Pharmacological Research 128 (2018) 359–365

Contents lists available at ScienceDirect

Pharmacological Research

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

Invited review

Apigenin as neuroprotective agent: Of mice and men

Seyed Fazel Nabavi[a], Haroon Khan[b,*], Grazia D'onofrio[c], Dunja Šamec[d], Samira Shirooie[e], Ahmad Reza Dehpour[e,f], Sandro Argüelles[g], Solomon Habtemariam[h], Eduardo Sobarzo-Sanchez[i,j]

[a] Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran 14359-16471, Iran
[b] Depatment of Pharmacy, Abdul Wali Khan University, Mardan 23200, Pakistan
[c] Gerontology-Geriatric Research Laboratory, Department of Medical Sciences, I.R.C.C.S. "Casa Sollievo della Sofferenza", Foggia, Italy
[d] Department of Molecular Biology, Institute 'Ruđer Bošković', Zagreb, Croatia
[e] Department of Pharmacology, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[f] Experimental Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran
[g] Department of Physiology, Faculty of Pharmacy, University of Seville, Seville, Spain
[h] Pharmacognosy Research Laboratories & Herbal Analysis Services UK, University of Greenwich, Chatham-Maritime, Kent ME4 4TB, UK
[i] Laboratory of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Santiago de Compostela 15782, Spain
[j] Instituto de Investigación en Innovación en Salud, Facultad de Ciencias de la Salud, Universidad Central de Chile, Santiago, Chile

ARTICLE INFO

Article history:
Received 29 September 2017
Received in revised form 13 October 2017
Accepted 16 October 2017
Available online 18 October 2017

Keywords:
Neuroprotection
Alzheimer's disease
Parkinson's disease
Apigenin
Flavonoids

ABSTRACT

Neurodegenerative disorders (NDDs) such as Alzheimer's and Parkinson's diseases are the most common age-related pathologies that affect millions of people all over the world. To date, effective therapy for NDDs is not available and current approaches to disease management include neuroprotection strategy with a hope of maintaining and enhancing the function of survising neurons. Of course, such an approach by its own will not offer a cure but is likely to delay the disease progression by ameliorating the increase of neurotoxic agents such reactive oxygen species (ROS) as well as the associated inflammatory cascades. In this regard, natural products including flavonods that offer neuroprotection through multiple mechanisms have gained a lot of interest in recent years. In this communication, evidences from the various experimental models and clinical trials on the therapeutic potential of one promising flavonod, apigenin, is presented. Its chemistry, mechanism of action and potential benefits in the various examples of NDDs are discussed in the light of drug discovery aspects.

Contents

* Corresponding author.
E-mail address: hkdr2006@gmail.com (H. Khan).

https://doi.org/10.1016/j.phrs.2017.10.008
1043-6618/

1. Introduction

Alzheimer's disease (AD) and other neurodegenerative disorders (NDDs) are characterized by a progressive deficit of neuronal function and structure, which eventually brings to neuronal death in the nervous system [1,2]. In NDDs, the pathological cellular and molecular events include oxidative stress, protein oligomerization and aggregation, axonal transport deficiency, calcium deregulation, impairment in the mitochondrial function and structure, neuroinflammation, abnormal neuron-glial interactions, aberrant RNA processing and DNA damage [2,3]. Possible risk factors for the NDDs include age, gender, endocrine conditions, poor education, inflammation and inflammatory related pathologies such as cardiovascular diseases and diabetes [2,4].

The failures of a great number of surgical and pharmacological treatments for NDDs bring to light the need for novel therapeutic approaches to regulate several targets and molecular pathways [5]. For this reason, designing new effective therapeutic strategy to improve the quality of life of people with NDDs has become one of the major focuses of the pharmaceutical industry. Hence, a huge number of effective compounds which typically targeted specific molecular pathways related to suppression of oxidative stress have been developed [6]. In this regard, an interesting compound that gained attention at experimental stage has been apigenin (API), chemically known as 4′,5,7-trihydroxyflavone ($C_{15}H_{10}O_5$) [7,8]. The compound is mainly found in different parts of *Hypericum perfo*ratum although several plants and other natural sources have been known to synthesise it. Of the several dietary plant foods that contain API include celery and turnip-rooted celery, garden parsley, thyme, *Matricaria chamomilla*, onions, *Melissa officinalis*, and citrus species [9]. A recent study on a double transgenic animal model of AD (APP/PS1) had shown that API could mitigate AD-associated memory deficiency, decrease the Aβ plaque burden and suppress oxidative damages [10,11]. In light of recent studies, API seems to have potent neuroprotective properties in animal models [12–14]. However, there is lack of clinical studies regarding to beneficial effects of apigenin on AD.

The aim of the present paper is to critically review the current scientific reports regarding API, its antioxidative activity and potential role as neuroprotective agent, to provide a snapshot of the chemistry, pharmacokinetic and metabolism of API, and to clarify the effects that API could have on patients' care with NNDs.

2. Chemistry, structure and biosynthesis

Apigenin is 4′,5,7-trihydroxyflavone (Fig. 1) belongs to the flavonoids subgroup, flavones, on the basis of 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one) skeleton. In its pure form, it occurs as a yellow needles, with slight solubility in hot alcohol, and freely soluble in dilute KOH and DMSO. It is unstable at room temperature and should be stored at −20° C or lower temperature. Apigenin occasionally occur in plants as aglycone: more often is found as glycoside form. Some authors even support the idea that free API is a product of postharvest degradation process [15,16]. In nature, the common flavonoid feature is formation of *O*-glycosides but other characteristic of flavones is the formation of C-glycosides attributed by a "carbon-carbon bond between the anomeric carbon of the sugar molecule and the C-6 or C-8 carbon of the flavone nucleus" [16,17]. Some of the known apigenin-glycosides, with their food/medicinal plant sources are shown in Table 1. In alfalfa, several groups have identified different acylated glycosides form of API [18,19]. In plants, API may exist in a wide range of different forms of glycosides whose presence and ratio are influenced by genetic background, environmental growth condition, development stage etc. [20,21]. In addition to glycosylattion, in some plants,

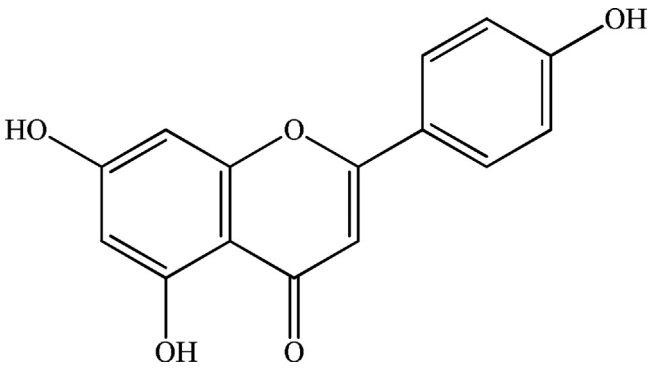

Fig. 1. Chemical structure of apigenin.

API form dimer molecules to form bioflavonoids and other diverse structural groups. The best studied API dimer of pharmacological importance is amentoflavone (3′, 8″-biapigenin) which is found in well-known medicinal herbs including St John's wort (*Hypericum perforatum* L.) [22,23], ginko (*Ginkgo biloba* L.) [24] and spike mosses (*Selaginella* sp.) [25].

Apigenin is biosynthesized in the cytoplasmic surface of the endoplasmic reticulum and the reaction is catalyzed by a series of enzymes [26]. The important step in the biosynthesis of flavonoids is the generation of naringenin chalcon (an intermediate chalcone) through condensation and then intramolecular cyclization of three malonyl-CoAs and Coumaroyl-CoAs by chalcone synthase (CHS). Further action by the stereospecific catalysis of chalcone isomerase (CHI) results in the synthesis of naringenin. Finally, naringenin serves as the substrate for the flavone synthase (FSI) which catalyze the formation of [27,28]. As mentioned earlier, API is just occasionally found in its free form, therefore its formation is usually followed by further action by certain glycosyl transferases, hydroxyl transferases and methyl transferases which catalyze methylation and hydroxylation of API to form diverse derivatives. It has been reported that one effective way of apigenin glucosides synthesis *in vitro* is via the glycosylation reaction using auridine diphosphate-glucosyltransferase YjiC, from *Bacillus licheniformis* DSM 13 [29]. Several methods are also available for the synthesis of apigenin including microwaves irradiation of β-ketoester as the starting material [30,31] or commercially available phloroglucinol [32,33]. Wide range of different synthetic API derivatives is also synthesized as potential pharmacologically active compounds [34,35].

3. Sources of apigenin

Apigenin, in free or conjugated form, is considered widespread through the plant kingdom and consequently found in edible and medicinal plants. The flavonoid content of 506 food items is listed in the United Sates Department of Agriculture (USDA) Database [36] and include API as a common component. The amount shown were in average value in mg/100 g of edible portion. The highest amount of API listed in the fresh parsley was 215.46 mg/100 g FW. According to the database, other food sources of API are also celery (the highest is Chinese celery 24.02 mg/100 g), kumquat (21.87 mg/100 g) and rutabaga (3.85 mg/g edible part). Apigenin is also present in plants used as spices such as oregano, mint, rosemary, sage and thyme. Miean and Mohamed (2001) evaluated API content after extraction and hydrolysis of the flavonoid glycosides in 62 species of edible plants and succeed to detect API in 11 of them. The highest amount had guava (579.0 ± 0.02 mg/kg dw) followed by wolfberry leaf (547.0 ± 0.07 mg/kg dw), belimbi fruit (458.0 ± 0.04 mg/kg dw) and celery (338.5 ± 0.04 mg/kg dw) [37]. Other tropical fruits where API was detected include (from the highest to lowest amount)

Table 1
Apigenin-glycosides, with their food/medicinal plant sources.

Common name	Glycoside	Source	Reference
Apiin	apigenin-7-apioglucoside	parsley (*Petroselinum crispum*) celery (*Apium graveolens*)	[106,107]
Apigetrin	apigenin 7-glucoside	chamomile (*Matricaria chamomilla*) Baikal skullcap (*Scutellaria baicalensis*)	[108]
Cosmosin	Apigenin 7-*O*-glucoside	*Tilia cordata*	[109]
Vitexin	apigenin 8-*C*-glucoside	hawthorn (*Crataegus sp.*)	[110]
Isovitexin	apigenin 6-*C*-glucoside	hawthorn (*Crataegus sp.*)	[110]
Rhoifolin	apigenin 7-*O*-neohesperidoside	kumquat (*Citrus japonica*)	[111]
Schaftoside	apigenin 6-*C*-glucoside 8-*C*-arabinoside	sugarcane (*Saccharum officinarum*)	[112]
Isoschaftoside	apigenin 6-*C*-glucoside 8-*C*-arabinoside	sugarcane (*Saccharum officinarum*)	[112]

bell pepper > garlic > Chinese cabbage > French peas > snake gourd daunturi > Kadok [38]. Apigenin is reported (common as flavonoid *C*-glycosides) also in different algae [39–41] which are available in the market as dietary supplements.

4. Role of oxidative stress in neurodegeneration

Under normal physiological conditions, oxidative stress originates from the excessive accumulation of free radicals which are generated as byproducts of aerobic cellular metabolism and also by exogenous oxidant agents [42]. Superoxide anion is one good example of ROS which must be rapidly converted into hydrogen peroxide by super-oxide dismutase (SOD) to avoid oxidative damage [43]. In the state of absence and/or lower activity of SOD, a serious of more reactive ROS including hydroxyl radical could be formed leading to lipid peroxidation and structural alterations of membranes, macromolecules and functional impairment of cellular components [42,44]. Hence, the levels of oxidative product including total hydroperoxide or lipid peroxidation byproduct such as malondialdehyde (MDA), and antioxidant systems including glutathione (GSH), catalase and SOD have been identified as reliable markers of oxidative stress [42].

By the free radical theory of Harman, aging and age-associated diseases, e.g. AD, are the consequence of ROS-induced damage to cellular macromolecules [45]. Since excessive ROS generation is considered to be a triggering factor in many neurodegenerative pathologies [46], the role of the oxidative stress in neurodegeneration has gained momentum in the last two decades [47]. This fact could be explained because, mammalian brain is metabolically more active than any other organ. Despite a relatively small size (about 2% of the body weight) it accounts for 20% of the oxygen (used mainly to oxidize glucose to carbon dioxide and water) and body's total energy requirement [48]. This fuel over-consumption comes from enhanced neuronal vulnerability to oxidative stress. Nuerodegeneration is an age-related process. In fact, when aging occurs, the chronic pro-oxidant environment is a challenge for neurons which lack the potential of mitotic renewal [46]. Progressive accumulation of macromolecules damaged by ROS such as lipid peroxidation, reactive carbonyl in proteins and oxidatively damaged nucleic acids severely compromise cell viability [46].

Previous studies have indicated that ROS contributes to the disruption of blood–brain barrier (BBB) by disturbing tight junction proteins [46,49,50]. Furthermore, oxidative stress serves as an important mechanism underlying detrimental effects of Aβ toxicity in which excessive generation of ROS leads to a elevation of Aβ burden through alteration of Aβ peptide kinetics [51,52]. Moreover, excessive production of lipid peroxidation products such as malondialdehyde and 4-hydroxynonenal have been associated with AD and PD [53]. As oxidative stress plays crucial role in neurodegeneration, there has been an increasing interest in the therapeutic possibilities of antioxidant agents against NDDs.

5. Apigenin as antioxidant in NDDs

Several studies *in vitro* and *in vivo* demonstrated that API possesses powerful anti-inflammatory, anti-carcinogenic and antioxidant effects [54–57]. Regarding its antioxidant activity, it was reported that API downregulates adhesion molecules [58] and suppresses oxidative stress through direct free radical scavenging action and upregulation of intracellular antioxidant defences (e.g. by enhancing glutathione level) [59].

In the last few years, several studies have shown the promising effect of API in experimental models of AD. For example, Zhao and colleagues using an experimental model of APP/PS1 double transgenic AD mouse treated with API (40 mg/kg for 3 months), found that this flavone was able to improve memory retention and learning impairment evaluated through Morris water maze (MWM) testing at the age of 7 months. The authors also found that fibrillar amyloid deposition was reduced in API-treated APP/PS1 mice by Thioflavin S staining test. Moreover, reduction of insoluble $A\beta_{1-40}/A\beta_{1-42}$ and β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) level, inhibition of *β-Amyloidogenesis* process and oxidative stress, as well as elevation of Brain-derived neurotrophic factor (BDNF) level which improved the phosphorylation of ERK1/2 and the expression of cAMPresponse element-binding protein (CREB) in the cerebral cortex of API-treated APP/PS1 mice [60]. In another study, Liu and colleagues found that in Aβ25-35-induced mouse model of amnesia, treatment with API (20 mg/kg) for 8 days enhanced the learning and memory functions, microvascular function and cholinergic system, reduction of oxidative damage as well as restoration of BNDF, TrkB, as well as phospho-CREB levels [58]

The anti-inflammatory activity of API has been studied by Smolinski and colleagues using mice co-treated with LPS. The authors found that treatment with API (50 mg/kg) reduced the serum levels of Interleukin 6 and TNF-α [61]. Moreover, using an API-treated spinal cord injury rat model, Zhang and colleagues found that the recovery of neuronal function was improved, the levels of malondialdehyde, superoxide dismutase activity, glutathione peroxidase activity, inflammatory markers as well as Bax, Bcl-2 and caspase-3 were significantly decreased after API (10–20 mg/kg) treatment [62]. So far the potential protector effect of API on human cognitive processes has not been elucidated.

6. Apigenin neurological effects

6.1. Preclinical studies

6.1.1. Effect in depression

The antidepressant-like effects of API has been reported by different authors. For example, Nakazawa and colleagues found that treatment with API decreased forced swim test-caused reduce of dopamine turnover in the amygdala and increase of dopamine turnover in the hypothalamus. The authors also found that

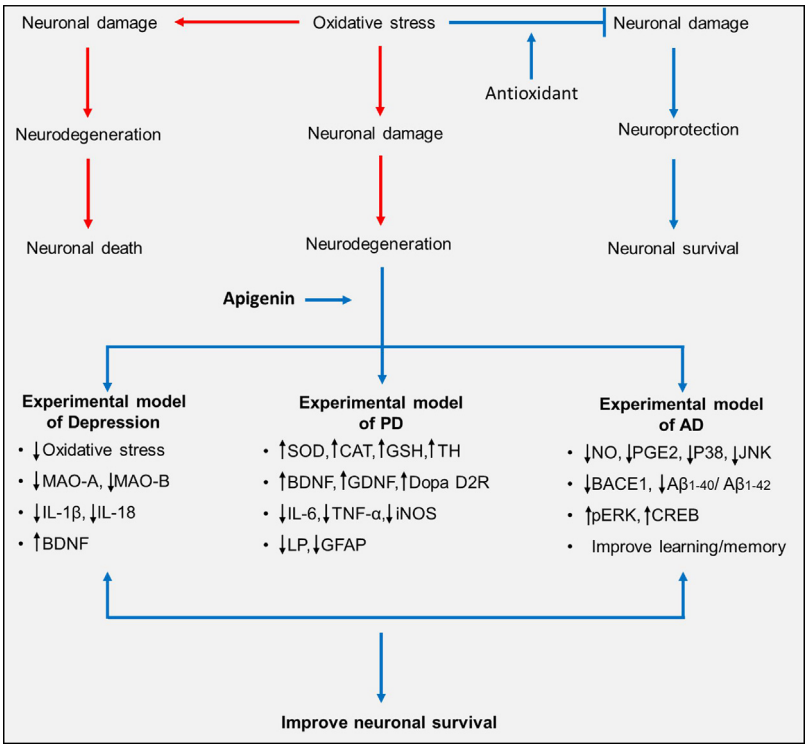

Fig. 2. Role of oxidative stress in neuronal death. Increase of oxidative stress is associated with neuronal death (1); in different experimental models of neurodegeneration-related diseases, Apigenin was able to improve neuronal survival through a molecular mechanisms involving increase of antioxidant and neurotrofic factor and decrease of oxidants and pro-inflammarory molecules (2); antioxidant can promote neuronal survival by controlling the increase of oxidative stress (3). Monoamine oxidase (MAO), Interleukin (IL), Brain-derived neurotrophic factor (BDNF), super-oxide dismutase (SOD), catalase (CAT), glutathione (GSH), Tyrosine hydroxylase (TH), Glial cell-derived neurotrophic factor (GDNF), dopamine D2 receptors (Dopa D2R), Glial fibrillary acidic protein (GFAP), Lipid peroxidation (LP), Tumor Necrosis Factor-alpha (TNF-α), inducible nitric oxide synthase (iNOS), Nitric oxide (NO), Prostaglandin E2 (PGE2), c-Jun N-terminal kinases (JNK), β-site AβPP-cleaving enzyme 1 (BACE1), extracellular-signal-regulated kinases (ERK), cAMP response element-binding protein (CREB), Parkinson's disease (PD), Alzheimer's disease (AD).

haloperidol (0.2 mg/kg i.p.), an atypical antipsychotic drug which increase D(2) receptor occupancy [63], blocked the API (25 mg/kg)-induced decrease in immobility in the forced swimming test [64,65]. Monoamine oxidase (MAO) in the brain has an essential role in removing some neurotransmitters such as norepinephrine, serotonin as well as dopamine. There are two clases of this enzyme, MAO-A and MAO-B. Selective inhibition of MAO-A is utilized for treatment of depression via increasing the levels serotonin and noradrenaline. On the other hand, selective inhibitors of MAO-B are utilized for the symptomatic treatment of PD [66]. In this context, Han and colleagues (2007) used API isolated from *Cayratia japonica* to evaluate its effect on MAO inhibition. The author found that API can inhibit both MAO-A and MOA-B, and the half maximal concentrations (IC_{50}) of MAO-A: 1.7 μM and MAO-B: 12.8 μM [67]. Chaurasiya and colleagues also have reported that API isolated from propolis selectivity inhibit MAO-A vs. MAO-B [68].

Similarly, Yi and colleagues reported that API restored the abnormality in central monoaminergic neurotransmitter, the hypothalamic-pituitary-adrenal axis, and adenylyl cyclase activity systems in the chronic mild stress (CMS) depressed rats. The authors also found that chronic treatment with API decrease CMS-induced increase in serum corticosterone [69].

It has been reported that the imbalance between pro-inflammatory (Interleukin-1β, TNF-α and interleukin-6) as well as anti-inflammatory cytokines (TGF-β and interleukin-10) in the brain of CMS-induced depression model [70] and elevated antioxidative enzyme activities (AEAs) and lipid peroxidation (LP) in major depressed patients [71]. In this context, recently Li and colleagues reported that by a mechanism involving PPARγ activity, API was able to inhibit oxidative stress, microglia and NLRP3 activation, and reduce the production of interleukin-1β and interleukin-18 in depression model of chronic unpredictable mild stress (CUMS) rat [72]. Moreover, Weng and colleagues showed that API restore the decrease of BDNF in mice treated with repeated corticosterone injection [73].

6.1.2. *Parkinson's disease (PD)*

The increase of oxidative stress has been associated with age-related neurodegenerative diseases including PD [74]. MPTP (1-mehtyl-4-phenyl-1,2,3,6-tetrahydropyridine) can progressively cause PD in experimental animals [75–77]. The pathophysiologcal hallmarks of PD include aggregation of α-synuclein in the Lewy body or neurites which led to the downregulation of dopamine expression and neuron death [78]. Tyrosine hydroxylase (TH) is an enzyme involved in the dopamine biosynthesis [79]. Other enzyme, MAO is also associated with PD because its overexpression contribute to PD progression while its inhibition may offer some neuroprotective effect [80].

Using the MPTP-induced induced parkinsonian mouse model, Patil and colleagues found that the neuroprotective role of API is mediated in part by its potent antioxidant activity (increased SOD, CAT, GSH and decreased LP), prevention of TH and BDNF decrease and Glial fibrillary acidic protein (GFAP) and TNF-α increase [81]. In a transgenic *Drosophila* model of PD exposed to API, Siddique and Jyoti reported an extend in lifespan, glutathione, and dopamine as well as a decrease too many as well as decreasing of glutathione-*S*-transferase activity, lipid peroxidation, monoamine oxidase, caspase-3, as well as caspase-9 activity [82]. Moreover, Anusha and colleagues studied the effect of API in rotenone-induced PD model, and found that API was able to prevent the increase of NF-κB and decrease of BDNF and GDNF. API also

decrease the levels of TNF-a, IL-6, iNOS-1, a-synuclein and increase TH and dopamine D2 receptors expression [83].

6.1.3. Alzheimer's disease (AD)

The activation of astrocytes and cellules microglial as result of chronic neuroinflammation can lead to functional neuronal decrease in the hippocampus and temporoparietal cortex in AD. The mechanism responsible of this neuronal loss involve beta amyloid precursor protein (βAPP) and upregulation or reduced degradation of beta amyloid (Aβ) in the brain (Blasko et al. [113]). It is known that reduction of insoluble Aβ concentrations may be a marker of AD treatment [84,85]. Several reports have studied the potential therapeutical role of API in PD. For example, Ha and colleagues found that API treatment in microglia cell exposed to LPS through a mechanisms involving decreased the levels of nitric oxide, prostaglandin E2, p38 and JNK phosphorylation decreased neuronal cell death *via* suppression of microglia cell [86]. This potent antioxidant and anti-inflammatory effects of API may be responsible of finding reported by Liang and colleague in GFAP-IL6 mouse model of chronic neuroinflammation. The finding included improvement of the spatial reference working memory and decreased microglia activation in the cerebellum and in the hippocampus [87].

Another problem of AD is loss of memory. Popovic and colleagues using retention performance and forgetting of a step-through passive avoidance task in animal experimental model found that pretreatment with API caused significant improvement in long-term memory but no significant effect on 24 h retention of fear memory [88]. Moreover, Liu and colleagues using Aβ25-35-induced amnesic mice found that API treatment was able to improve learning and memory capabilities, maintenance of neurovascular functions, decrease neurovascular oxidative damage dysregulation of BDNF, its receptor, tropomyosin receptor kinase B (TrkB), and phospho-CREB levels [58]. Zhao and colleagues also have studied the potential role of API on cognitive function in AD. The authors found that API caused improvement of memory retention and learning deficits in APP/PS1 mice evaluated through Morris water maze (MWM) [60].

It was reported that ERK/CREB/BDNF, an important signaling pathway whose dysregulation has been associated with AD [89,90], could be restored by API treatment [91,92]. API also has been reported by improve the cholinergic system through suppression of AChE activity and increasing of ACh level [58]. Take together all these evidence show that the potential protecction of API against the progression of PD include multiple mechanisms.

6.1.4. Human model of AD

Apigenin treatment caused marked protection to neurites and cell viability against inflammation by modulating downstream regulation of mediators of inflammation such as cytokine and nitric oxide (NO) that released during inflammation [93,94]. API treatment significantly decreased the neurite length and this diverse anti-inflammatory effect could interfere with onset and or progression of AD.

In human iPSC-derived model of AD, API exhibited marked downregulation of caspase-3/7 activity, and thus preventing cells from apoptosis which was consistent with reported animal studies [95]. However, it had no anticytotoxic effect towards neurons and thus it was suggested that API might have caspase-specific mechanism for anti-apoptotic action which in turn could be helpful against synaptic loss and cognitive decline and a molecule with great clinical potential in the treatment of AD.

Additionally, pretreatment with API caused marked downregulation of Ca^{2+} signals in the AD neurons and more specific protective mechanism against AD. As it has been shown previously in various animal and human studies that neuronal networks are hyperactive during different stages of AD, especially in initial phases of the disorder [96,97]. The hyperactivity of neuron could also be due to NO over expression [98] and as API showed scavenging effect on NO so it could be very versatile molecule for the treatment of AD by ameliorating the disease through multiple disease modifying mechanisms.

6.1.5. Effect in early brain injury (EBI)

A large number of causalities have been reported from subarachnoid hemorrhage (SAH) around the world [99]. It has been reported that the initial 72 h is curial in the prognosis of EBI due to SAH [44]. The EBI has indeed a very complex mechanism, however, oxidative stress is considered as an important biomarker for EBI due to SAH [100]. When EBI due to SAH was induced in experimental models of epilepsy, administration of API caused significant inhibition of EBI by modulating TLR4-mediated inflammatory pathway [101]. Similarly, the SAH was induced in endovascular puncture model to validate the possible effect of API. After 24 h of SAH, treatment with the API caused significant inhibition of various markers of oxidative stress and apoptosis in brain cortex [42]. For anti- apoptotic action, over-expression of caspase-3 and Bax which is mostly activated in oxidative stress [102].

7. General summary and conclusions

Nature has been the source of medicine for mankind from ancient time to date. Medicinal foods and herbal medicines with various composition of secondary and primary metabolites still can play vital role in managing complex diseases. Some of these compounds can act through specific mechanism including biological targets such as enzymes, and receptors. However, API effects through multiple mechanisms and/or by multifunctional compounds appear to be the best compromise to overcome complex diseases such as NDDs (Fig. 2). With respect to neuroprotection, a recent article from our laboratories has shown the potential benefit of the various classes of natural products in amaliorating the pathology of NDDs [102–104]. We have also shown that numerous flavonoids such as chrysin [103], fisetin [104] and rutin [105] among others can offer health benefits and neuroprotective effects through multiple mechanisms. In this report, extensive literature search on the flavonoid, API, revealed that it has neuroprotective role in experimental animal models of AD and PD as well in preclinical and clinical trial studies in humans. Beyond the well-known antioxidant activity of flavonoids, the observed neuroprotection effect appears to be linked to ameliorating the inflammatory components of AD and PD. Specific markers of oxidative and neuro-pathological markers such as the amyloids-beta accumulation as well as pathology also appear to be targeted by this promising bioactive compound. Considering the readily available natural sources of apigenin that can be exploited in industrial scale, future clinical trials that specifically target the various NDDs should be encouraged.

References

[1] E. Cho, M. Park, Palmitoylation in Alzheimer's disease and other neurodegenerative diseases, Pharmacol. Res. 111 (2016) 133–151.
[2] H.K. Karnati, M.K. Panigrahi, R.K. Gutti, N.H. Greig, I.A. Tamargo, miRNAs: key players in neurodegenerative disorders and epilepsy, J. Alzheimer's Dis. 48 (2015) 563–580.
[3] L. Koric, E. Guedj, M.O. Habert, F. Semah, P. Branger, P. Payoux, F. Le Jeune, Molecular imaging in the diagnosis of Alzheimer's disease and related disorders, Rev. Neurol. 172 (2016) 725–734.
[4] S. Pugazhenthi, L. Qin, P.H. Reddy, Common neurodegenerative pathways in obesity diabetes, and Alzheimer's disease, Biochim. Biophys. Acta (BBA) – Mol. Basis Dis. 1863 (2017) 1037–1045.
[5] J.-L. Chen, W.-C. Ko, Relaxation of isolated guinea-pig trachea by apigenin a constituent of celery, via inhibition of phosphodiesterase, Eur. J. Pharmacol. 811 (2017) 129–133.

[6] S.W. French, A.S. Mendoza, Y. Peng, The mechanisms of Mallory–Denk body formation are similar to the formation of aggresomes in Alzheimer's disease and other neurodegenerative disorders, Exp. Mol. Pathol. 100 (2016) 426–433.
[7] M. Venigalla, S. Sonego, E. Gyengesi, M.J. Sharman, G. Münch, Novel promising therapeutics against chronic neuroinflammation and neurodegeneration in Alzheimer's disease, Neurochem. Int. 95 (2016) 63–74.
[8] M. Bakhtiari, Y. Panahi, J. Ameli, B. Darvishi, Protective effects of flavonoids against Alzheimer's disease-related neural dysfunctions, Biomed. Pharmacother. 93 (2017) 218–229.
[9] S.M. Nabavi, S. Habtemariam, M. Daglia, S.F. Nabavi, Apigenin and breast cancers: from chemistry to medicine, Anticancer Agents Med. Chem. 15 (2015) 728–735.
[10] L. Zhao, J.-L. Wang, R. Liu, X.-X. Li, J.-F. Li, L. Zhang, Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an Alzheimer's disease mouse model, Molecules 18 (2013) 9949–9965.
[11] S.H. Omar, C.J. Scott, A.S. Hamlin, H.K. Obied, The protective role of plant biophenols in mechanisms of Alzheimer's disease, J. Nutr. Biochem. 47 (2017) 1–20.
[12] A.Y. Choi, J.H. Choi, J.Y. Lee, K.-S. Yoon, W. Choe, J. Ha, E.-J. Yeo, I. Kang, Apigenin protects HT22 murine hippocampal neuronal cells against endoplasmic reticulum stress-induced apoptosis, Neurochem. Int. 57 (2010) 143–152.
[13] J.-Y. Han, S.-Y. Ahn, C.-S. Kim, S.-K. Yoo, S.-K. Kim, H.-C. Kim, J.T. Hong, K.-W. Oh, Protection of apigenin against kainate-induced excitotoxicity by anti-oxidative effects, Biol. Pharm. Bull. 35 (2012) 1440–1446.
[14] T. Zhang, J. Su, B. Guo, K. Wang, X. Li, G. Liang, Apigenin protects blood–brain barrier and ameliorates early brain injury by inhibiting TLR4-mediated inflammatory pathway in subarachnoid hemorrhage rats, Int. Immunopharmacol. 28 (2015) 79–87.
[15] S. Karakaya, S.N. EL, Quercetin, luteolin, apigenin and kaempferol contents of some foods, Food Chem. 66 (1999) 289–292.
[16] N. Cook, S. Samman, Flavonoids—chemistry metabolism, cardioprotective effects, and dietary sources, J. Nutr. Biochem. 7 (1996) 66–76.
[17] J.M. Baranac, N.A. Petranović, J.M. Dimitrić-Marković, Spectrophotometric study of anthocyan copigmentation reactions. 4. Malvin and apigenin 7-glucoside, J. Agric. Food Chem. 45 (1997) 1701–1703.
[18] V. Švehlíková, R.N. Bennett, F.A. Mellon, P.W. Needs, S. Piacente, P.A. Kroon, Y. Bao, Isolation, identification and stability of acylated derivatives of apigenin 7-O-glucoside from chamomile (Chamomilla recutita [L.] Rauschert), Phytochemistry 65 (2004) 2323–2332.
[19] F. Cuyckens, M. Claeys, Mass spectrometry in the structural analysis of flavonoids, J. Mass Spectrom. 39 (2004) 1–15.
[20] C. Muñoz, J.F. Sánchez-Sevilla, M.A. Botella, T. Hoffmann, W. Schwab, V. Valpuesta, Polyphenol composition in the ripe fruits of Fragaria species and transcriptional analyses of key genes in the pathway, J. Agric. Food Chem. 59 (2011) 12598–12604.
[21] D. Giuntini, V. Lazzeri, V. Calvenzani, C. Dall'Asta, G. Galaverna, C. Tonelli, K. Petroni, A. Ranieri, Flavonoid profiling and biosynthetic gene expression in flesh and peel of two tomato genotypes grown under UV-B-depleted conditions during ripening, J. Agric. Food Chem. 56 (2008) 5905–5915.
[22] I.L. Wong, K.-F. Chan, Y. Zhao, T.H. Chan, L.M. Chow, Quinacrine and a novel apigenin dimer can synergistically increase the pentamidine susceptibility of the protozoan parasite Leishmania, J. Antimicrob. Chemother. 63 (2009) 1179–1190.
[23] J. Barnes, L.A. Anderson, J.D. Phillipson, St John's wort (Hypericum perforatum L.): a review of its chemistry, pharmacology and clinical properties, J. Pharm. Pharmacol. 53 (2001) 583–600.
[24] K. Mandery, K. Bujok, I. Schmidt, M. Keiser, W. Siegmund, B. Balk, J. König, M.F. Fromm, H. Glaeser, Influence of the flavonoids apigenin kaempferol, and quercetin on the function of organic anion transporting polypeptides 1A2 and 2B1, Biochem. Pharmacol. 80 (2010) 1746–1753.
[25] S. Handayani, A. Hermawan, E. Meiyanto, Z. Udin, Induction of apoptosis on MCF-7 cells by Selaginella fractions, J. Appl. Pharm. Sci. 3 (2013) 31–34.
[26] Y.J. Seo, B.S. Kim, S.Y. Chun, Y.K. Park, K.S. Kang, T.G. Kwon, Apoptotic effects of genistein: biochanin-A and apigenin on LNCaP and PC-3 cells by p21 through transcriptional inhibition of polo-like kinase-1, J. Korean Med. Sci. 26 (2011) 1489–1494.
[27] Y. Luo, B.-Z. Li, D. Liu, L. Zhang, Y. Chen, B. Jia, B.-X. Zeng, H. Zhao, Y.-J. Yuan, Engineered biosynthesis of natural products in heterologous hosts, Chem. Soc. Rev. 44 (2015) 5265–5290.
[28] M.S. Siddiqui, K. Thodey, I. Trenchard, C.D. Smolke, Advancing secondary metabolite biosynthesis in yeast with synthetic biology tools, FEMS Yeast Res. 12 (2012) 144–170.
[29] R.B. Gurung, E.-H. Kim, T.-J. Oh, J.K. Sohng, Enzymatic synthesis of apigenin glucosides by glucosyltransferase (YjiC) from Bacillus licheniformis DSM 13, Mol. Cells 36 (2013) 355–361.
[30] J.A. Seijas, M.P. Vázquez-Tato, R. Carballido-Reboredo, Solvent-free synthesis of functionalized flavones under microwave irradiation, J. Org. Chem. 70 (2005) 2855–2858.
[31] A.K. Verma, R. Pratap, Chemistry of biologically important flavones, Tetrahedron 68 (2012) 8523–8538.
[32] S.K. Chauthe, R.J. Sharma, F. Aqil, R.C. Gupta, I.P. Singh, Quantitative NMR: an applicable method for quantitative analysis of medicinal plant extracts and herbal products, Phytochem. Anal. 23 (2012) 689–696.
[33] S.-H. Chai, J.Y. Howe, X. Wang, M. Kidder, V. Schwartz, M.L. Golden, S.H. Overbury, S. Dai, D.-e. Jiang, Graphitic mesoporous carbon as a support of promoted Rh catalysts for hydrogenation of carbon monoxide to ethanol, Carbon 50 (2012) 1574–1582.
[34] R.S. Keri, S. Budagumpi, R.K. Pai, R.G. Balakrishna, Chromones as a privileged scaffold in drug discovery: a review, Eur. J. Med. Chem. 78 (2014) 340–374.
[35] Y. Liu, X. Song, J. He, X. Zheng, H. Wu, Synthetic derivatives of chrysin and their biological activities, Med. Chem. Res. 23 (2014) 555–563.
[36] S. Bhagwat, D.B. Haytowitz, J.M. Holden, USDA Database for the Flavonoid Content of Selected Foods Release 3.1., US Department of Agriculture, Beltsville, 2011, pp. 01–03.
[37] K.H. Miean, S. Mohamed, Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) content of edible tropical plants, J. Agric. Food Chem. 49 (2001) 3106–3112.
[38] R. Mustafa, A.A. Hamid, S. Mohamed, F.A. Bakar, Total phenolic compounds, flavonoids, and radical scavenging activity of 21 selected tropical plants, J. Food Sci. 75 (2010), http://dx.doi.org/10.1111/j.1750-3841.2009.01401.x.
[39] T. Iwashina, The structure and distribution of the flavonoids in plants, J. Plant Res. 113 (2000) 287–299.
[40] J.M.M. Salmani, X.-P. Zhang, J.A. Jacob, B.-A. Chen, Apigenin's anticancer properties and molecular mechanisms of action: recent advances and future prospectives, Chin. J. Nat. Med. 15 (2017) 321–329.
[41] Y. Xia, Y. Li, X. Shen, M. Mizu, T. Furuta, C. Li, Effect of dietary supplementation with sugar cane extract on meat quality and oxidative stability in finishing pigs, Anim. Nutr. 3 (2017) 295–299.
[42] Y. Han, T. Zhang, J. Su, Y. Zhao, Wang Chenchen, X. Li, Apigenin attenuates oxidative stress and neuronal apoptosis in early brain injury following subarachnoid hemorrhage, J. Clin. Neurosci. 40 (2017) 157–162.
[43] Q. Ruan, J. Ruan, W. Zhang, F. Qian, Z. Yu, Targeting NAD+ degradation: The therapeutic potential of flavonoids for Alzheimer's disease and cognitive frailty, Pharmacol. Res. (2017), http://dx.doi.org/10.1016/j.phrs.2017.08.010.
[44] W.J. Cahill, J.H. Calvert, J.H. Zhang, Mechanisms of early brain injury after subarachnoid hemorrhage, J. Cereb. Blood Flow Metab. 26 (2006) 1341–1353.
[45] D. Harraan, Aging: a theory based on free radical and radiation chemistry, J. Gerontol. 11 (1956) 298–300.
[46] B. Obermeier, R. Daneman, R.M. Ransohoff, Development: maintenance and disruption of the blood-brain barrier, Nat. Med. 19 (2013) 1584–1596.
[47] R. Franco, E. Martínez-Pinilla, Chemical rules on the assessment of antioxidant potential in food and food additives aimed at reducing oxidative stress and neurodegeneration, Food Chem. 235 (2017) 318–323.
[48] S. Cunnane, S. Nugent, M. Roy, A. Courchesne-Loyer, E. Croteau, S. Tremblay, A. Castellano, F. Pifferi, C. Bocti, N. Paquet, Brain fuel metabolism aging, and Alzheimer's disease, Nutrition 27 (2011) 3–20.
[49] H.-T. Roh, S.-Y. Cho, W.-Y. So, Obesity promotes oxidative stress and exacerbates blood-brain barrier disruption after high-intensity exercise, J. Sport Health Sci. 6 (2017) 225–230.
[50] B.V. Zlokovic, The blood-brain barrier in health and chronic neurodegenerative disorders, Neuron 57 (2008) 178–201.
[51] D.A. Butterfield, J. Drake, C. Pocernich, A. Castegna, Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid β-peptide, Trends Mol. Med. 7 (2001) 548–554.
[52] A. Nunomura, G. Perry, G. Aliev, K. Hirai, A. Takeda, E.K. Balraj, P.K. Jones, H. Ghanbari, T. Wataya, S. Shimohama, Oxidative damage is the earliest event in Alzheimer disease, J. Neuropathol. Exp. Neurol. 60 (2001) 759–767.
[53] A. Ayala, M.F. Muñoz, S. Argüelles, Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal, Oxid. Med. Cell. Longev. 2014 (2014) 360438.
[54] L. Chen, W. Xie, W. Xie, W. Zhuang, C. Jiang, N. Liu, Apigenin attenuates isoflurane-induced cognitive dysfunction via epigenetic regulation and neuroinflammation in aged rats, Arch. Gerontol. Geriatr. 73 (2017) 29–36.
[55] Y. Zhong, C. Jin, J. Gan, X. Wang, Z. Shi, X. Xia, X. Peng, Apigenin attenuates patulin-induced apoptosis in HEK293 cells by modulating ROS-mediated mitochondrial dysfunction and caspase signal pathway, Toxicon 137 (2017) 106–113.
[56] J.S. Choi, M. Nurul Islam, M. Yousof Ali, E.J. Kim, Y.M. Kim, H.A. Jung, Effects of C-glycosylation on anti-diabetic: anti-Alzheimer's disease and anti-inflammatory potential of apigenin, Food Chem. Toxicol. 64 (2014) 27–33.
[57] D.R. Telange, A.T. Patil, A.M. Pethe, H. Fegade, S. Anand, V.S. Dave, Formulation and characterization of an apigenin-phospholipid phytosome (APLC) for improved solubility in vivo bioavailability, and antioxidant potential, Eur. J. Pharm. Sci. 108 (2017) 36–49.
[58] R. Liu, T. Zhang, H. Yang, X. Lan, J. Ying, G. Du, The flavonoid apigenin protects brain neurovascular coupling against amyloid-β25-35-induced toxicity in mice, J. Alzheimer's Dis. 24 (2011) 85–100.
[59] M. Venigalla, E. Gyengesi, G. Münch, Curcumin and apigenin –novel and promising therapeutics against chronic neuroinflammation in Alzheimer's disease, Neural Regener. Res. 10 (2015) 1181–1185.
[60] L. Zhao, J.-L. Wang, R. Liu, X.-X. Li, J.-F. Li, L. Zhang, Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an alzheimer's disease mouse model, Molecules 18 (2013) 9949.
[61] A.T. Smolinski, J.J. Pestka, Modulation of lipopolysaccharide-induced proinflammatory cytokine production in vitro and in vivo by the herbal constituents apigenin (chamomile), ginsenoside Rb 1 (ginseng) and parthenolide (feverfew), Food Chem. Toxicol. 41 (2003) 1381–1390.

[62] F. Zhang, F. Li, G. Chen, Neuroprotective effect of apigenin in rats after contusive spinal cord injury, Neurol. Sci. 35 (2014) 583–588.
[63] S. Kapur, P. Roy, J. Daskalakis, G. Remington, R. Zipursky, Increased dopamine D2 receptor occupancy and elevated prolactin level associated with addition of haloperidol to clozapine, Am. J. Psychiatry 158 (2001) 311–314.
[64] J.D. Salamone, M. Correa, S. Yohn, L. Lopez Cruz, N. San Miguel, L. Alatorre, The pharmacology of effort-related choice behavior: dopamine depression, and individual differences, Behav. Process. 127 (2016) 3–17.
[65] T. Nakazawa, T. Yasuda, J. Ueda, K. Ohsawa, Antidepressant-like effects of apigenin and 2 4, 5-trimethoxycinnamic acid from Perilla frutescens in the forced swimming test, Biol. Pharm. Bull. 26 (2003) 474–480.
[66] M.B. Youdim, D. Edmondson, K.F. Tipton, The therapeutic potential of monoamine oxidase inhibitors, Nat. Rev. Neurosci. 7 (2006) 295.
[67] X.H. Han, S.S. Hong, J.S. Hwang, M.K. Lee, B.Y. Hwang, J.S. Ro, Monoamine oxidase inhibitory components from *Cayratia japonica*, Arch. Pharmacol. Res. 30 (2007) 13.
[68] N. Chaurasiya, M. Ibrahim, I. Muhammad, L. Walker, B. Tekwani, Monoamine oxidase inhibitory constituents of propolis: kinetics and mechanism of inhibition of recombinant human MAO-A and MAO-B, Molecules 19 (2014) 18936.
[69] L.-T. Yi, J.-M. Li, Y.-C. Li, Y. Pan, Q. Xu, L.-D. Kong, Antidepressant-like behavioral and neurochemical effects of the citrus-associated chemical apigenin, Life Sci. 82 (2008) 741–751.
[70] Z. You, C. Luo, W. Zhang, Y. Chen, J. He, Q. Zhao, R. Zuo, Y. Wu, Pro-and anti-inflammatory cytokines expression in rat's brain and spleen exposed to chronic mild stress: involvement in depression, Behav. Brain Res. 225 (2011) 135–141.
[71] M. Bilici, H. Efe, M.A. Köroğlu, H.A. Uydu, M. Bekaroğlu, O. Değer, Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments, J. Affect. Disord. 64 (2001) 43–51.
[72] R. Li, X. Wang, T. Qin, R. Qu, S. Ma, Apigenin ameliorates chronic mild stress-induced depressive behavior by inhibiting interleukin-1β production and NLRP3 inflammasome activation in the rat brain, Behav. Brain Res. 296 (2016) 318–325.
[73] L. Weng, X. Guo, Y. Li, X. Yang, Y. Han, Apigenin reverses depression-like behavior induced by chronic corticosterone treatment in mice, Eur. J. Pharmacol. 774 (2016) 50–54.
[74] H. Cui, Y. Kong, H. Zhang, Oxidative stress, mitochondrial dysfunction, and aging, J. Signal Transduct. (2012) 2011.
[75] J. Langston, L. Forno, J. Tetrud, A. Reeves, J. Kaplan, D. Karluk, Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine exposure, Ann. Neurol. 46 (1999) 598–605.
[76] S. Przedborski, M. Vila, The 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine mouse model, Ann. N. Y. Acad. Sci. 991 (2003) 189–198.
[77] K.-S. Lee, J.-K. Lee, H.-G. Kim, H.R. Kim, Differential effects of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine on motor behavior and dopamine levels at brain regions in three different mouse strains, Korean J. Physiol. Pharmacol. 17 (2013) 89–97.
[78] S. Guhathakurta, E. Bok, B.A. Evangelista, Y.-S. Kim, Deregulation of α-synuclein in Parkinson's disease: insight from epigenetic structure and transcriptional regulation of SNCA, Prog. Neurobiol. 154 (2017) 21–36.
[79] A.-S. Rolland, T. Kareva, N. Kholodilov, R.E. Burke, A quantitative evaluation of a 2 5-kb rat tyrosine hydroxylase promoter to target expression in ventral mesencephalic dopamine neurons in vivo, Neuroscience 346 (2017) 126–134.
[80] M. Naoi, W. Maruyama, Monoamine oxidase inhibitors as neuroprotective agents in age-dependent neurodegenerative disorders, Curr. Pharm. Des. 16 (2010) 2799–2817.
[81] S.P. Patil, P.D. Jain, J.S. Sancheti, P.J. Ghumatkar, R. Tambe, S. Sathaye, Neuroprotective and neurotrophic effects of Apigenin and Luteolin in MPTP induced parkinsonism in mice, Neuropharmacology 86 (2014) 192–202.
[82] H. Siddique, S. Jyoti, Alteration in biochemical parameters in the brain of transgenic *Drosophila melanogaster* model of Parkinson's disease exposed to apigenin, Integr. Med. Res. 6 (2017) 245–253.
[83] C. Anusha, T. Sumathi, L.D. Joseph, Protective role of apigenin on rotenone induced rat model of Parkinson's disease: suppression of neuroinflammation and oxidative stress mediated apoptosis, Chem. Biol. Interact. 269 (2017) 67–79.
[84] C.J. Phiel, C.A. Wilson, V.M. Lee, P.S. Klein, GSK-3alpha regulates production of Alzheimer's disease amyloid-beta peptides, Nature 423 (2003) 435.
[85] R. Holsinger, C.A. McLean, K. Beyreuther, C.L. Masters, G. Evin, Increased expression of the amyloid precursor β-secretase in Alzheimer's disease, Ann. Neurol. 51 (2002) 783–786.
[86] S.K. Ha, P. Lee, J.A. Park, H.R. Oh, S.Y. Lee, J.-H. Park, E.H. Lee, J.H. Ryu, K.R. Lee, S.Y. Kim, Apigenin inhibits the production of NO and PGE 2 in microglia and inhibits neuronal cell death in a middle cerebral artery occlusion-induced focal ischemia mice model, Neurochem. Int. 52 (2008) 878–886.
[87] H. Liang, S. Sonego, E. Gyengesi, A. Rangel, G. Niedermayer, T. Karl, G. Münch, Anti-Inflammatory and neuroprotective effect of apigenin: studies in the GFAP-IL6 mouse model of chronic neuroinflammation, Free Radic. Biol. Med. 108 (2017) S4–S13.
[88] M. Popović, M. Caballero-Bleda, O. Benavente-García, J. Castillo, The flavonoid apigenin delays forgetting of passive avoidance conditioning in rats, J. Psychopharmacol. 28 (2014) 498–501.
[89] C. Meng, Z. He, D. Xing, Low-level laser therapy rescues dendrite atrophy via upregulating BDNF expression: implications for Alzheimer's disease, J. Neurosci. 33 (2013) 13505–13517.
[90] S. Moghbelinejad, M. Nassiri-Asl, T.N. Farivar, E. Abbasi, M. Sheikhi, M. Taghiloo, F. Farsad, A. Samimi, F. Hajiali, Rutin activates the MAPK pathway and BDNF gene expression on beta-amyloid induced neurotoxicity in rats, Toxicol. Lett. 224 (2014) 108–113.
[91] L. Zhao, J.-L. Wang, R. Liu, X.-X. Li, J.-F. Li, L. Zhang, Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an Alzheimer's disease mouse model, Molecules 18 (2013) 9949–9965.
[92] D. Sheeja Malar, K. Pandima Devi, Dietary polyphenols for treatment of Alzheimer's disease–future research and development, Curr. Pharm. Biotechnol. 15 (2014) 330–342.
[93] T. Guzik, R. Korbut, T. Adamek-Guzik, Nitric oxide and superoxide in inflammation, J. Physiol. Pharmacol. 54 (2003) 469–487.
[94] R.B. Goodman, J. Pugin, J.S. Lee, M.A. Matthay, Cytokine-mediated inflammation in acute lung injury, Cytokine Growth Factor Rev. 14 (2003) 523–535.
[95] S.S. Kang, J.Y. Lee, Y.K. Choi, G.S. Kim, B.H. Han, Neuroprotective effects of flavones on hydrogen peroxide-induced apoptosis in SH-SY5Y neuroblostoma cells, Bioorg. Med. Chem. Lett. 14 (2004) 2261–2264.
[96] M.A. Busche, G. Eichhoff, H. Adelsberger, D. Abramowski, K.-H. Wiederhold, C. Haass, M. Staufenbiel, A. Konnerth, O. Garaschuk, Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease, Science 321 (2008) 1686–1689.
[97] J.J. Palop, L. Mucke, Amyloid-[beta]-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks, Nat. Neurosci. 13 (2010) 812–818.
[98] M.A. Smith, P.L.R. Harris, L.M. Sayre, J.S. Beckman, G. Perry, Widespread peroxynitrite-mediated damage in Alzheimer's disease, J. Neurosci. 17 (1997) 2653–2657.
[99] F.A. Sehba, J. Hou, R.M. Pluta, J.H. Zhang, The importance of early brain injury after subarachnoid hemorrhage, Prog. Neurobiol. 97 (2012) 14–37.
[100] Y. Hasegawa, H. Suzuki, T. Sozen, O. Altay, J.H. Zhang, Apoptotic mechanisms for neuronal cells in early brain injury after subarachnoid hemorrhage, in: Early Brain Injury or Cerebral Vasospasm, Springer, 2011, pp. 43–48.
[101] M. Méndez-Armenta, C. Nava-Ruíz, D. Juárez-Rebollar, E. Rodríguez-Martínez, P. Yescas Gómez, Oxidative stress associated with neuronal apoptosis in experimental models of epilepsy, Oxid. Med. Cell. Longev. 2014 (2014).
[102] R.P. Ostrowski, A. Colohan, J.H. Zhang, Molecular mechanisms for early brain injury after subarachnoid hemorrhage, in: Handbook of Neurochemistry and Molecular Neurobiology, Springer, 2007, pp. 235–253.
[103] S.F. Nabavi, N. Braidy, S. Habtemariam, I.E. Orhan, M. Daglia, A. Manayi, O. Gortzi, S.M. Nabavi, Neuroprotective effects of chrysin: from chemistry to medicine, Neurochem. Int. 90 (2015) 224–231.
[104] S. Fazel Nabavi, N. Braidy, S. Habtemariam, A. Sureda, A. Manayi, S. Mohammad Nabavi, Neuroprotective effects of fisetin in Alzheimer's and parkinson's diseases: from chemistry to medicine, Curr. Top. Med. Chem. 16 (2016) 1910–1915.
[105] S. Habtemariam, Rutin as a natural therapy for Alzheimer's disease: insights into its mechanisms of action, Curr. Med. Chem. 23 (2016) 860–873.
[106] H. Meyer, A. Bolarinwa, G. Wolfram, J. Linseisen, Bioavailability of apigenin from apiin-rich parsley in humans, Ann. Nutr. Metabol. 50 (2006) 167–172.
[107] T. Mencherini, A. Cau, G. Bianco, R.D. Loggia, R. Aquino, An extract of *Apium graveolens* var. dulce leaves: structure of the major constituent apiin, and its anti-inflammatory properties, J. Pharm. Pharmacol. 59 (2007) 891–897.
[108] V. Svehlıkova, R.N. Bennett, F.A. Mellon, P.W. Needs, S. Piacente, P.A. Kroon, Y. Bao, Isolation: identification and stability of acylated derivatives of apigenin 7-O-glucoside from chamomile (*Chamomilla recutita* [L.] Rauschert), Phytochemistry 65 (2004) 2323–2332.
[109] O.K. Kosakowska, K. Bączek, J.L. Przybył, M. Ejdys, P. Kuźma, M. Obiedziński, Z. Węglarz, Intraspecific variability in the content of phenolic compounds: essential oil and mucilage of small-leaved lime (*Tilia cordata* Mil.) from Poland, Ind. Crops Prod. 78 (2015) 58–65.
[110] M. He, J.-W. Min, W.-L. Kong, X.-H. He, J.-X. Li, B.-W. Peng, A review on the pharmacological effects of vitexin and isovitexin, Fitoterapia 115 (2016) 74–85.
[111] S.-N. Lou, Y.-C. Lai, Y.-S. Hsu, C.-T. Ho, Phenolic content: antioxidant activity and effective compounds of kumquat extracted by different solvents, Food Chem. 197 (2016) 1–6.
[112] R. Colombo, J.H. Yariwake, E.F. Queiroz, K. Ndjoko, K. Hostettmann, On-line identification of further flavone C-and O-glycosides from sugarcane (*Saccharum officinarum* L., Gramineae) by HPLC-UV-MS, Phytochem. Anal. 17 (2006) 337–343.
[113] I. Blasko, M. Stampfer-Kountchev, P. Robatscher, R. Veerhuis, P. Eikelenboom, B. Grubeck-Loebenstein, How chronic inflammation can affect the brain and support the development of Alzheimer's disease in old age: the role of microglia and astrocytes, Aging Cell 3 (2004) 169–176.