysfunction in AD is a reduction of the number of adrenoceptors including cholinergic and acetylcholine receptors (Sabri et al., 2008). The vital enzyme implicated in controlling the synaptic level of Ach is acetylcholinesterase (AChE) (Greig et al., 2002). Several studies have shown that AChE also encourages Aβ accumulation resulting of neuronal damage in AD patients (Inestrosa et al., 2000). Therefore, AChE inhibition is considered a potential target for AD, increasing the supply of Ach in regions of the brain and reducing Aβ uptake (Anand and Singh, 2013; Colović et al., 2013). The treatment with AChE antagonists for AD patients in current symptomatic treatment is mild to moderate (Murray et al., 2013).

In AD patients, AChE inhibitors improve nicotinic receptor expression, thereby enhancing cognitive memory (Parsons et al., 2013). Additionally, AChE blockers not only amplified the synthesis of amyloid precursor protein (APP) but also attenuated Aβ toxicity (Inestrosa et al., 2000). QUR is therefore now a key component that shows AChE inhibiting activity (Islam et al., 2013). Under several *in vitro* condition, evaluation of QUR inhibitory AChE operation shown that this effect is competitive (Jung and Park, 2007). In *in vivo* PD models, elevated level QUR dosage dramatically reduces the effect of AChE in the hippocampal zone (Sriraksa et al., 2012).

Modulation of Abnormal Protein Aggregation

In many neurodegenerative diseases, the typical pathological hallmarks are protein collapse and aggregation along with neurodegeneration (Salehi et al., 2020a). In the folding and aggregation of the protein, posttranslational changes play a pivotal part. Protein phosphorylation plays a key role in accumulation and sensitivity in most neurodegenerative disorders (Salazar and Höfer, 2009; Salehi et al., 2021b).

Abrogate Alpha-Synuclein Fibrillisation

Alpha-synuclein (alpha-Syn) is part of the pathological hallmark of PD as well as other diseases commonly known as synucleinopathies (Baba et al., 1998). S129, a main component of alpha-Syn, is generally associated with cytoskeletal, vesicular trafficking proteins and enzymes associated with protein serine phosphorylation (Waxman and Giasson, 2011). Multiple protein kinases such as casein kinases, G-protein coupled receptor kinases, and polo-like kinases) phosphorylation of S129 contributes to the agglomeration of alpha-Syn producing amalgamations and homeostasis of synaptic vesicles and neurotransmission defects (Saha et al., 2004). In a plethora of PD patients along with synucleinopathies including as dementia, multiple system atrophy and others, aggregate types of alpha-Syn developing amalgamations were commonly observed (Waxman and Giasson, 2008). QUR demonstrated a protective effect against synucleinopathies by effectively inhibiting alpha-Syn aggregation. QUR attaches to alpha-Syn covalently, generating QUR-alpha-Syn complex that increases hydrophilicity and prevents fibrillation. Therefore, QUR efficiently breaks down fibrils through protein-QUR interaction and separated them into stable oligomers (Zhu et al., 2013).

Tau Protein Alteration

Tau proteins are microtubule-associated and expressed protein in the neurons of CNS and PNS that are necessary for microtubule stabilization (Wang and Liu, 2008) (**Figure 2**). To determine the ability to bind to microtubules, Tau protein phosphorylation is necessary. Hyper-phosphorylation contributes to isolation, self-aggregation, and de-polymerization of the microtubule leads to final neuronal death (Tai et al., 2012). The HSP 70 and glycogen synthase kinase 3β (GSK3β) exert a critical role in tau phosphorylation and related cognitive damage in AD (Blair et al., 2013).

Updated therapeutics for attenuating tau pathologies such as drugs that inhibit tau aggregation or modify tau-effector protein activity such as kinase inhibitors (GSK3β), microtubule stabilizer and HSP70 inhibitor (Sharifi-Rad et al., 2020e). Most researchers have stated that QUR can inhibit tau pathology caused by okadaic acid by dramatically suppressing tau protein hyper-phosphorylation (Jiang et al., 2016). The inhibition of tau protein phosphorylation is made by inactivating GSK3β (Johnson et al., 2011), through the modulation of the PI3K/Akt/GSK3β pathway (Lu et al., 2006; Jiang et al., 2016).

Anti-Amyloidogenic Effect

Intraneuronal neurofibrillary tangles, extracellular senile plaque deposition, and vascular amyloid are found in AD (Selkoe, 2001; Sharifi-Rad et al., 2020a). Aβ peptide is formed by an aberration in APP, main sections of senile plaques, proteolytic processing, and Aβ (1–42) peptide aggregation is neurotoxic (Portelius et al., 2006). Therefore, the development of drugs that prevent the formation of amyloid or attenuate the aggregation of Aβ and facilitate the reduction of irregular fibrillary aggregates serves as an important therapeutic approach to AD care (Salloway et al., 2008).

Several *in vitro* reports demonstrate that QUR inhibits Aβ fibrils formation by enhancing the hydrophobic bond between the phenyl rings with β-sheet structures of Aβ and destabilizes the preformed mature fibrils (Ono et al., 2003; Jiménez-Aliaga et al., 2011; Zaplatic et al., 2019) (**Figure 2**). In addition, the B ring group 30′40-dihydroxyl plays a vital activity in the anti-aggregation effect (Jiménez-Aliaga et al., 2011).

Moreover, QUR represses Aβ peptides aggregation by promoting macroautophagy and proteasomal degradation pathways (Regitz et al., 2014). Furthermore, by direct abrogation QUR binds and inhibits β-site APP cleaving enzyme-1 (BACE-1) activity and thus prevents Aβ (1–42) formation (Shimmyo et al., 2008). Via their keto-enol group, QUR can also interact competitively with Aβ on its metal-binding site, avoiding oxidation reactive stress induced by the interaction of Aβ-Cu2+. QUR prevents amyloid aggregation through its dual inhibitory action (metal chelator and Aβ interactor) (Tay et al., 2013).

Autophagy Induced Neuroprotective Effect

Autophagy, a cellular destructive mechanism involving the recycling of cellular components and the removal of damaged and aggregated protein by a lysosomal degradative process. The basal autophagy process is the key functional integral component of the CNS, preventing damaged components and protein consumption in the nervous system through its defensive protocol (Siokas et al., 2021).

Mutations contribute to neurodegeneration via amplifying the gene-related to autophagic processes (Nixon, 2013). Reports have shown that QUR serves as an efficient autophagy simulator in high glucose Schwann cells (Qu et al., 2014), and QUR antagonizes Aβ (1–42) mediated neurotoxicity by inducing autophagy processes (Regitz et al., 2014).

Quercetin and Neurotrophic Factors

For the development of a functionally improved nervous system, there are neurite formation and synaptic patterning (Nussbaum et al., 2017). As the injured brain which an absence of regenerative ability, natural bioactive phytochemicals can improve the action of the neurotrophic factors that help to promote neurite outgrowth, contributing to neurological regeneration (Moore et al., 2006). *In vitro* studies showed that QUR and its derivative (isoquercetin) induced substantial neurotrophin (NGF) and BDNF-induced neurite outgrowth through activation of Na+/K+/2Cl-cotransporter isoform (NKCC1) (Nakajima et al., 2011) and modulate Rho GTPase enzyme activity (Palazzolo et al., 2012).

QUR significantly induces neuritis and neurite duration at a lower concentration (1 nM) by triggering the P13K/AKT pathway (Tangsaengvit et al., 2013). QUR has increased neurotrophic neurite-related proteins (e.g., growth-related protein-43 expression, microtubule-related protein (MAP) and tau, synaptophysin and synapsin) and promotes neuronal survival (Moosavi et al., 2016). In addition, QUR showed improved brain development and synapses through CREB (cyclic AMP response element-binding protein) phosphorylation which important for growth of neurite, thus increasing the rate of a neurotrophic factor generated from the brain that is essential for neurogenesis (Tchantchou et al., 2009). **Table 1** summarized the neuroprotective effects of QUR in several *in vitro* and *in vivo* models.

Targeting of Sirtuins in Age-Related Neurodegenerative Disorders

Sirtuins (SIRT 1–7), a member of signal proteins that exert a role in metabolic regulation, stress and longevity responses. SIRT1 is predominantly located in the hippocampus of the brain. A few studies showed that the induction of SIRT1 by calorie restriction (CR) diet determine the protective effect against dopamine receptor neurodegenerative disorder (Tchantchou et al., 2009; Gräff et al., 2013), attenuating Aβ peptide formation, and enhancing longevity (Nazir and Jadiya, 2013).

SIRT-1 is responsible for Aβ peptide inhibition, Bax-induced apoptosis suppression and suppression of a plethora of other pro-apoptotic factors (Aloizou et al., 2021). Natural bioactive compounds or drugs may act as neuroprotective agents by modulation of SIRT1 protein expression (Salehi et al., 2021a). QUR has been reported to exhibit neuroprotective effect and anti-ageing effect via induction and activation SIRT1 (de Boer et al., 2006) (**Figure 2**). Studies indicate that QUR can activate SIRT1-dependent pathways and modulate pro-inflammatory substances, indicating its use to treat MS and ALS (Hendriks et al., 2003).

Memory Enhancement Effect

In various *in situ* models, QUR has been documented to penetrate the blood-brain barrier (Youdim et al., 2004), which may be one of the competing variables for its cognitive enhancement ability. Many studies have shown that in several neurodegenerative disorders, including PA, AD and chronic cerebral ischemia models, QUR can alleviate behavioral and cognitive disability (Yao et al., 2010). QUR improves learning and memory in the AD animal model, decreases senile plaques, mitochondrial

TABLE 1 | Neuroprotective effects of quercetin and/or its derivatives against various neurodegenerative diseases and other brain disorders.

Quercetin/Derivatives/ Source	Test model *in vitro/in vivo*	Exposure	Effects/Molecular mechanisms	References
Alzheimer's disease				
Quercetin	HT-22 mouse hippocampal cells/*in vitro*	Glutamate induced toxicity	↓lipid peroxidation, ↓GSH oxidation, ↓ROS	Ishige et al. (2001)
	HEK 293 human embryonic kidney cells/*in vitro*	Aβ (1–42)	↓ Aβ peptides, ↓the performed mature fibrils	Ono et al. (2003)
	HT22 murine neuroblastoma cells/*in vitro*	Aβ (25–35)	↓ amyloidogenic Aβ peptides	Kim et al. (2005)
	Primary hippocampal cultures/*in vitro*	Aβ (1–42)	↓apoptosis, ↓ ROS, ↓mediated damage	Ansari et al. (2009)
Quercetin/*Ginkgo biloba*	SHSY5Y human neuroblastoma cells/*in vitro*	Aβ (1–42)	↓Akt signaling pathways, ↓ERK1/2, ↓JNK, ↓Aβ toxicity, ↓platelet-activating factor	Shi et al. (2009)
Quercetin-3′-glucoside	PC12 cells/*in vitro*	Aβ	↓H_2O_2 ↑CREB/BDNF signaling pathway, ↓Aβ, ↓ROS	Yu et al. (2020)
Quercetin/ginkgoflavonols	Double Transgenic (TgAPP/PS1) mice/*in vivo*	-	Reversed the spatial learning deficit	Hou et al. (2010)
Quercetin	APP stable cells/*in vitro*	Aβ (25–35)	↓ROS, ↓BACE, ↓ Aβ, ↓GSH, ↓lipid peroxidation	Jiménez-Aliaga et al. (2011)
Quercetin-3-*O* glucuronide	APP695-transfected SH-SY5Y cells/*in vitro* Tg2576 AD primary neuron cultures/*in vitro*	Aβ (1–42)	↓Aβ peptides, ↑CREB signaling, ↓Aβ aggregation, ↑mitogen-activated protein kinase, ↑neuronal survival, ↑c-Jun N-terminal kinases, ↓stress-induced impairments	Ho et al. (2013)
Quercetin/*Acanthopanax henr*	Cell free system/*in vitro*	-	↓ acetylcholinesterase, ↑antioxidant activity	Zhang et al. (2014)
Quercetin	Triple-transgenic mouse model of AD/*in vivo*	-	↓tauopathy, ↓β-amyloidosis, ↑memory, ↑learning ↓microgliosis, ↓astrogliosis	Sabogal-Guáqueta et al. (2015)
	APP23 AD model mice/*in vivo*	-	↓eIF2α, ↓ATF4, ↓GADD34, ↑memory in aged mice, ↓deterioration in memory at the early stage of AD	Hayakawa et al. (2015)
Parkinson's disease				
Quercetin	Microglial (N9)-neuronal (PC12) cells/*in vitro*	MPP	↓iNOS in microglial cells, ↓DNA fragmentation, ↑apoptosis, ↓nuclear translocation of apoptosis-inducing factor, ↓caspase-3 activation	Bournival et al. (2012)
Quercetin glycoside	PC12 cells/*in vitro*	6-OHDA	↑antioxidant activity, ↑GSH, ↑GPx	Magalingam et al. (2016)
Quercetin	Wistar rats/*in vivo*	6-OHDA	↑spatial memory, ↓oxidative stress, ↓AChE activity, ↑antioxidant activity, ↓neuronal damage	Sriraksa et al. (2012)
Quercetin	Mice/*in vivo*	MPTP	↓striatal dopamine depletion, ↓motor deficits, ↑GPx, ↑SOD	Lv et al. (2012)
Quercetin	Cell-free system	α-Synuclein	↓Aβ fibrillation	Zhu et al. (2013)
Quercetin	Wistar rats/*in vivo*	Roteno	↓nigral GSH depletion, ↓ROS, ↓striatal DA loss, ↑mitochondrial complex, ↑activity and scavenging hydroxyl radical, ↓ neuronal death	Karuppagounder et al. (2013)
Isoquercetin	PC12 cells/*in vitro*	6-OHDA	↓ROS, ↑SOD, ↑ antioxidant enzymes (GSH, catalase, glutathione peroxidase)	Magalingam et al. (2014)
Quercetin	Wistar rats/*in vivo*	Haloperidol MPTP	↑the cataleptic score, ↓actophotometer activity, ↑GSH, ↓lipid peroxidation, ↓ROS	Pany et al. (2014)
Quercetin + fish oil	Wistar rats/*in vivo*	Rotenone	↑mitochondrial functions, ↑GSH, ↑antioxidant defences	Denny Joseph and Muralidhara (2013)
Hutington's disease				
Quercetin	Wistar rats/*in vivo*	3-NP	↑ATP, ↑activity of complex II and V enzyme of respiratory chain complex, ↓ROS, ↑SOD, ↑catalase, ↓lipid peroxidation	Sandhir and Mehrotra (2013)
Quercetin + fish oil	Wistar rats/*in vivo*	3-NP	↓oxidative stress, ↑motor function	Denny Joseph and Muralidhara (2013)
Quercetin + sesamol	Wistar rats/*in vivo*	QA	↓neurochemical alterations in the rat brain, ↓behavioral, ↓biochemical, ↑antioxidant effects, ↑ anti-inflammatory activity	Kuhad et al. (2013)
Quercetin + lycopene	Wistar rats/*in vivo*	3-NP	↓anxiety, ↓depression	Jain and Gangshettiwar (2014)
Quercetin	Sprague dawley rats/*in vivo*	3-NP	↓gait despair, ↓microglial proliferation, ↓anxiety, ↑astrocyte numbers in the lesion core, ↓motor coordination deficits, ↓serotonin metabolism	Chakraborty et al. (2014)

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TABLE 1 | (*Continued*) Neuroprotective effects of quercetin and/or its derivatives against various neurodegenerative diseases and other brain disorders.

Quercetin/Derivatives/ Source	Test model *in vitro/in vivo*	Exposure	Effects/Molecular mechanisms	References
Multiple sclerosis				
Quercetin	Human umbilical cord blood-derived cultured mast cells/ *in vitro*	IL-1	↓demyelination, ↑PKC phosphorylation, ↑IL-6, ↓IL-1, ↑p38, ↓mast cell activation	Kandere-Grzybowska et al. (2006)
Quercetin	Peripheral blood mononuclear cells isolated from MS patients/*in vitro*	-	↑IL-6, ↓immune response, ↓TNF-α, ↓demyelination	Sternberg et al. (2008)
Brain ischemic injury				
Quercetin	Sprague- dawley rats/*in vivo*	Traumatic brain injury	↓neutrophil infiltration, ↑GSH, ↓myeloperoxidase activity	Graham et al. (2000)
Quercetin	Sprague- dawley rats/*in vivo*	Acute traumatic spinal cord injury	↑iron clearance in the spinal cord through its ↑chelating effect, ↑motor function	Schultke et al. (2010)
Quercetin	Swiss albino mice/*in vivo*	High altitude hypoxia	↓HIF1α, ↓hypoxia, ↓VEGF, ↓brain dysfunction, ↓active caspase 3, ↓ubiquitin	Sarkar et al. (2012)
Quercetin-3-O methyl ether	Sprague- dawley rats/*in vivo*	MCAO rat model	↓ oedema, ↓oxidative stress-mediated damage, ↓behavioral deficit	Jung et al. (2012), Lee et al. (2015)
Quercetin	Sprague– Dawley rats/*in vivo*	MCAO rat model	↑PI3K/Akt, ↑antioxidative, ↑anti-apoptotic signaling	Chang et al. (2014)
Quercetin	Wistar rats/*in vivo*	Global cerebral ischemia	↑AKT, ↑anti-apoptotic signaling pathway, ↑antioxidant activity, ↓ROS	Lei et al. (2015)
Quercetin	Sprague-dawley rats/*in vivo*	Transient focal cerebral ischemia	↑Ca^{2+} into the mitochondrial matrix, ↑electron transport chain activity	Nichols et al. (2015)
Quercetin + vitamin E	Primary cortical neurons/ *in vitro*	Induced ischemic stroke	↑CREB phosphorylation, ↑ NO, ↑autophosphorylation of CaMK II, IV, ↑Ca^{2+}/ calmodulin-dependent kinases II, IV, ↑mitochondrial biogenesis, ↑ BCl-2	Nichols et al. (2015)
Epilepsy				
Quercetin/*Anisomeles malabarica*	Wistar rats/*in vivo*	Diazepam + PTZ	Stimulating $GABA_A$ receptors, NMDA receptors' antagonist	Choudhary et al. (2011)
Quercetin	Wistar rats/*in vivo*	PTZ	↑anticonvulsant effects, ↓seizure severity, ↓lipid peroxidation via its ↑antioxidant effect, ↑memory retrieval in the passive avoidance task	Nassiri-Asl et al. (2013)
Quercetin	Albino rats/*in vivo*	PTZ	↑ antiseizure effect, ↑anticonvulsant effect	Sefil et al. (2014)
Quercetin	Wistar rats/*in vivo*	6-OHDA	↓excitability in neurons involved in epilepsy,↓neuroplastic changes in neural circuits, ↓NMDA receptor functionality	Mehdizadeh et al. (2009)
Miscellaneous neurotoxin				
Quercetin,/*Opuntia ficus-indica*	Rat cortical cells/*in vitro*	H_2O_2; xanthine/xanthine oxide	↑antioxidant activity	Dok-Go et al. (2003)
Quercetin	Mice/*in vivo*	Ethanol intoxication	↓cognitive impairment, ↑antioxidant mechanisms	Singh et al. (2003)
Quercetin	SH-SY5Y neuroblastoma cells/*in vitro*	6-OHDA	↑antioxidant activity	Kaariainen et al. (2008)
Quercetin/*Ginkgo biloba*	N2a cells/*in vitro*	Juglone (5- hydroxy-1, 4-napthoquinone)	↓ROS	Smith and Luo (2003)
Quercetin-3-O-galactoside)/ *Hypericum perforatum*	PC12 cells/*in vitro*	H_2O_2/tert-butyl hydroperoxide	↓apoptosis mediated cell death, ↓ROS, chelates the transition metal ions	Liu et al. (2005)
Quercetin-3-O-β-D-glucopyranoside/ *Echinophora cinerea*	PC12 cells/*in vitro*	H_2O_2	↓ ROS	Shokoohinia et al. (2015)
Quercetin	PC12 cells/*in vitro*	H_2O_2/Xanthine oxidase	↓neuronal injury (IC_{50} = 0.5–0.7 μg/ml), ↑antioxidative effect	Shokoohinia et al. (2015)
Quercetin	SH-SY5Y cells/*in vitro*	H_2O_2	↓pro-apoptotic bax gene, ↓lactate dehydrogenase, ↑antiapoptotic Bcl-2, ↓caspase cascade, ↑DNA fragmentation, ↑apoptosis	Suematsu et al. (2011)
Quercetin	ICR mice/*in vivo*	Trimethyltin	↓acetylcholinesterase; ↓peroxidation of polyunsaturated fatty acid in membrane, ↑cognitive ability	Choi et al. (2012)
Quercetin	Mice/*in vivo*	High cholesterol-induced neurotoxicity	↑AMPK, ↓activation of microglia, ↓iNOS, ↓COX-2, ↓IL-1β, ↓TNF-α, ↓BACE1	Lu et al. (2010)
Quercetin	Wistar rats/*in vivo*	Cadmium intoxication	↓AChE, ↓NTPDase, ↓ADA activities in cerebral cortex synaptosomes	Abdalla et al. (2013)

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TABLE 1 | (*Continued*) Neuroprotective effects of quercetin and/or its derivatives against various neurodegenerative diseases and other brain disorders.

Quercetin/Derivatives/ Source	Test model *in vitro/in vivo*	Exposure	Effects/Molecular mechanisms	References
Quercetin	Swiss Albino mice/*in vivo*	Olfactory bulbectomy	↓NMDA receptors, ↑NO, ↓depression, ↑antioxidant activity	Holzmann et al. (2015)
Quercetin	Chinese kunming mice/*in vivo*	High-fat diet	↑HDL decrease, ↓ total cholesterol, ↑CREB, ↓oxidative damage, ↑PI3 K/AKT/Nrf2, ↓ROS, ↓MDA, ↑cognitive impairment	Xia et al. (2015)
3′-O-(3-chloropivaloyl) quercetin (CPQ)	BV-2 microglial cells/*in vitro*	Lipopolysaccharides	↓NF-κB, ↓inflammatory mediators: ↓NO, ↓TNF-α, ↓iNOS; ↓ proliferation of BV-2 microglial cells	Mrvova et al. (2015)
Quercetin	Albino rats/*in vivo*	Aluminum	↓mitochondrial DNA oxidation, ↓ROS, ↓oxidative stress, ↑Bcl-2,, ↓p53, ↑MnSOD, ↓translocation of cytochrome-c, ↓Bax, ↓caspase-3, ↓DNA damage	Sharma et al. (2016)
Aging and cognitive function				
Quercetin	Kunming mice/*in vivo*	Galactose	↑SOD, ↑cognitive impairment, maintain Ca^{2+} homeostasis, ↑GAP43 mRNA expression, ↑normal function of neurons	Lu et al. (2006)
Quercetin	*Caenorhabditis elegans/in vivo*	Thermal stress	↑radical scavenging activity, ↓MnSOD	Saul et al. (2008)
Quercetin/Quercetin caprylate	HFL-1 primary human fibroblasts/*in vitro*	-	↑cellular lifespan, ↑proteasome activation, ↑neuronal survival, ↑antiaging effect; ↑rejuvenating effect, ↑antioxidant properties	Chondrogianni et al. (2010)

dysfunction and increases the antioxidative mechanism through AMP protein kinase, and can enhance cognitive deficits (Wang et al., 2014).

QUR has oxidative defense and anti-apoptotic activity and enhanced memory dysfunction caused by hypoxia (Prasad et al., 2013; Boyina et al., 2020). By suppressing oxidative stress, QUR improves cognitive deficit (Mohammadi et al., 2014). QUR has also increased learning and memory problems (Kumar et al., 2008; Richetti et al., 2011; Sharma et al., 2013). In addition, by increasing GSH level, scavenge hydroxyl free radical, Na+/K+ adenosine triphosphatase and suppressing iNOS activity, QUR attenuated cognitive impairments and neurological changes in the brain of mice (Sun et al., 2007).

In addition, QUR strengthened AD's spatial memory through antioxidant and scavenging properties (Ashrafpour et al., 2015). In mice, QUR supplements administered showed improved learning and memory function (Liu et al., 2006).

DISCUSSION

The most serious health conditions in the modern period are known to be brain disorders (Salehi et al., 2019b). More than 600 diseases affect the CNS, including the 21st century scourge of neurodegenerative conditions includes AD, ALS, PD, and HD (Magalingam et al., 2018; Sharifi-Rad et al., 2020c). Due to the differences in signs involved with any of these CNS diseases, the basic mechanisms of neurodegeneration are interrelated (Calina et al., 2020). Oxidative damage, mitochondrial malfunction, glutamate excitotoxicity, inflammatory reaction, protein accumulation and modification in metal ion homeostasis are the principal factors leading to CNS disorders (Chen et al., 2005; Nieoullon, 2011; Rasool et al., 2014).

In the current analysis, the multitargeted molecular mechanisms highlighted in preclinical studies have been outlined concerning QUR and its potential neuroprotective impact (**Figure 3**).

A strong point of this paper is that many studies have been included with recent meta-analyses and reviews that contain the most important data synthesized by the mechanisms of action and molecular targets of Quercetin on its neuroprotective effect.

Through this ability to modify the functioning of chemical synapses, QUR has an important role in neural plasticity. Plasticity is a key factor in the neuronal development of the brain, the proper functioning of the nervous system, adaptation to the changing environment, aging and other chronic diseases (Barreca et al., 2016).

The main therapeutic limitation derives from the fact that studies have shown that the absorption of QUR through food is quite low. Also due to reduced oral bioavailability, QUR should be administered parenterally to exert its neuroprotective effects. New therapeutic horizons were opened with obtaining recent nano-pharmaceutical formulations such as micelles, phytosomes or encapsulated QUR, that increase its brain concentration. (Benameur et al., 2021).

The QUR's activity in food depends on the method of preparation, harvest time and storage conditions. The absorption of QUR is enhanced by the presence of dietary fats (being a lipophilic compound), and the presence of insoluble fibers. Bioavailability is better if whole foods are consumed (Dabeek and Marra, 2019). Although QUR is present in many foods, the diet covers between 0 and 30 mg of QUR per day (Batiha et al., 2020). No clear studies are indicating the daily requirement, but it is assumed that this dose is well below our needs.

QUR is a compound that is part of bioflavonoids, a potent anti-oxidative and anti-inflammatory natural compound found in several vegetables and fruits (Chen et al., 2020; Sharifi-Rad et al., 2020d). Due to its anti-inflammatory effect, some studies have shown that QUR can be useful as a complementary treatment for neurodegenerative diseases such as AD or PD, by stimulating the expression of HO-1, which reduces NO production and suppress pro-inflammatory markers, TNF-α and IL-1α. QUR also protects the brain from the toxicity associated with D-galactose. This protection is associated with QUR's ability to elevate superoxide

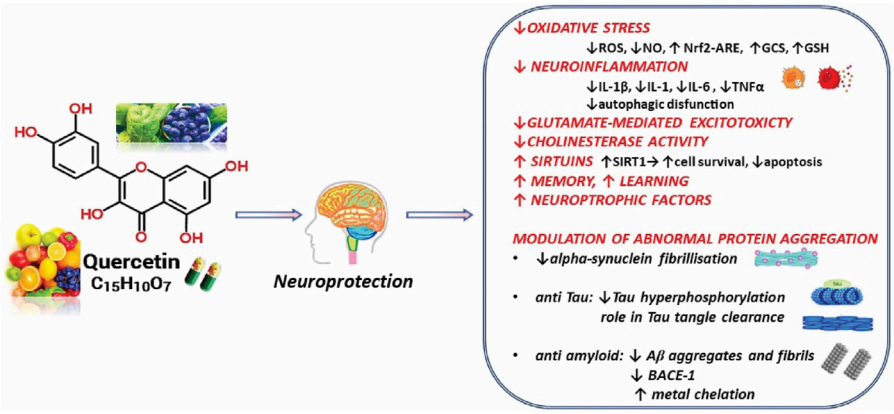

FIGURE 3 | Summarized scheme with relevant neuroprotective effects of Quercetin. *Abbreviations:* ↑, increase; ↓, decrease; Aβ, amyloid beta-peptide; BACE1, beta-secretase 1; GCS, γ-glutamyl-cysteine synthetase; GSH, glutathione; IL, interleukin; NO, nitric oxide; Nrf2-ARE, Nuclear factor erythroid-derived 2-like 2-antioxidant responsive element; ROS, reactive oxygen species; SIRT1, sirtuin 1; TNF-α, tumor necrosis factor-alfa.

dismutase (SOD) activity and downturn malondialdehyde (MDA) levels. These antioxidant properties of QUR can also be useful in mitigation of the normal aging of the brain when oxidative stress increases through multiple mechanisms such as lipid peroxidation, protein oxidation and the release of ROS from mitochondria (Elumalai and Lakshmi, 2016).

Since it is a food-derived biomolecule, QUR seems to be safe and has low risks. The recommended dietary allowance approved by the FDA as GRAS (Generally Accepted as Safe) for pure QUR is 1.5 g/day (FDA, 2010). However, interaction with other drugs is possible. Co-administration of QUR with some antibiotics can reduce antibiotic efficacy and, owing to its antiplatelet and anticoagulant properties, it is not recommended that antibiotics be used concurrently with other antithrombotics. Among QUR's pharmacodynamic interactions with other medications, those with blood clotting effects are the most important. There are no known associations with food, other plants or other supplements. Taken together, these studies demonstrate that dietary QUR supplementation can serve as a potential candidate in the prevention of neurological and neurodegenerative conditions at minimum dose levels.

CONCLUSION REMARKS AND FUTURE PERSPECTIVES

To conclude, QUR serves as an effective therapeutic agent against various neurological disorders by reducing stress, inflammatory response and fostering brain growth. The overall analysis highlights the various neuroprotection aspects of QUR. Therefore, QUR can be considered as a strong dietary supplement with minimal toxicity as part of plant matrices. While QUR demonstrates pluripotent neuroprotective effects due to its poor solubility, bioavailability and instability in different *in vitro* and *in vivo* degenerative experimental models, its application in the pharmaceutical sector is restricted. Scientific data mostly on clinical studies and toxicity of QUR is also negligible.

Therefore, a need for more study to concentrate firstly on drug delivery mechanisms such as prodrugs, nanoencapsulation and microemulsion to enhance bioavailability and permeability of the blood-brain; 2) more clinical trials to evaluate the effective dose for the treatment of neurodegenerative disorders; 3) further study of the distribution of QUR metabolites in the experimental mod CNS; 4) To assess the neurotoxic effect, up-to-date profiling of *in vivo* toxicity.

AUTHOR CONTRIBUTIONS

MI, JS-R, and DC contributed to the study conception and design, the acquisition of data, the analysis and interpretation of data. MI, RH, AM, AS, NA, BA, AD and MI contributed to drafting the manuscript and critically revising the manuscript. All authors prepared the manuscript, contributed equally, read and approved the final manuscript.

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