Current Neuropharmacology, 2021, *19*, 2205-2213

REVIEW ARTICLE

Cholinesterase Inhibitory Potential of Quercetin towards Alzheimer's Disease - A Promising Natural Molecule or Fashion of the Day? - A Narrowed Review

Ilkay Erdogan Orhan[1,*]

[1]*Department of Pharmacognosy, Faculty of Pharmacy, Gazi University, 06330 Ankara, Turkey*

ARTICLE HISTORY

Received: October 11, 2020
Revised: October 22, 2020
Accepted: November 15, 2020

DOI:
10.2174/1570159X18666201119153807

Abstract: Natural substances are known to have strong protective effects against neurodegenerative diseases. Among them, phenolic compounds, especially flavonoids, come to the fore with their neuroprotective effects. Since quercetin, which is found in many medicinal plants and foods, is also taken through diet, its physiological effects on humans are imperative. Many studies have been published up to date on the neuroprotective properties of quercetin, a flavanol derivative. However, there is no review published so far summarizing the effect of quercetin on the cholinesterase (ChE) enzymes related to the cholinergic hypothesis, which is one of the pathological mechanisms of Alzheimer's Disease (AD). However, ChE inhibitors, regardless of natural or synthetic, play a vital role in the treatment of AD. Although the number of studies on the ChE inhibitory effect of quercetin is limited, it deserves to be discussed in a review article. With this sensitivity, the neuroprotective effect of quercetin against AD through ChE inhibition was scrutinized in the current review study. In addition, studies on the bioavailability of quercetin and its capacity to cross the blood-brain barrier and how this capacity and bioavailability can be increased were given. Generally, studies containing data published in recent years were obtained from search engines such as PubMed, Scopus, and Medline and included herein. Consequently, quercetin should not be considered as a fashionable natural compound and should be identified as a promising compound, especially with increased bioavailability, for the treatment of AD.

Keywords: Quercetin, Alzheimer's disease, cholinesterase inhibition, bioavailability, neuroprotection, flavonoid.

1. INTRODUCTION

Natural products have always been interesting to researchers to explore novel drug candidates. For the diseases threatening human health, many natural products have been served as the lead compounds to design novel drugs. Among them, quercetin as a well-known flavonoid derivative, a flavanol to be more specific, is commonly found in plant kingdom and food plants such as red wine, onions, green tea, apples, berries, *Ginkgo biloba*, St. John's wort, American elder, propolis, and many others [1-3]. Its chemical structure is described as 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one by the formal chemical name according to International Union of Pure and Applied Chemistry (IUPAC).

Quercetin as a popular bioflavonoid has been reported to display a wide range of desired biological activities such as anticancer, anti-inflammatory, immunomodulatory, antidiabetic, cardioprotective, neuroprotective, antihypertensive, chemopreventive, antioxidant, anti-obesity, antibacterial, wound healing, *etc.* [3-24]. Among all the above-mentioned biological activities of quercetin, special attention should be given to its potential neuroprotective impact [7, 8]. Results of numerous studies at *in vitro*, *in vivo*, *in silico*, and clinical levels performed against neurodegenerative diseases pointed out a notable protection by quercetin in several reviews [25-29]. This effect has been shown to emerge *via* many different complicated mechanisms, *e.g.* stimulating cellular defenses against oxidative stress such as through induction of nuclear erythroid 2-related factor 2 (Nrf2)-antioxidant responsive element (ARE) and induction of the antioxidant/anti-inflammatory enzyme; paraoxonase-2 (PON2) and activating sirtuins (SIRT1) to induce autophagy [5, 29-31], degradation of learning and memory loss induced by inhibition of amyloid beta (Aβ) fibrils [32-34], increasing neurotrophin brain-derived neurotrophic factor in neurons [35, 36], inhibition of cholinesterases (ChEs) [37, 38], modulating the inflammatory responses involved in neurodegenerative diseases such as inhibition of Nitric Oxide (NO) excess production and inducible Nitric Oxide Synthase (iNOS) overexpression. The other mechanisms relevant to neuroprotective action of quercetin can be mentioned as downregulation of the overexpression of pro-inflammatory genes [*e.g.* Interleukin (IL)-1ß, Tumor Necrosis Factor (TNF)-α and cyclooxygenase (COX)-2] [39], regulating activity of kinases [40, 41], activation of apoptotic pathways affecting caspase-3 and Poly ADP Ri-

*Address correspondence to this author at the Department of Pharmacognosy, Faculty of Pharmacy, Gazi University, Ankara, Turkey;
E-mail: iorhan@gazi.edu.tr

1875-6190/21 $65.00+.00

bose Polymerase (PARP) expression [42], reducing the Gamma-Aminobutyric Acid (GABA)-activated currents in cortical neurons [43], inhibition of monoamine oxidase (MAO) and secretase enzyme families [44-47], halting the damaging toxic effects of L-dopa [48], inhibition of tyrosinase [49-51], attenuating radiation, traumatic or hypoxia-ischemia induced brain injury [52, 53], decreasing neuronal autophagy and apoptosis [54, 55], reversing mitochondrial dysfunction through such as the adenosine monophosphate-activated protein kinase/sirtuin 1 (AMPK/SIRT1) signaling pathway [56], increasing cellular NAD^+/NADH and activation of peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α)-mediated pathways [57], regulating mitochondrial redox status [58]. On the other hand, potent hydroxyl (OH), hydrogen peroxide (H_2O_2), and superoxide anion (O_2^-) scavenging ability of quercetin was reported in numerous papers [59-62].

As aforementioned, cumulative evidence showed the neuroprotective potential of quercetin by diverse mechanisms of action. Among them, cholinergic system related to cognitive function through ChE enzyme family as well as Aβ in the form of neurofibrillary tangles and amyloid plaques plays a critical role in pathogenesis of Alzheimer's Disease (AD) [63, 64] and inhibitors of ChEs have been considered to be the first-line symptomatic drugs for the treatment of AD [65-69]. AD, associated mainly with cognitive disability and memory loss, particularly influencing the elderly, is known to be a neurodegenerative disease with progressive character whose pathology has been described by two major mechanisms, *i.e.* cholinergic hypothesis and amyloid hypothesis [70, 71]. As the topic of the current review giving priority to the cholinergic hypothesis, the serine protease-type of "sister" enzymes, *i.e.* acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), are linked to the regulation of cholinergic transmission among neurons [72]. Thus, deficit in the neurotransmitter acetylcholine (ACh) level in the synaptic gap between neurons or overexpression of ChE has been demonstrated to induce AD pathology. AChE functions to break down ACh and hence, its inhibition is an important target in drug design for effective treatment of AD [73]. On the other hand, BChE, the enzyme also closely allied with AChE, assists and co-regulates hydrolysis of ACh in cholinergic system as well as butyrylcholine [74, 75]. Actually, it should be noted that AChE and BChE possess various structural resemblances (50-55% species-dependent sequence similarity) to each other and the active gorge of BChE (Ser198, His438, and Glu325) and oxyanion hole (Gly116, Gly117, and Ala199) are matching to those of AChE [76].

Since no exact cure is available to stop AD, yet, inhibition of both ChEs is the target for developing new drugs towards the disease. In this regard, natural products have given hope as lead molecules. For instance, galanthamine, an alkaloid isolated from the bulbs of *Galanthus woronowii* Losinks. (snowdrop) as well as *Leucojum* species belonging to Amaryllidaceae has been in clinical use for AD treatment as the last generation ChE inhibitory drug [77-81]. Consistently, many flavonoids, being the most abundant class of natural products, have been identified with a promising ChE inhibitory activity [82-84]. Among those flavonoids, the present review aims to focus specifically on ChE inhibitory capacity of quercetin through scrutinizing the reported data obtained from the bibliographic databases, *e.g.* PubMed, Scopus, and Medline. In addition, capacity of quercetin to across Blood Brain Barrier (BBB) is touched.

2. ChE INHIBITORY EFFECT OF QUERCETIN

Although evidence indicated the strong neuroprotective effect of quercetin against not only AD, but also other neurological diseases, various mechanisms for its mentioned effect have been proposed. Nevertheless, only limited studies have been performed on ChE inhibitory potential of quercetin in a pure form as one of the mechanisms of action towards AD. On the other hand, more papers are available on ChE inhibitory effect of plant extracts containing with quercetin and its derivatives, *e.g. Leiotulus dasyanthus* (K. Koch) Pimenov & Ostr, *Bauhinia forficata* Link subsp. *pruinosa* (Vogel) Fortunato & Wunderlin, *Davallia cylindrica* Ching, *Pistacia atlantica* Desf., *Zingiber officinale* Roscoe, *etc.* [85-92].

In an earlier study [93], quercetin isolated from *Agrimonia pilosa* Ledeb was revealed to inhibit AChE with IC_{50} value of 19.8 μM, where dehydroevodiamine hydrochloride, the reference compound of natural origin, had IC_{50} value of 37.8 μM. This indicated that quercetin inhibited AChE twice effectively than the reference, whereas its anti-AChE capacity was weaker in comparison to that of tacrine (IC_{50} = 0.1 μM), a clinically used ChE inhibitor. The authors stated quercetin with therapeutic potential against AD.

In a screening study, some selected flavonoid derivatives, including galangin, kaempferol, quercetin, myricetin, fisetin, apigenin, luteolin, and rutin were reported to inhibit BChE of human origin reversibly [94]. Among them, the most selective and effective flavonoid against BChE was galangin, having 12 times higher selectivity against BChE than AChE. The results showed that a number of hydroxyl groups and their locations on the phenyl ring are quite imperative in inhibition. According to molecular docking experiments, the flavonoids tested were shown to bind to the active gorge of BChE through making multiple hydrogen bonds and pi-pi interactions. Quercetin was identified to have a reversible inhibition with K_i value of 38.3 ± 9.8 μM, while its binding pattern to BChE was shown to be opposite to that of galangin in docking simulations. Hydrogen binding lengths for quercetin were between 1.83 and 2.02 Å, while it interacted with Asp70, Glu197, O17, Gly115, and Tyr128 at the active site. Besides, the flavonoids did not display cytotoxicity in HepG2 and A549 cell lines, when tested up to 200 μM. Consistently, in our earlier work in which we screened a number of phenolic acids and flavonoids, 76.2 ± 0.99% inhibition against AChE of electric eel origin was exhibited by quercetin at 100 μg/mL, whereas it displayed 46.8 ± 1.35% of inhibition on BChE of horse serum origin [95]. Similar to our results, quercetin from *Croton menyharthii* Pax exhibited 56.6 ± 0.93% inhibition against AChE of electric eel (IC_{50}= 41.6 ± 6.0 μg/mL) [96]. When compared to that of galanthamine (88.3 ± 2.0%, IC_{50}= 0.3 ± 0.1 μg/mL), its effect was at mild level.

Conversely, quercetin from paper mulberry (*Broussonetia papyrifera* (L.) L'Her. ex Vent., syn. *Morus papyrifera* L.) was inactive against AChE (electric eel) (IC_{50} > 500 μM) [97]. In fact, some studies pointed out a good anti-

BChE activity and a weak inhibition towards insect AChE by quercetin, while it did not exert a blocking effect on human AChE [98-100]. Relevantly, low ChE inhibitory activity of quercetin obtained from *Ficus foveolata* (Wall. ex Miq.) (syn. *Ficus sarmentosa* Buch.-Ham. ex Sm.) was reported [101]. It showed 18.8 ± 0.2% and 31.0 ± 0.1% of inhibition at 100 µg/mL against AChE (electric eel) and BChE (horse serum), respectively, while corresponding AChE and BChE inhibitory effect of galanthamine (the reference compound) was 95.6 ± 1.4 and 93.1 ± 0.4% at the same concentration [102]. In another study, quercetin was revealed to inhibit BChE (IC_{50}= 19.08 µM) in a better capacity than AChE (IC_{50}= 55.44 µM) [103]. However, the inhibitory effect was rather mild when compared to that of galanthamine (IC_{50}= 0.59 µM).

According to docking data obtained with quercetin in the former work that we screened four phenolic compounds, several hydrogen bonds with the amino acid residues located at the anionic subsite of BChE were formed [104]. Besides, another hydrogen bond was observed between the hydroxyl group at 5th carbon of A ring as well as carbonyl group in C ring in quercetin structure and TYR133. Additionally, another hydrogen bond was detected between the hydroxyl group at 3rd carbon of A ring and TYR86 at the anionic region of BChE. In a relevant study in which 646 small natural molecules were screened for their AChE inhibitory potential through *in silico* experiments, caffeine, ascorbic acid, and gallic acid were identified as the strong AChE inhibitors [105]. Then the mentioned four molecules were subjected to *in vitro* AChE inhibition assay and confirmed again to be the active inhibitors of this enzyme in comparison to the reference drugs, *i.e.* donepezil and begacestat. Among them, quercetin and caffeine had the identical level of AChE inhibition to those of the references. Besides, the four active molecules did not display toxicity in hippocampal neurons. Therefore, predominantly quercetin and caffeine were concluded as disease-modifying drugs with encouraging therapeutic potential in AD. Quercetin was shown to inhibit AChE and BChE successfully, having IC_{50} values of 0.181 mM and 0.203 mM, respectively. According to this data, the compound seems to be a slightly better inhibitor of AChE [106]. At this point, it should be definitely noted once more that the use of different enzyme sources affects the biological activity of a compound.

In an *in vivo* study, quercetin was reported to prevent chlorpyrifos (an organophosphorus pesticide)-induced neurotoxicity through inhibition of AChE along with choline acyltransferase in female Wistar rats administrated at a dose of 50 mg/kg (body weight, b.w./day) during eight weeks [107]. Hence, it was stated to be a prophylactic neuroprotective agent against chlorpyrifos-induced neurotoxicity by the authors. In a similar study, diazinon-induced neurotoxicity was blocked by quercetin as well as in combination with curcumin in male albino rats, which were treated with different combinations of both compounds during four weeks [108]. Quercetin alone led to a decrease in AChE level from 133.62 IU/mL to 110.04 IU/mL, while combination of quercetin and curcumin caused a decline down to 129.62 IU/mL given at dose of 100 mg/kg (b.w./day). In another *in vivo* study, oral co-administration of quercetin with manganese at 10 and 20 mg/kg (b.w./day) for 45 sequential days led to a significant decrease in AChE level and improved the locomotor functions in adult male Wistar rats [109]. In more detail, when manganese was administrated alone in rats, excessive increase was determined in AChE activity in the hypothalamus, cerebrum, and cerebellum (101, 50, and 59%, respectively). Nevertheless, co-administration of quercetin significantly reversed the AChE activity in the above-mentioned brain areas of the rats. The diminution in AChE activity was 38 and 59% in the hypothalamus; 42 and 50% in cerebrum, and 33 and 38% in cerebellum for manganese + quercetin combination given at 10 and 20 mg/kg (b.w./day), respectively.

3. PERMEABILITY AND BIOAVAILABILITY OF QUERCETIN

Many flavonoids owe their neuroprotective effects to their ability to cross the BBB [110, 111]. However, their ability to cross BBB still remains as the main issue for most of them. Doubtlessly, hydrophobicity and lipophilicity play a critical role in transmembrane transport, bioavailability, toxicity, and biological activity of molecules. Passing a biological membrane for any drug or drug candidate is an essential step for their absorption and bioavailability. In this sense, Caco-2 cell line monolayer model is widely used as an *in vitro* model to determine drug transport and many studies have revealed that flavonoids are usually transported by passive diffusion [112-116]. In fact, Fang *et al.* demonstrated that the bilateral permeation of five groups of flavonoids was as follows; flavanones ≥ isoflavones > flavones ≥ chalcones > flavonols [117].

There have been a number of studies investigating BBB crossing capability of quercetin, a hydrophobic flavonol with low bioavailability (<2%) and low brain permeability [118]. For instance, 65.54% of quercetin was successfully able to across BBB in primary Brain Microvessel Endothelial Cell (BMVEC) and primary astroglia cell cultures [119]. In a study conducted on a number of flavonoid derivatives, *i.e.* puerarin, rutin, hesperidin, quercetin, genistein, kaempferol, apigenin, and isoliquiritigenin, their transmembrane transport was examined *via* the rat BBB cell and Caco-2 cell monolayer models [120]. The apparent permeability coefficients (P_{app}, pregnancy-associated plasma protein) of the flavonoids were calculated from the unilateral transport assays, where the P_{app} values were shown to be time-dependent. The results indicated that quercetin through the BBB cell layer model possessed the lowest permeation (P_{app} value 2.20 ± 0.34 × 10^{-6} cm/s) among the tested flavonoids. In Caco-2 cells, the data showed that permeation order of the eight flavonoids was genistein, isoliquiritigenin, kaempferol, apigenin, hesperidin, quercetin, puercetin, and rutin from the high to low, where P_{app} value of quercetin was established 16.23 ± 0.42 × 10^{-6} cm/s. Actually, Chabane *et al.* reported poor absorption of quercetin and naringenin in Caco-2 cells. Absorption of quercetin by passive diffusion was observed in a pH-dependent mechanism mediated by the Organic Anion Transporting Protein B (OATP-B) [121]. It was not connected to multidrug resistance associated protein (MRP)-1 substrate, but was the substrate of the MRP-2 efflux transporter and not P glycoprotein (Pgp). This finding may bring an explanation for low bioavailability of the compound. Quercetin was found to be a Pgp inhibitor [122-124]. On the other

hand, in rat brain tissues, quercetin and its methylated derivative were analyzed by high-performance liquid chromatography (HPLC) after oral administration of quercetin at dose of 50 mg/kg (b.w.) using brain capillary endothelial cell line as the implementation of BBB model [125].

Nanostructures such as polymer nanoparticles, lipid nanoparticles, nanoliposomes, nanomicelles and carbon nanotubes are known to cause significant consequences, including tremendous stability and controlled release, elevated bioavailability, enhancement of therapeutic efficacy, improvement of pharmacokinetic, and marked ability of crossing the BBB for drugs and natural products such as quercetin having a hydrophobic character and poor solubility [126-128]. In recent years, diverse nanostructure forms of quercetin have been reported to help improving the bioavailability of quercetin particularly referring to its neurodefensive potential [129, 130]. In order to increase permeability of quercetin across BBB and inhibitory potential of Aβ aggregation towards AD, a nanoparticulated formulation of the compound sphered with RGV29 peptide was successfully implemented, which led to an improvement of delivery and neuroprotective effect of quercetin [131]. Another nanoparticle form of quercetin prepared with hydroxypropyl methylcellulose (HMPC) was tested in aluminum-induced neurodegeneration rat model [130]. The nanoparticulated quercetin administrated at 30 mg/kg (b.w.) led to improve neuronal degeneration parameters such as formation of amyloid peptides and neurofibrillary tangles, downregulation of tyrosine hydroxylase, astrogliosis and inhibition. As another example, quercetin-Solid Lipid Nanoparticle (SLN) form appreciably ameliorated aluminum-induced neurotoxicity [132]. In addition, this system caused meaningful improvement in behavioral and memory retention in animal models of dementia and AD. The SLN form of quercetin also exhibited neuroprotection in pentylenetetrazole (PTZ)-induced cognitive impairment of wild-type adult male *Danio rerio* (zebrafish) species at doses of 5 and 10 mg/kg through anti-inflammatory, antioxidant, and regulation of enzymes linked to cholinergic neurotransmission [133]. Relevantly, quercetin-SLN caused a reduction in AChE in the brains of zebrafish in that study.

Quercetin nanoparticles with gold-palladium core shell were reported to be effective to ameliorate autophagic dysfunction in AD using SH-SY5Y human neuroblastoma cells, which led to decrease degeneration due to Aβ toxicity [134]. Improving effect of superparamagnetic iron oxide-nanoparticulated quercetin at the dose of 25 mg/kg (b.w.) given during 35 sequential days was described against diabetes-related memory deficit [135]. A similar result was obtained with nanoparticulation of quercetin again with superparamagnetic iron oxide, which led to augment bioavailability of quercetin in the brains of Wistar male rats [136]. Approximately, 10-fold increase was observed in the bioavailability of free quercetin. Liposome form of quercetin encapsulated with RMP-7, a bradykinin analogue, co-prepared with lactoferrin, was shown to pass the BBB without inducing robust toxicity and harming the tight junction [137]. Besides this drug delivery system decreased the neurotoxicity due to Aβ fibrils in SK-N-MC cells. In another work, quercetin nanoparticulated with polylactic-co-glycolic acid (PLGA), a biodegradable copolymer, was lowered toxicity induced by Aβ in SH-SY5Y cells and improved therapeutic efficacy in APP/PS1 mice in terms of learning and cognitive function.

CONCLUSION

Quercetin, as a popular dietary flavonoid-type of compound has attracted huge interest from scientists due to its desired biological effects on human health. At this point, a special part should be devoted to the neuroprotective properties of quercetin. In fact, a large number of action mechanisms referring to its neuroprotective potential have been elucidated due to complicated pathological features of neurodegeneration process. In many cases, quercetin was concluded to exert significant protection against neurodegenerative diseases, including AD. One of the principle pathological mechanisms of AD is known as cholinergic hypothesis and in this regard, ChE inhibitors related to AChE and BChE have been the most prescribed drug class for AD treatment. A good number of natural products have been identified with promising ChE inhibitory effect, including quercetin. Therefore, special attention was paid to ChE inhibition by quercetin in this context through the present review. Although most of the studies revealed the strong ChE inhibitory activity of quercetin, sometimes conflicting results have also been obtained. This contradiction may be due to various factors. However, the most important factor may be the difference in the enzyme source. The test methods used can also lead to differences in the inhibitory activity results. The reported data on ChE inhibitory potential of quercetin indicates that it has the ability so far to inhibit ChEs in *in vitro*, *in vivo* and *in silico* studies. Nevertheless, low bioavailability of quercetin stands as a big problem before us. As aforementioned, a wide variety of studies are being done to increase the bioavailability and BBB-passing ability of quercetin, which seems to be the most effective one being the nanoparticle form. Based on the current data available on quercetin, the question in the title of the current review can be answered that quercetin is not the fashion of the day. It can be considered one of the most effective and promising natural products and multifunctional natural agents against AD acting through a number of mechanisms related to neurodegeneration provided that its bioavailability and its ability to cross the BBB should be increased.

LIST OF ABBREVIATIONS

ACh	=	Acetylcholine
AChE	=	Acetylcholinesterase
AD	=	Alzheimer's Disease
Aβ	=	Amyloid Beta
AMPK/SIRT1	=	Adenosine Monophosphate-activated Protein Kinase/Sirtuin 1
ARE	=	Antioxidant Responsive Element
BBB	=	Blood Brain Barrier
BChE	=	Butyrylcholinesterase
BMVEC	=	Brain Microvessel Endothelial Cell
b.w.	=	Body Weight
ChE	=	Cholinesterase

COX	=	Cyclooxygenase
GABA	=	Gamma-aminobutyric Acid
HMPC	=	Hydroxypropyl Methylcellulose
HPLC	=	High Performance Liquid Chromatography
IC	=	Inhibitory Concentration
iNOS	=	Inducible Nitric Oxide Synthase
IUPAC	=	International Union of Pure and Applied Chemistry
MAO	=	Monoamine Oxidase
MRP	=	Multidrug Resistance Associated Protein
NO	=	Nitric Oxide
Nrf2	=	Nuclear Erythroid 2-related Factor 2
OATP-B	=	Organic Anion Transporting Protein B
P_{app}	=	Pregnancy-associated Plasma Protein
PARP	=	Poly ADP Ribose Polymerase
PGC-1α	=	Peroxisome Proliferator-activated Receptor-gamma Coactivator
Pgp	=	P glycoprotein
PON2	=	Paraoxonase-2
PTZ	=	Pentylenetetrazole
SIRT1	=	Sirtuins-1
SLN	=	Solid Lipid Nanoparticle
TNF-α	=	Tumor Necrosis Factor-α

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The author declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Griffiths, G.; Trueman, L.; Crowther, T.; Thomas, B.; Smith, B. Onions--a global benefit to health. *Phytother. Res.,* **2002**, *16*(7), 603-615. http://dx.doi.org/10.1002/ptr.1222 PMID: 12410539

[2] Nishimuro, H.; Ohnishi, H.; Sato, M.; Ohnishi-Kameyama, M.; Matsunaga, I.; Naito, S.; Ippoushi, K.; Oike, H.; Nagata, T.; Akasaka, H.; Saitoh, S.; Shimamoto, K.; Kobori, M. Estimated daily intake and seasonal food sources of quercetin in Japan. *Nutrients,* **2015**, *7*(4), 2345-2358. http://dx.doi.org/10.3390/nu7042345 PMID: 25849945

[3] Polerà, N.; Badolato, M.; Perri, F.; Carullo, G.; Aiello, F. Quercetin and its natural sources in wound healing management. *Curr. Med. Chem.,* **2019**, *26*(31), 5825-5848. http://dx.doi.org/10.2174/0929867325666180713150626 PMID: 30009700

[4] Brito, A.F.; Ribeiro, M.; Abrantes, A.M.; Pires, A.S.; Teixo, R.J.; Tralhão, J.G.; Botelho, M.F. Quercetin in cancer treatment, alone or in combination with conventional therapeutics? *Curr. Med. Chem.,* **2015**, *22*(26), 3025-3039. http://dx.doi.org/10.2174/0929867322666150812145435 PMID: 26264923

[5] Costa, L.G.; Garrick, J.M.; Roquè, P.J.; Pellacani, C. Mechanisms of neuroprotection by quercetin: counteracting oxidative stress and more. *Oxid. Med. Cell. Longev.,* **2016**, *2016*2986796 http://dx.doi.org/10.1155/2016/2986796 PMID: 26904161

[6] Barreca, D.; Bellocco, E.; D'Onofrio, G.; Nabavi, S.F.; Daglia, M.; Rastrelli, L.; Nabavi, S.M. Neuroprotective effects of quercetin: from chemistry to medicine. *CNS Neurol. Disord. Drug Targets,* **2016**, *15*(8), 964-975. http://dx.doi.org/10.2174/1871527315666160813175406 PMID: 27528470

[7] Velmurugan, B.K.; Rathinasamy, B.; Lohanathan, B.P.; Thiyagarajan, V.; Weng, C.F. Neuroprotective role of phytochemicals. *Molecules,* **2018**, *23*(10), 2485. http://dx.doi.org/10.3390/molecules23102485 PMID: 30262792

[8] Amanzadeh, E.; Esmaeili, A.; Rahgozar, S.; Nourbakhshnia, M. Application of quercetin in neurological disorders: from nutrition to nanomedicine. *Rev. Neurosci.,* **2019**, *30*(5), 555-572. http://dx.doi.org/10.1515/revneuro-2018-0080 PMID: 30753166

[9] Li, Y.; Yao, J.; Han, C.; Yang, J.; Chaudhry, M.T.; Wang, S.; Liu, H.; Yin, Y. Quercetin, inflammation and immunity. *Nutrients,* **2016**, *8*(3), 167. http://dx.doi.org/10.3390/nu8030167 PMID: 26999194

[10] Mlcek, J.; Jurikova, T.; Skrovankova, S.; Sochor, J. Quercetin and its anti-allergic immune response. *Molecules,* **2016**, *21*(5), 623. http://dx.doi.org/10.3390/molecules21050623 PMID: 27187333

[11] Serban, M.C.; Sahebkar, A.; Zanchetti, A.; Mikhailidis, D.P.; Howard, G.; Antal, D.; Andrica, F.; Ahmed, A.; Aronow, W.S.; Muntner, P.; Lip, G.Y.; Graham, I.; Wong, N.; Rysz, J.; Banach, M. Lipid and blood pressure meta-analysis collaboration (LBPMC) group. Effects of quercetin on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J. Am. Heart Assoc.,* **2016**, *5*(7), e002713. http://dx.doi.org/10.1161/JAHA.115.002713 PMID: 27405810

[12] Chen, S.; Jiang, H.; Wu, X.; Fang, J. Therapeutic effects of quercetin on inflammation, obesity, and type 2 diabetes. *Mediators Inflamm.,* **2016**, *2016,* 9340637. http://dx.doi.org/10.1155/2016/9340637 PMID: 28003714

[13] Eid, H.M.; Haddad, P.S. The antidiabetic potential of quercetin: underlying mechanisms. *Curr. Med. Chem.,* **2017**, *24*(4), 355-364. http://dx.doi.org/10.2174/0929867323666160909153707 PMID: 27633685

[14] Zhao, Y.; Chen, B.; Shen, J.; Wan, L.; Zhu, Y.; Yi, T.; Xiao, Z. The beneficial effects of quercetin, curcumin, and resveratrol in obesity. *Oxid. Med. Cell Longev,* **2017**, *2017,*1459497. http://dx.doi.org/10.1155/2017/1459497

[15] Rauf, A.; Imran, M.; Khan, I.A.; Ur-Rehman, M.; Gilani, S.A.; Mehmood, Z.; Mubarak, M.S. Anticancer potential of quercetin: A comprehensive review. *Phytother. Res.,* **2018**, *32*(11), 2109-2130. http://dx.doi.org/10.1002/ptr.6155 PMID: 30039547

[16] Patel, R.V.; Mistry, B.M.; Shinde, S.K.; Syed, R.; Singh, V.; Shin, H.S. Therapeutic potential of quercetin as a cardiovascular agent. *Eur. J. Med. Chem.,* **2018**, *155*, 889-904. http://dx.doi.org/10.1016/j.ejmech.2018.06.053 PMID: 29966915

[17] Babaei, F.; Mirzababaei, M.; Nassiri-Asl, M. Quercetin in food: possible mechanisms of its effect on memory. *J. Food Sci.,* **2018**, *83*(9), 2280-2287. http://dx.doi.org/10.1111/1750-3841.14317 PMID: 30103275

[18] Ożarowski, M.; Mikołajczak, P.Ł.; Kujawski, R.; Wielgus, K.; Klejewski, A.; Wolski, H.; Seremak-Mrozikiewicz, A. Pharmacological effect of quercetin in hypertension and its potential application in pregnancy-induced hypertension: review of *in vitro, in vivo*, and clinical studies. *Evid. Based Complement. Alternat. Med.,* **2018**, *2018,* 7421489. http://dx.doi.org/10.1155/2018/7421489 PMID: 30622610

[19] Shafabakhsh, R.; Asemi, Z. Quercetin: a natural compound for ovarian cancer treatment. *J. Ovarian Res.,* **2019**, *12*(1), 55.

http://dx.doi.org/10.1186/s13048-019-0530-4 PMID: 31202269

[20] Xu, D.; Hu, M.J.; Wang, Y.Q.; Cui, Y.L. Antioxidant activities of quercetin and its complexes for medicinal application. *Molecules,* **2019**, *24*(6), 1123. http://dx.doi.org/10.3390/molecules24061123 PMID: 30901869

[21] Kashyap, D.; Garg, V.K.; Tuli, H.S.; Yerer, M.B.; Sak, K.; Sharma, A.K.; Kumar, M.; Aggarwal, V.; Sandhu, S.S. Fisetin and quercetin: promising flavonoids with chemopreventive potential. *Biomolecules,* **2019**, *9*(5), 174. http://dx.doi.org/10.3390/biom9050174 PMID: 31064104

[22] Memariani, H.; Memariani, M.; Ghasemian, A. An overview on anti-biofilm properties of quercetin against bacterial pathogens. *World J. Microbiol. Biotechnol.,* **2019**, *35*(9), 143. http://dx.doi.org/10.1007/s11274-019-2719-5 PMID: 31493142

[23] Nakagawa, T.; Ohta, K. Quercetin regulates the integrated stress response to improve memory. *Int. J. Mol. Sci.,* **2019**, *20*(11), 2761. http://dx.doi.org/10.3390/ijms20112761 PMID: 31195662

[24] Bule, M.; Abdurahman, A.; Nikfar, S.; Abdollahi, M.; Amini, M. Antidiabetic effect of quercetin: A systematic review and meta-analysis of animal studies. *Food Chem. Toxicol.,* **2019**, *125*, 494-502. http://dx.doi.org/10.1016/j.fct.2019.01.037 PMID: 30735748

[25] Ossola, B.; Kääriäinen, T.M.; Männistö, P.T. The multiple faces of quercetin in neuroprotection. *Expert Opin. Drug Saf.,* **2009**, *8*(4), 397-409. http://dx.doi.org/10.1517/14740330903026944 PMID: 19538101

[26] Malik, A.; Khan, F.A.; Mumtaz, A.; Mehmood, A.; Azhar, S.; Atif, M.; Karim, S.; Altaf, Y.; Tariq, I. Pharmacological applications of quercetin and its derivatives: a short review. *Trop. J. Pharm. Res.,* **2014**, *13*(9), 1561-1566. http://dx.doi.org/10.4314/tjpr.v13i9.26

[27] Babaei, F.; Mirzababaei, M.; Nassiri-Asl, M. Quercetin in food: possible mechanisms of ıts effect on memory. *J. Food Sci.,* **2018**, *83*(9), 2280-2287. http://dx.doi.org/10.1111/1750-3841.14317 PMID: 30103275

[28] Zaplatic, E.; Bule, M.; Shah, S.Z.A.; Uddin, M.S.; Niaz, K. Corrigendum to "Molecular mechanisms underlying protective role of quercetin in attenuating Alzheimer's disease". [Life Sci. 221 (2019) 109-119]. *Life Sci.,* **2019**, *231,* 116616. http://dx.doi.org/10.1016/j.lfs.2019.116616 PMID: 31326083

[29] Khan, H.; Ullah, H.; Aschner, M.; Cheang, W.S.; Akkol, E.K. Neuroprotective effects of quercetin in Alzheimer's disease. *Biomolecules,* **2019**, *10*(1), 59. http://dx.doi.org/10.3390/biom10010059 PMID: 31905923

[30] Dong, F.; Wang, S.; Wang, Y.; Yang, X.; Jiang, J.; Wu, D.; Qu, X.; Fan, H.; Yao, R. Quercetin ameliorates learning and memory *via* the Nrf2-ARE signaling pathway in d-galactose-induced neurotoxicity in mice. *Biochem. Biophys. Res. Commun.,* **2017**, *491*(3), 636-641. http://dx.doi.org/10.1016/j.bbrc.2017.07.151 PMID: 28757412

[31] Li, Y.; Tian, Q.; Li, Z.; Dang, M.; Lin, Y.; Hou, X. Activation of Nrf2 signaling by sitagliptin and quercetin combination against β-amyloid induced Alzheimer's disease in rats. *Drug Dev. Res.,* **2019**, *80*(6), 837-845. http://dx.doi.org/10.1002/ddr.21567 PMID: 31301179

[32] Jiménez-Aliaga, K.; Bermejo-Bescós, P.; Benedí, J.; Martín-Aragón, S. Quercetin and rutin exhibit antiamyloidogenic and fibril-disaggregating effects *in vitro* and potent antioxidant activity in APPswe cells. *Life Sci.,* **2011**, *89*(25-26), 939-945. http://dx.doi.org/10.1016/j.lfs.2011.09.023 PMID: 22008478

[33] Kanter, M.; Unsal, C.; Aktas, C.; Erboga, M. Neuroprotective effect of quercetin against oxidative damage and neuronal apoptosis caused by cadmium in hippocampus. *Toxicol. Ind. Health,* **2016**, *32*(3), 541-550. http://dx.doi.org/10.1177/0748233713504810 PMID: 24193051

[34] Li, Y.L.; Guo, H.; Zhao, Y.Q.; Li, A.F.; Ren, Y.Q.; Zhang, J.W. Quercetin protects neuronal cells from oxidative stress and cognitive degradation induced by amyloid β-peptide treatment. *Mol. Med. Rep.,* **2017**, *16*(2), 1573-1577. http://dx.doi.org/10.3892/mmr.2017.6704 PMID: 28586024

[35] Rahvar, M.; Owji, A.A.; Mashayekhi, F.J. Effect of quercetin on the brain-derived neurotrophic factor gene expression in the rat brain. *Bratisl. Lek Listy,* **2018**, *119*(1), 28-31. http://dx.doi.org/10.4149/BLL_2018_006 PMID: 29405727

[36] Chatterjee, J.; Langhnoja, J.; Pillai, P.P.; Mustak, M.S. Neuroprotective effect of quercetin against radiation-induced endoplasmic reticulum stress in neurons. *J. Biochem. Mol. Toxicol.,* **2019**, *33*(2), e22242. http://dx.doi.org/10.1002/jbt.22242 PMID: 30368985

[37] Abdalla, F.H.; Cardoso, A.M.; Pereira, L.B.; Schmatz, R.; Gonçalves, J.F.; Stefanello, N.; Fiorenza, A.M.; Gutierres, J.M.; Serres, J.D.; Zanini, D.; Pimentel, V.C.; Vieira, J.M.; Schetinger, M.R.; Morsch, V.M.; Mazzanti, C.M. Neuroprotective effect of quercetin in ectoenzymes and acetylcholinesterase activities in cerebral cortex synaptosomes of cadmium-exposed rats. *Mol. Cell. Biochem.,* **2013**, *381*(1-2), 1-8. http://dx.doi.org/10.1007/s11010-013-1659-x PMID: 23797318

[38] de Oliveira, T.S.; Thomaz, D.V.; da Silva Neri, H.F.; Cerqueira, L.B.; Garcia, L.F.; Gil, H.P.V.; Pontarolo, R.; Campos, F.R.; Costa, E.A.; Dos Santos, F.C.A.; de Souza Gil, E.; Ghedini, P.C. Neuroprotective effect of *Caryocar brasiliense* Camb. leaves is associated with anticholinesterase and antioxidant properties. *Oxid. Med. Cell. Longev.,* **2018**, *2018*9842908 http://dx.doi.org/10.1155/2018/9842908 PMID: 30420910

[39] Spagnuolo, C.; Moccia, S.; Russo, G.L. Anti-inflammatory effects of flavonoids in neurodegenerative disorders. *Eur. J. Med. Chem.,* **2018**, *153*, 105-115. http://dx.doi.org/10.1016/j.ejmech.2017.09.001 PMID: 28923363

[40] Zhang, Z.J.; Cheang, L.C.; Wang, M.W.; Lee, S.M. Quercetin exerts a neuroprotective effect through inhibition of the iNOS/NO system and pro-inflammation gene expression in PC12 cells and in zebrafish. *Int. J. Mol. Med.,* **2011**, *27*(2), 195-203. PMID: 21132259

[41] Dajas, F.; Abin-Carriquiry, J.A.; Arredondo, F.; Blasina, F.; Echeverry, C.; Martínez, M.; Rivera, F.; Vaamonde, L. Quercetin in brain diseases: Potential and limits. *Neurochem. Int.,* **2015**, *89*, 140-148. http://dx.doi.org/10.1016/j.neuint.2015.07.002 PMID: 26160469

[42] Park, D.J.; Shah, F.A.; Koh, P.O. Quercetin attenuates neuronal cells damage in a middle cerebral artery occlusion animal model. *J. Vet. Med. Sci.,* **2018**, *80*(4), 676-683. http://dx.doi.org/10.1292/jvms.17-0693 PMID: 29563391

[43] Fan, H.R.; Du, W.F.; Zhu, T.; Wu, Y.J.; Liu, Y.M.; Wang, Q.; Wang, Q.; Gu, X.; Shan, X.; Deng, S.; Zhu, T.; Xu, T.L.; Ge, W.H.; Li, W.G.; Li, F. Quercetin reduces cortical GABAergic transmission and alleviates MK-801-induced hyperactivity. *EBioMedicine,* **2018**, *34*, 201-213. http://dx.doi.org/10.1016/j.ebiom.2018.07.031 PMID: 30057312

[44] Shimmyo, Y.; Kihara, T.; Akaike, A.; Niidome, T.; Sugimoto, H. Flavonols and flavones as BACE-1 inhibitors: structure-activity relationship in cell-free, cell-based and in silico studies reveal novel pharmacophore features. *Biochim. Biophys. Acta,* **2008**, *1780*(5), 819-825. http://dx.doi.org/10.1016/j.bbagen.2008.01.017 PMID: 18295609

[45] Saaby, L.; Rasmussen, H.B.; Jäger, A.K. MAO-A inhibitory activity of quercetin from *Calluna vulgaris* (L.) Hull. *J. Ethnopharmacol.,* **2009**, *121*(1), 178-181. http://dx.doi.org/10.1016/j.jep.2008.10.012 PMID: 19013512

[46] Dhiman, P.; Malik, N.; Sobarzo-Sánchez, E.; Uriarte, E.; Khatkar, A. Quercetin and related chromenone derivatives as monoamine oxidase inhibitors: targeting neurological and mental disorders. *Molecules,* **2019**, *24*(3), 418. http://dx.doi.org/10.3390/molecules24030418 PMID: 30678358

[47] Naushad, M.; Durairajan, S.S.K.; Bera, A.K.; Senapati, S.; Li, M. Natural compounds with anti-BACE1 activity as promising therapeutic drugs for treating Alzheimer's disease. *Planta Med.,* **2019**, *85*(17), 1316-1325. http://dx.doi.org/10.1055/a-1019-9819 PMID: 31618777

[48] Boyina, H.K.; Geethakhrishnan, S.L.; Panuganti, S.; Gangarapu, K.; Devarakonda, K.P.; Bakshi, V.; Guggilla, S.R. *In silico* and *in vivo* studies on quercetin as potential anti-Parkinson agent. *Adv. Exp. Med. Biol.,* **2020**, *1195*, 1-11. http://dx.doi.org/10.1007/978-3-030-32633-3_1 PMID: 32468451

[49] Chen, Q.X.; Kubo, I. Kinetics of mushroom tyrosinase inhibition by quercetin. *J. Agric. Food Chem.,* **2002**, *50*(14), 4108-4112. http://dx.doi.org/10.1021/jf011378z PMID: 12083892

[50] Fan, M.; Zhang, G.; Hu, X.; Xu, X.; Gong, D. Quercetin as a tyrosinase inhibitor: Inhibitory activity, conformational change and mechanism. *Food Res. Int.,* **2017**, *100*(Pt 1), 226-233. http://dx.doi.org/10.1016/j.foodres.2017.07.010 PMID: 28873682

[51] Du, G.; Zhao, Z.; Chen, Y.; Li, Z.; Tian, Y.; Liu, Z.; Liu, B.; Song, J. Quercetin protects rat cortical neurons against traumatic brain injury. *Mol. Med. Rep.,* **2018**, *17*(6), 7859-7865. http://dx.doi.org/10.3892/mmr.2018.8801 PMID: 29620218

[52] Kale, A.; Piskin, Ö.; Bas, Y.; Aydin, B.G.; Can, M.; Elmas, Ö.; Büyükuysal, Ç. Neuroprotective effects of Quercetin on radiation-induced brain injury in rats. *J. Radiat. Res. (Tokyo),* **2018**, *59*(4), 404-410. http://dx.doi.org/10.1093/jrr/rry032 PMID: 29688418

[53] Wu, M.; Liu, F.; Guo, Q. Quercetin attenuates hypoxia-ischemia induced brain injury in neonatal rats by inhibiting TLR4/NF-κB signaling pathway. *Int. Immunopharmacol.,* **2019**, *74*105704 http://dx.doi.org/10.1016/j.intimp.2019.105704 PMID: 31228815

[54] Yang, T.; Kong, B.; Gu, J.W.; Kuang, Y.Q.; Cheng, L.; Yang, W.T.; Xia, X.; Shu, H.F. Anti-apoptotic and anti-oxidative roles of quercetin after traumatic brain injury. *Cell. Mol. Neurobiol.,* **2014**, *34*(6), 797-804. http://dx.doi.org/10.1007/s10571-014-0070-9 PMID: 24846663

[55] Du, G.; Zhao, Z.; Chen, Y.; Li, Z.; Tian, Y.; Liu, Z.; Liu, B.; Song, J. Quercetin attenuates neuronal autophagy and apoptosis in rat traumatic brain injury model via activation of PI3K/Akt signaling pathway. *Neurol. Res.,* **2016**, *38*(11), 1012-1019. http://dx.doi.org/10.1080/01616412.2016.1240393 PMID: 27690831

[56] Qiu, L.; Luo, Y.; Chen, X. Quercetin attenuates mitochondrial dysfunction and biogenesis *via* upregulated AMPK/SIRT1 signaling pathway in OA rats. *Biomed. Pharmacother.,* **2018**, *103*, 1585-1591. http://dx.doi.org/10.1016/j.biopha.2018.05.003 PMID: 29864946

[57] Houghton, M.J.; Kerimi, A.; Tumova, S.; Boyle, J.P.; Williamson, G. Quercetin preserves redox status and stimulates mitochondrial function in metabolically-stressed HepG2 cells. *Free Radic. Biol. Med.,* **2018**, *129*, 296-309. http://dx.doi.org/10.1016/j.freeradbiomed.2018.09.037 PMID: 30266680

[58] Teixeira, J.; Chavarria, D.; Borges, F.; Wojtczak, L.; Wieckowski, M.R.; Karkucinska-Wieckowska, A.; Oliveira, P.J. Dietary Polyphenols and mitochondrial function: role in health and disease. *Curr. Med. Chem.,* **2019**, *26*(19), 3376-3406. http://dx.doi.org/10.2174/0929867324666170529101810 PMID: 28554320

[59] Shirai, M.; Kawai, Y.; Yamanishi, R.; Kinoshita, T.; Chuman, H.; Terao, J. Effect of a conjugated quercetin metabolite, quercetin 3-glucuronide, on lipid hydroperoxide-dependent formation of reactive oxygen species in differentiated PC-12 cells. *Free Radic. Res.,* **2006**, *40*(10), 1047-1053. http://dx.doi.org/10.1080/10715760600794287 PMID: 17015249

[60] Lee, D.E.; Shin, B.J.; Hur, H.J.; Kim, J.H.; Kim, J.; Kang, N.J.; Kim, D.O.; Lee, C.Y.; Lee, K.W.; Lee, H.J. Quercetin, the active phenolic component in kiwifruit, prevents hydrogen peroxide-induced inhibition of gap-junction intercellular communication. *Br. J. Nutr.,* **2010**, *104*(2), 164-170. http://dx.doi.org/10.1017/S0007114510000346 PMID: 20302682

[61] Chen, J.; Han, J.; Wang, J. Prevention of cytotoxicity of nickel by quercetin: the role of reactive oxygen species and histone acetylation. *Toxicol. Ind. Health,* **2013**, *29*(4), 360-366. http://dx.doi.org/10.1177/0748233711433940 PMID: 22294440

[62] Dudylina, A.L.; Ivanova, M.V.; Shumaev, K.B.; Ruuge, E.K. Superoxide formation in cardiac mitochondria and effect of phenolic antioxidants. *Cell Biochem. Biophys.,* **2019**, *77*(1), 99-107. http://dx.doi.org/10.1007/s12013-018-0857-2 PMID: 30218405

[63] Lane, R.M.; Kivipelto, M.; Greig, N.H. Acetylcholinesterase and its inhibition in Alzheimer disease. *Clin. Neuropharmacol.,* **2004**, *27*(3), 141-149. http://dx.doi.org/10.1097/00002826-200405000-00011 PMID: 15190239

[64] Macdonald, I.R.; Rockwood, K.; Martin, E.; Darvesh, S. Cholinesterase inhibition in Alzheimer's disease: is specificity the answer? *J. Alzheimers Dis.,* **2014**, *42*(2), 379-384. http://dx.doi.org/10.3233/JAD-140219 PMID: 24898642

[65] Wilkinson, D.G.; Francis, P.T.; Schwam, E.; Payne-Parrish, J. Cholinesterase inhibitors used in the treatment of Alzheimer's disease: the relationship between pharmacological effects and clinical efficacy. *Drugs Aging,* **2004**, *21*(7), 453-478. http://dx.doi.org/10.2165/00002512-200421070-00004 PMID: 15132713

[66] Shanks, M.; Kivipelto, M.; Bullock, R.; Lane, R. Cholinesterase inhibition: is there evidence for disease-modifying effects? *Curr. Med. Res. Opin.,* **2009**, *25*(10), 2439-2446. http://dx.doi.org/10.1185/03007990903209332 PMID: 19678754

[67] Orhan, G.; Orhan, I.; Subutay-Oztekin, N.; Ak, F.; Sener, B. Contemporary anticholinesterase pharmaceuticals of natural origin and their synthetic analogues for the treatment of Alzheimer's disease. *Recent Patents CNS Drug Discov.,* **2009**, *4*(1), 43-51. http://dx.doi.org/10.2174/157488909787002582 PMID: 19149713

[68] Orhan, I.E. Implications of some selected flavonoids towards Alzheimer's disease with the emphasis on cholinesterase inhibition and their bioproduction by metabolic engineering. *Curr. Pharm. Biotechnol.,* **2014**, *15*(4), 352-361. http://dx.doi.org/10.2174/1389201015666140813123204 PMID: 25312618

[69] Saxena, M.; Dubey, R. Target enzyme in Alzheimer's disease: acetylcholinesterase inhibitors. *Curr. Top. Med. Chem.,* **2019**, *19*(4), 264-275. http://dx.doi.org/10.2174/1568026619666190128125912 PMID: 30706815

[70] Ladner, C.J.; Lee, J.M. Pharmacological drug treatment of Alzheimer disease: the cholinergic hypothesis revisited. *J. Neuropathol. Exp. Neurol.,* **1998**, *57*(8), 719-731. http://dx.doi.org/10.1097/00005072-199808000-00001 PMID: 9720487

[71] Anand, P.; Singh, B. A review on cholinesterase inhibitors for Alzheimer's disease. *Arch. Pharm. Res.,* **2013**, *36*(4), 375-399. http://dx.doi.org/10.1007/s12272-013-0036-3 PMID: 23435942

[72] Sharma, K. Cholinesterase inhibitors as Alzheimer's therapeutics (Review). *Mol. Med. Rep.,* **2019**, *20*(2), 1479-1487. PMID: 31257471

[73] Colombres, M.; Sagal, J.P.; Inestrosa, N.C. An overview of the current and novel drugs for Alzheimer's disease with particular reference to anti-cholinesterase compounds. *Curr. Pharm. Des.,* **2004**, *10*(25), 3121-3130. http://dx.doi.org/10.2174/1381612043383359 PMID: 15544502

[74] Mesulam, M.M.; Guillozet, A.; Shaw, P.; Levey, A.; Duysen, E.G.; Lockridge, O. Acetylcholinesterase knockouts establish central cholinergic pathways and can use butyrylcholinesterase to hydrolyze acetylcholine. *Neuroscience,* **2002**, *110*(4), 627-639. http://dx.doi.org/10.1016/S0306-4522(01)00613-3 PMID: 11934471

[75] Darvesh, S. Butyrylcholinesterase as a diagnostic and therapeutic target for Alzheimer's disease. *Curr. Alzheimer Res.,* **2016**, *13*(10), 1173-1177. http://dx.doi.org/10.2174/1567205013666160404120542 PMID: 27040140

[76] Szwajgier, D. Anticholinesterase activity of selected phenolic acids and flavonoids - interaction testing in model solutions. *Ann. Agric. Environ. Med.,* **2015**, *22*(4), 690-694. http://dx.doi.org/10.5604/12321966.1185777 PMID: 26706979

[77] Lilienfeld, S. Galantamine--a novel cholinergic drug with a unique dual mode of action for the treatment of patients with Alzheimer's disease. *CNS Drug Rev.,* **2002**, *8*(2), 159-176. http://dx.doi.org/10.1111/j.1527-3458.2002.tb00221.x PMID: 12177686

[78] Marco, L.; do Carmo Carreiras, M. Galanthamine, a natural product for the treatment of Alzheimer's disease. *Recent Patents CNS Drug Discov.,* **2006**, *1*(1), 105-111. http://dx.doi.org/10.2174/157488906775245246 PMID: 18221196

[79] Georgieva, L.; Berkov, S.; Kondakova, V.; Bastida, J.; Viladomat, F.; Atanassov, A.; Codina, C. Alkaloid variability in *Leucojum aestivum* from wild populations. *Z. Natforsch. C J. Biosci.,* **2007**, *62*(9-10), 627-635. http://dx.doi.org/10.1515/znc-2007-9-1002 PMID: 18069233

[80] Heinrich, M. Galanthamine from *Galanthus* and other Amaryllidaceae--chemistry and biology based on traditional use. *Alkaloids Chem. Biol.,* **2010**, *68*, 157-165.

http://dx.doi.org/10.1016/S1099-4831(10)06804-5 PMID: 20334038

[81] Demir, A. Medical resource value appraisal for *Leucojum aestivum* in Turkey. *Am. J. Alzheimers Dis. Other Demen.,* **2014**, *29*(5), 448-451. http://dx.doi.org/10.1177/1533317514535334 PMID: 24833647

[82] Pinho, B.R.; Ferreres, F.; Valentão, P.; Andrade, P.B. Nature as a source of metabolites with cholinesterase-inhibitory activity: an approach to Alzheimer's disease treatment. *J. Pharm. Pharmacol.,* **2013**, *65*(12), 1681-1700. http://dx.doi.org/10.1111/jphp.12081 PMID: 24236980

[83] Khan, H.; Marya, ; Amin, S.; Kamal, M.A.; Patel, S. Flavonoids as acetylcholinesterase inhibitors: Current therapeutic standing and future prospects. *Biomed. Pharmacother.,* **2018**, *101*, 860-870. http://dx.doi.org/10.1016/j.biopha.2018.03.007 PMID: 29635895

[84] Uddin, M.S.; Kabir, M.T.; Niaz, K.; Jeandet, P.; Clément, C.; Mathew, B.; Rauf, A.; Rengasamy, K.R.R.; Sobarzo-Sánchez, E.; Ashraf, G.M.; Aleya, L. Molecular insight into the therapeutic promise of flavonoids against Alzheimer's disease. *Molecules,* **2020**, *25*(6), 1267. http://dx.doi.org/10.3390/molecules25061267 PMID: 32168835

[85] Czernicka, L.; Ludwiczuk, A.; Rój, E.; Marzec, Z.; Jarzab, A.; Kukula-Koch, W. Acetylcholinesterase inhibitors among *Zingiber officinale* terpenes-extraction conditions and thin layer chromatography-based bioautography studies. *Molecules,* **2020**, *25*(7), 1643. http://dx.doi.org/10.3390/molecules25071643 PMID: 32260053

[86] Karakaya, S.; Koca, M.; Sytar, O.; Duman, H. The natural phenolic compounds and their antioxidant and anticholinesterase potential of herb *Leiotulus dasyanthus* (K. Koch) Pimenov & Ostr. *Nat. Prod. Res.,* **2020**, *34*(9), 1303-1305. http://dx.doi.org/10.1080/14786419.2018.1557176 PMID: 30657333

[87] Ferreres, F.; Gil-Izquierdo, A.; Vinholes, J.; Silva, S.T.; Valentão, P.; Andrade, P.B. *Bauhinia forficata* Link authenticity using flavonoids profile: relation with their biological properties. *Food Chem.,* **2012**, *134*(2), 894-904. http://dx.doi.org/10.1016/j.foodchem.2012.02.201 PMID: 23107705

[88] Cao, J.; Xia, X.; Dai, X.; Wang, Q.; Xiao, J. Chemical composition and bioactivities of flavonoids-rich extract from *Davallia cylindrica* Ching. *Environ. Toxicol. Pharmacol.,* **2014**, *37*(2), 571-579. http://dx.doi.org/10.1016/j.etap.2014.01.011 PMID: 24562055

[89] Jabir, N.R.; Khan, F.R.; Tabrez, S. Cholinesterase targeting by polyphenols: A therapeutic approach for the treatment of Alzheimer's disease. *CNS Neurosci. Ther.,* **2018**, *24*(9), 753-762. http://dx.doi.org/10.1111/cns.12971 PMID: 29770579

[90] Tung, B.T.; Thu, D.K.; Thu, N.T.K.; Hai, N.T. Antioxidant and acetylcholinesterase inhibitory activities of ginger root (*Zingiber officinale* Roscoe) extract. *J. Complement. Integr. Med.,* **2017**, *14*(4)20160116 http://dx.doi.org/10.1515/jcim-2016-0116 PMID: 29345437

[91] Szwajger, D.; Borowiec, K.; Zapp, J. Activity-guided isolation of cholinesterase inhibitors quercetin, rutin and kaempferol from *Prunus persica* fruit. *Z. Naturforsch. C,* **2020**, *75*(3-4), 87-96. http://dx.doi.org/10.1515/znc-2019-0079

[92] Achili, I.; Amrani, A.; Bensouici, C.; Gül, F.; Altun, M.; Demirtas, I.; Zama, D.; Benayache, F.; Benayache, S. Chemical constituents, antioxidant, anticholinesterase and antiproliferative effects of Algerian *Pistacia atlantica* Desf. extracts. *Recent Pat. Food Nutr. Agric.,* **2020,** *11*(3),249-256. PMID: 32031082

[93] Jung, M.; Park, M. Acetylcholinesterase inhibition by flavonoids from *Agrimonia pilosa. Molecules,* **2007**, *12*(9), 2130-2139. http://dx.doi.org/10.3390/12092130 PMID: 17962731

[94] Katalinić, M.; Rusak, G.; Domaćinović Barović, J.; Sinko, G.; Jelić, D.; Antolović, R.; Kovarik, Z. Structural aspects of flavonoids as inhibitors of human butyrylcholinesterase. *Eur. J. Med. Chem.,* **2010**, *45*(1), 186-192. http://dx.doi.org/10.1016/j.ejmech.2009.09.041 PMID: 19879672

[95] Orhan, I.; Kartal, M.; Tosun, F.; Sener, B. Screening of various phenolic acids and flavonoid derivatives for their anticholinesterase potential. *Z. Natforsch. C J. Biosci.,* **2007**, *62*(11-12), 829-832. http://dx.doi.org/10.1515/znc-2007-11-1210 PMID: 18274286

[96] Aderogba, M.A.; Ndhlala, A.R.; Rengasamy, K.R.R.; Van Staden, J. Antimicrobial and selected *in vitro* enzyme inhibitory effects of leaf extracts, flavonols and indole alkaloids isolated from *Croton menyharthii. Molecules,* **2013**, *18*(10), 12633-12644. http://dx.doi.org/10.3390/molecules181012633 PMID: 24126380

[97] Ryu, H.W.; Curtis-Long, M.J.; Jung, S.; Jeong, I.Y.; Kim, D.S.; Kang, K.Y.; Park, K.H. Anticholinesterase potential of flavonols from paper mulberry (*Broussonetia papyrifera*) and their kinetic studies. *Food Chem.,* **2012**, *132*(3), 1244-1250. http://dx.doi.org/10.1016/j.foodchem.2011.11.093 PMID: 29243607

[98] Sivori, L.J.; Casabe, N.B.; Zerba, E.N.; Wood, E.J. Fenitrothion toxicity in *Triatoma infestans* synergized by quercetin or thymol blue. *Pestic. Sci.,* **1999**, *55*, 18-26.

[99] Zhang, H.Y. Same causes, same cures. *Biochem. Biophys. Res. Commun.,* **2006**, *351*(3), 578-581. http://dx.doi.org/10.1016/j.bbrc.2006.10.086 PMID: 17081501

[100] Zhang, H.Y.; Yang, D.P.; Tang, G.Y. Multipotent antioxidants: from screening to design. *Drug Discov. Today,* **2006**, *11*(15-16), 749-754. http://dx.doi.org/10.1016/j.drudis.2006.06.007 PMID: 16846803

[101] Sermboonpaisarn, T.; Sawasdee, P. Potent and selective butyrylcholinesterase inhibitors from *Ficus foveolata. Fitoterapia,* **2012**, *83*(4), 780-784. http://dx.doi.org/10.1016/j.fitote.2012.03.009 PMID: 22450264

[102] Ding, X.; Ouyang, M.A.; Liu, X.; Wang, R.Z. Acetylcholinesterase ınhibitory activities of flavonoids from the leaves of *Ginkgo biloba* against brown planthopper. *J. Chem.,* **2013**, *2013*645086 http://dx.doi.org/10.1155/2013/645086

[103] Omar, S.H.; Scott, C.J.; Hamlin, A.S.; Obied, H.K. Biophenols: Enzymes (β-secretase, Cholinesterases, histone deacetylase and tyrosinase) inhibitors from olive (*Olea europaea* L.). *Fitoterapia,* **2018**, *128*, 118-129. http://dx.doi.org/10.1016/j.fitote.2018.05.011 PMID: 29772299

[104] Khan, M.T.; Orhan, I.; Senol, F.S.; Kartal, M.; Sener, B.; Dvorská, M.; Smejkal, K.; Slapetová, T. Cholinesterase inhibitory activities of some flavonoid derivatives and chosen xanthone and their molecular docking studies. *Chem. Biol. Interact.,* **2009**, *181*(3), 383-389. http://dx.doi.org/10.1016/j.cbi.2009.06.024 PMID: 19596285

[105] Kumar, A.; Mehta, V.; Raj, U.; Varadwaj, P.K.; Udayabanu, M.; Yennamalli, R.M.; Singh, T.R. Computational and *in vitro* validation of natural molecules as potential acetylcholinesterase inhibitors and neuroprotective agents. *Curr. Alzheimer Res.,* **2019**, *16*(2), 116-127. http://dx.doi.org/10.2174/1567205016666181212155147 PMID: 30543170

[106] Ademosun, A.O.; Oboh, G.; Bello, F.; Ayeni, P.O. Antioxidative properties and effect of quercetin and its glycosylated form (rutin) on acetylcholinesterase and butyrylcholinesterase activities. *J. Evid. Based Complementary Altern. Med.,* **2016**, *21*(4), NP11-NP17. http://dx.doi.org/10.1177/2156587215610032 PMID: 26438716

[107] Kaur, S.; Singla, N.; Dhawan, D.K. Neuro-protective potential of quercetin during chlorpyrifos induced neurotoxicity in rats. *Drug Chem. Toxicol.,* **2019**, *42*(2), 220-230. http://dx.doi.org/10.1080/01480545.2019.1569022 PMID: 30747009

[108] Abdel-Diam, M.M.; Samak, D.H.; El-Sayed, Y.S.; Aleya, L.; Alarifi, S.; Alkahtani, S. Curcumin and quercetin synergistically attenuate subacute diazinon-induced inflammation and oxidative neurohepatic damage, and acetylcholinesterase inhibition in albino rats. *Environ. Sci. Pollut. Res. Int.,* **2019**, *26*(4), 3659-3665. http://dx.doi.org/10.1007/s11356-018-3907-9 PMID: 30535736

[109] Adedara, I.A.; Ego, V.C.; Subair, T.I.; Oyediran, O.; Farombi, E.O. Quercetin improves neurobehavioral performance through restoration of brain antioxidant status and acetylcholinesterase activity in manganese-treated rats. *Neurochem. Res.,* **2017**, *42*(4), 1219-1229. http://dx.doi.org/10.1007/s11064-016-2162-z PMID: 28144805

[110] Youdim, K.A.; Shukitt-Hale, B.; Joseph, J.A. Flavonoids and the brain: interactions at the blood-brain barrier and their physiological effects on the central nervous system. *Free Radic. Biol. Med.,* **2004**, *37*(11), 1683-1693.

http://dx.doi.org/10.1016/j.freeradbiomed.2004.08.002 PMID: 15528027

[111] Rossi, L.; Mazzitelli, S.; Arciello, M.; Capo, C.R.; Rotilio, G. Benefits from dietary polyphenols for brain aging and Alzheimer's disease. *Neurochem. Res.,* **2008**, *33*(12), 2390-2400. http://dx.doi.org/10.1007/s11064-008-9696-7 PMID: 18415677

[112] Liu, L.; Guo, L.; Zhao, C.; Wu, X.; Wang, R.; Liu, C. Characterization of the intestinal absorption of seven flavonoids from the flowers of *Trollius chinensis* using the Caco-2 cell monolayer model. *PLoS One,* **2015**, *10*(3)e0119263 http://dx.doi.org/10.1371/journal.pone.0119263 PMID: 25789809

[113] Luo, Z.; Morgan, M.R.; Day, A.J. Transport of trans-tiliroside (kaempferol-3-β-D-(6"-*p*-coumaroyl-glucopyranoside) and related flavonoids across Caco-2 cells, as a model of absorption and metabolism in the small intestine. *Xenobiotica,* **2015**, *45*(8), 722-730. http://dx.doi.org/10.3109/00498254.2015.1007492 PMID: 25761590

[114] Shi, J.; Zhu, L.; Li, Y.; Zheng, H.; Yu, J.; Lu, L.; Liu, Z. *In vitro* study of UGT metabolism and permeability of orientin and isoorientin, two active flavonoid C-glycosides. *Drug Metab. Lett.,* **2016**, *10*(2), 101-110. http://dx.doi.org/10.2174/1872312810666160219121217 PMID: 26891873

[115] Luo, L.Y.; Fan, M.X.; Zhao, H.Y.; Li, M.X.; Wu, X.; Gao, W.Y. Pharmacokinetics and bioavailability of the isoflavones formononetin and ononin and their *in vitro* absorption in using chamber and caco-2 cell models. *J. Agric. Food Chem.,* **2018**, *66*(11), 2917-2924. http://dx.doi.org/10.1021/acs.jafc.8b00035 PMID: 29504397

[116] Chen, Y.; Xue, F.; Xia, G.; Zhao, Z.; Chen, C.; Li, Y.; Zhang, Y. Transepithelial transport mechanisms of 7,8-dihydroxyflavone, a small molecular TrkB receptor agonist, in human intestinal Caco-2 cells. *Food Funct.,* **2019**, *10*(8), 5215-5227. http://dx.doi.org/10.1039/C9FO01007F PMID: 31384856

[117] Fang, Y.; Cao, W.; Xia, M.; Pan, S.; Xu, X. Study of structure and permeability relationship of flavonoids in Caco-2 cells. *Nutrients,* **2017**, *9*(12), 1301. http://dx.doi.org/10.3390/nu9121301 PMID: 29186068

[118] Kumar, P.; Sharma, G.; Kumar, R.; Singh, B.; Malik, R.; Katare, O.P.; Raza, K. Promises of a biocompatible nanocarrier in improved brain delivery of quercetin: Biochemical, pharmacokinetic and biodistribution evidences. *Int. J. Pharm.,* **2016**, *515*(1-2), 307-314. http://dx.doi.org/10.1016/j.ijpharm.2016.10.024 PMID: 27756627

[119] Ren, S.C.; Suo, Q.F.; Du, W.T.; Pan, H.; Yang, M.M.; Wang, R.H.; Liu, J. Quercetin permeability across blood-brain barrier and its effect on the viability of U251 cells. *Sichuan Da Xue Xue Bao Yi Xue Ban,* **2010**, *41*(5), 751-754, 759. PMID: 21302433

[120] Yang, Y.; Bai, L.; Li, X.; Xiong, J.; Xu, P.; Guo, C.; Xue, M. Transport of active flavonoids, based on cytotoxicity and lipophilicity: an evaluation using the blood-brain barrier cell and Caco-2 cell models. *Toxicol. In Vitro,* **2014**, *28*(3), 388-396. http://dx.doi.org/10.1016/j.tiv.2013.12.002 PMID: 24362044

[121] Nait Chabane, M.; Al Ahmad, A.; Peluso, J.; Muller, C.D.; Ubeaud, G. Quercetin and naringenin transport across human intestinal Caco-2 cells. *J. Pharm. Pharmacol.,* **2009**, *61*(11), 1473-1483. http://dx.doi.org/10.1211/jpp.61.11.0006 PMID: 19903372

[122] Limtrakul, P.; Khantamat, O.; Pintha, K. Inhibition of P-glycoprotein function and expression by kaempferol and quercetin. *J. Chemother.,* **2005**, *17*(1), 86-95. http://dx.doi.org/10.1179/joc.2005.17.1.86 PMID: 15828450

[123] DiCenzo, R.; Frerichs, V.; Larppanichpoonphol, P.; Predko, L.; Chen, A.; Reichman, R.; Morris, M. Effect of quercetin on the plasma and intracellular concentrations of saquinavir in healthy adults. *Pharmacotherapy,* **2006**, *26*(9), 1255-1261. http://dx.doi.org/10.1592/phco.26.9.1255 PMID: 16945047

[124] Sormunen, H.; Ruponen, M.; Laitinen, R. The effect of co-amorphization of glibenclamide on its dissolution properties and permeability through an MDCKII-MDR1 cell layer. *Int. J. Pharm.,* **2019**, *570,* 118653. http://dx.doi.org/10.1016/j.ijpharm.2019.118653 PMID: 31472218

[125] Ishisaka, A.; Ichikawa, S.; Sakakibara, H.; Piskula, M.K.; Nakamura, T.; Kato, Y.; Ito, M.; Miyamoto, K.; Tsuji, A.; Kawai, Y.; Terao, J. Accumulation of orally administered quercetin in brain tissue and its antioxidative effects in rats. *Free Radic. Biol. Med.,* **2011**, *51*(7), 1329-1336. http://dx.doi.org/10.1016/j.freeradbiomed.2011.06.017 PMID: 21741473

[126] Sun, D.; Li, N.; Zhang, W.; Zhao, Z.; Mou, Z.; Huang, D.; Liu, J.; Wang, W. Design of PLGA-functionalized quercetin nanoparticles for potential use in Alzheimer's disease. *Colloids Surf. B Biointerfaces,* **2016**, *148*, 116-129. http://dx.doi.org/10.1016/j.colsurfb.2016.08.052 PMID: 27591943

[127] Hashemian, M.; Ghasemi-Kasman, M.; Ghasemi, S.; Akbari, A.; Moalem-Banhangi, M.; Zare, L.; Ahmadian, S.R. Fabrication and evaluation of novel quercetin-conjugated Fe_3O_4-β-cyclodextrin nanoparticles for potential use in epilepsy disorder. *Int. J. Nanomed.,* **2019**, *14*, 6481-6495. http://dx.doi.org/10.2147/IJN.S218317 PMID: 31496698

[128] Moradi, S.Z.; Momtaz, S.; Bayrami, Z.; Farzaei, M.H.; Abdollahi, M. Nanoformulations of herbal extracts in treatment of neurodegenerative disorders. *Front. Bioeng. Biotechnol.,* **2020**, *8*, 238. http://dx.doi.org/10.3389/fbioe.2020.00238 PMID: 32318551

[129] Di Martino, P.; Censi, R.; Gigliobianco, M.R.; Zerrillo, L.; Magnoni, F.; Agas, D.; Quaglia, W.; Lupidi, G. Nano-medicine improving the bioavailability of small molecules for the prevention of neurodegenerative diseases. *Curr. Pharm. Des.,* **2017**, *23*(13), 1897-1908. http://dx.doi.org/10.2174/1381612822666161227154447 PMID: 28025942

[130] Rifaai, R.A.; Mokhemer, S.A.; Saber, E.A.; El-Aleem, S.A.A.; El-Tahawy, N.F.G. Neuroprotective effect of quercetin nanoparticles: A possible prophylactic and therapeutic role in Alzheimer's disease. *J. Chem. Neuroanat.,* **2020**, *107*101795 http://dx.doi.org/10.1016/j.jchemneu.2020.101795 PMID: 32464160

[131] Pinheiro, R.G.R.; Granja, A.; Loureiro, J.A.; Pereira, M.C.; Pinheiro, M.; Neves, A.R.; Reis, S. RVG29-Functionalized lipid nanoparticles for quercetin brain delivery and Alzheimer's disease. *Pharm. Res.,* **2020**, *37*(7), 139. http://dx.doi.org/10.1007/s11095-020-02865-1 PMID: 32661727

[132] Dhawan, S.; Kapil, R.; Singh, B. Formulation development and systematic optimization of solid lipid nanoparticles of quercetin for improved brain delivery. *J. Pharm. Pharmacol.,* **2011**, *63*(3), 342-351. http://dx.doi.org/10.1111/j.2042-7158.2010.01225.x PMID: 21749381

[133] Rishitha, N.; Muthuraman, A. Therapeutic evaluation of solid lipid nanoparticle of quercetin in pentylenetetrazole induced cognitive impairment of zebrafish. *Life Sci.,* **2018**, *199*, 80-87. http://dx.doi.org/10.1016/j.lfs.2018.03.010 PMID: 29522770

[134] Liu, Y.; Zhou, H.; Yin, T.; Gong, Y.; Yuan, G.; Chen, L.; Liu, J. Quercetin-modified gold-palladium nanoparticles as a potential autophagy inducer for the treatment of Alzheimer's disease. *J. Colloid Interface Sci.,* **2019**, *552*, 388-400. http://dx.doi.org/10.1016/j.jcis.2019.05.066 PMID: 31151017

[135] Ebrahimpour, S.; Esmaeili, A.; Beheshti, S. Effect of quercetin-conjugated superparamagnetic iron oxide nanoparticles on diabetes-induced learning and memory impairment in rats. *Int. J. Nanomed.,* **2018**, *13*, 6311-6324. http://dx.doi.org/10.2147/IJN.S177871 PMID: 30349252

[136] Enteshari Najafabadi, R.; Kazemipour, N.; Esmaeili, A.; Beheshti, S.; Nazifi, S. Using superparamagnetic iron oxide nanoparticles to enhance bioavailability of quercetin in the intact rat brain. *BMC Pharmacol. Toxicol.,* **2018**, *19*(1), 59. http://dx.doi.org/10.1186/s40360-018-0249-7 PMID: 30253803

[137] Kuo, Y.C.; Tsao, C.W. Neuroprotection against apoptosis of SK-N-MC cells using RMP-7- and lactoferrin-grafted liposomes carrying quercetin. *Int. J. Nanomed.,* **2017**, *12*, 2857-2869. http://dx.doi.org/10.2147/IJN.S132472 PMID: 28435263