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Central nervous system diseases and *Scutellaria*: a review of current mechanism studies

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ABSTRACT

Scutellaria comprises many species traditionally used for cognitive and neurological conditions. *In vitro* and *in vivo* studies have supported the value of bioactive compounds of the genus *Scutellaria* for CNS disorders such as Alzheimer, cerebral ischemia, depression and anxiety. In particular, the effects of plants belonging to the genus *Scutellaria* and their components are detailed on cognitive ability such as memory, attention and learning. In this review, the pharmacology of CNS effect and the related molecular mechanisms of the plants belonging to the genus *Scutellaria* and active constituents have been discussed.

1. Introduction

Scutellaria commonly known as skullcaps is a member of the Labiatae family which is an important perennial and annual herbs includes about 360–400 species [1,2]. The genus has widespread distribution in tropical mountains of North America, Europe and Asia and is found in Siberia to the tropics of South America [3]. *Scutellaria* been traditionally used in medicine as anti-allergic, anti-hepatitis, anti-inflammatory, antithrombotic, anti-bacterial, hepato-protective, anti-mutagenic and antioxidant [4,5].

Most plants of *Scutellaria* are annual or perennial herbs with 5 cm to 1 m height, but some are aquatic and a few are subshrubs. They have opposite leaves and four-angled stems. The flowers of this genus have upper and lower lips [6]. Up to now 300 compounds have been isolated from different species of the genus *Scutellaria*. Two main groups of component including terpenes (triterpenes, diterpenes and iridoid glycosides) and phenolic compounds (flavonoids and phenylethanoid glycosides) isolated from skullcaps. Alkaloids, phytosterols and polysaccharides are among other compounds presented in the genus *Scutellaria* [7–10]. Baicalin, baicalein and wogonin are flavonoids possess anti-HIV, anti-inflammatory, free radical scavenging, lipid peroxidation, antioxidant and anticancer activities [11–19]. Diterpenes such as scutalbin A, jodrellin A and jodrellin B, have anti-feedant effects.

In this review, neuro-psychologic activity of the plants belonging to the genus *Scutellaria* and active constituents, the related mechanism are summarized. In detail we have discussed the effect on cognitive ability such as memory, attention and learning. The potential effect of *Scutellaria* in dementia, including Alzheimer's disease is also reviewed. Finally, future researches are needed to increase our understanding of the potential health benefits of *Scutellaria* plants.

2. Main constituents in *Scutellaria* species

From the genus *Scutellaria*, 300 compounds including flavonoids, diterpenes, triterpenoids, phenylethanoid glycosides, iridoid glycosides, alkaloids, polysaccharides and phytosterols were isolated. *Scutellaria* plants are rich source of flavonoid and over 160 flavonoids have been identified from different species of the genus *Scutellaria*. Flavonoids include flavones and flavanonols, flavanones and flavonols, chalcones, flavonolignans and biflavonoids. The main flavonoids isolated from

Abbreviation: MMP-2 and MMP-9, matrix metalloproteinases; VEGF, vascular endothelial growth factor; NF-κB, nuclear factor-kappa B; HO-1, heme oxygenase-1; Nrf2, nuclear factor erythroid 2-related factor; INOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; P-ERK, phospho extracellular signal–regulated kinases; P-JNK, phospho c-Jun N-terminal kinase; NO, nitric oxide; PGE2, prostaglandin E2; IL-6, interleukin 6; IL-8, interleukin 8; HMC-1, human mast cell line; IL-1β, interleukin-1β; IL-2, interleukin-2; IL-12, interleukin 12; TNF-α, tumor necrosis factor-alpha; MAPK, mitogen activated protein kinases; BHT, butylated hydroxytoluene; GI, gingival index; BDNF, brain-derived neurotrophic factor; PDE, phosphodiesterases; PCREB, phosphorylation of cyclic AMP response element binding; VaD, ventricular assist device; MAO A and B, L-Monoamine oxidases; NMDA, N-methyl-D-Aspartate receptor; BDS, benzodiazepine binding site; AAPH, 2,2′ Azobis (2-Amidinopropane) hydrochloride; ChAT, choline acetyltransferase; GABA, γ-aminobutyric acid; NSAIDs, non-steroidal anti-inflammatory drugs; MCAO, middle cerebral artery occlusion; AD, Alzheimer's disease; BCCAo, bilateral common carotid artery occlusion; LPS, lipopolysaccharide; T-PA, tissue-plasminogen activator; PGs, prostaglandins; NSAIDs, non-steroidal anti-inflammatory drugs; MS, multiple sclerosis

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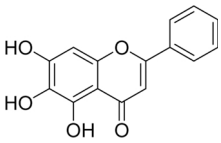
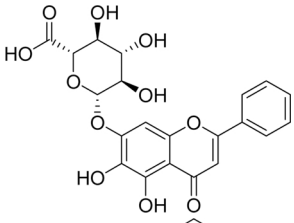
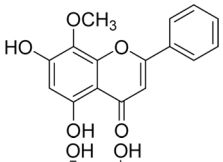
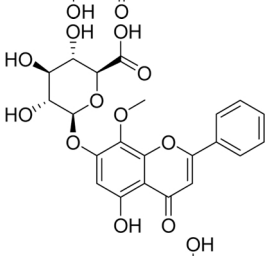
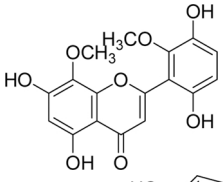
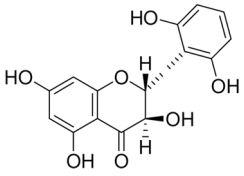
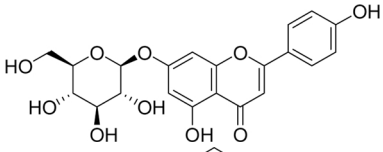
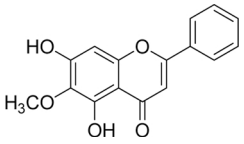
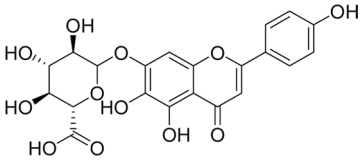
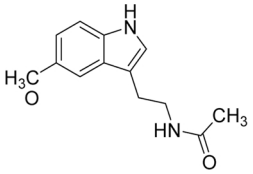
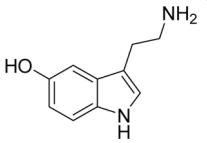
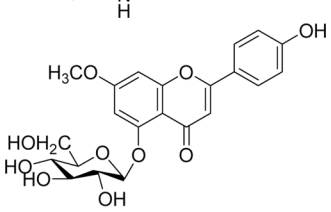
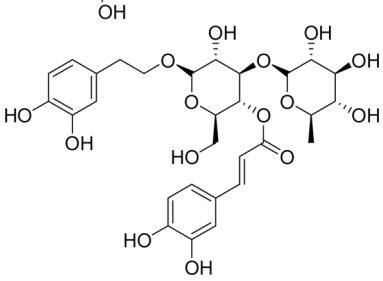
Table 1
Structure of main constituents from the genus *Scutellaria.*

Species	Active component	structure	Ref
S. baicalensis *S. litwindowii*	Baicalein		[14,55,57,68,73,89,92,99,106,108]
S. baicalensis *S. litwindowii*	Baicalin		
S. baicalensis *S. litwindowii*	Wogonin		
S. baicalensis *S. litwindowii*	Wogonoside		
S. baicalensis	5,7,2, 5 -tetrahydroxy-8,6 -dimethoxyflavone		[84]
S. baicalensis	2(*R*), 3(*R*)-2′,3,5,6′,7-pentahydroxyflavanone		
S. baicalensis	Apigetrin		[112]
S. baicalensis	Oroxylin A		
S. baicalensis *S. racemosa* *S. lateriflora*	Scutellarin		[108]

(*continued on next page*)

Table 1 (*continued*)

Species	Active component	structure	Ref
S. baicalensis *S. racemosa* *S. lateriflora*	Melatonin		[93]
S. baicalensis *S. racemosa* *S. lateriflora*	Serotonin		
S. baicalensis	Wogonin 7-O-b-D-ethylglucuronide		[76]
S. altissima	Verbascoside		[67]

Scutellaria are baicalin, baicalein, and wogonin (Tables 1). Moreover, *Scutellaria* is rich source of neoclerodane diterpenoids such as jodrellin A, jodrellin B, scutalbin A and scutecyprol B. Despite the presence of flavonoids and terpenoids of different structure in *Scutellaria* species there are only eleven alkaloids isolated from *Scutellaria* [6].

Lee et al. reported wogonin through inhibiting microglial activation exerts anti-inflammatory activity and protect against neurodegenerative diseases [20]. Another study found that scutellarin has been used to treat different diseases such as sleep disorders, migraines, depression, decreasing the viscosity of blood and memory impairment [21–23].

3. *Scutellaria* and its pharmacodynamics influences on the brain

Cognitive activity can be influenced by a group of biochemical and neurological factors. Neural damage can induce cognitive impairment, and there is an increasing concern of the influence of different neurotransmitters and hormones on cognitive performance. Because of its rich array of chemical constituents, *Scutellaria* is a valuable plant which influences multiple physiological pathways and protect against beta amyloid (Aβ), peptide toxicity, cerebral ischemia, depression and anxiety (Fig. 1 and 2 , Tables 2–5

3.1. Scutellaria and amyloid-β

The accumulation of the Aβ and defect in neural functions is a characteristic of Alzheimer's disease (AD). Aβ has been renowned for inducing memory loss and to cause specific learning and memory impairment in AD patients [24]. AD patients show behavior abnormality in learning and memory that is related to the defects on a cellular layer [25,26]. The major reason of these abnormal behaviors in AD patients is defects of cholinergic system in the hippocampal and the cortical areas [27] (Fig. 2).

Scutellaria baicalensis extracts improved spatial memory functions and rescued neuronal cells immunoreactive to choline acetyltransferase (a marker for cholinergic neurons) and the NMDA receptor subunit, NR2Ain the hippocampus of Ibo model. *Scutellaria baicalensis* extract facilitate the generation of the cholinergic marker, ChAT and inhibited cell death. Generally, *S. baicalensis* extract has significant neuroprotective activity on the Ibo model [28].

Hwang et al. showed treatments with *S. baicalensis* reduced the spatial memory impairments that were produced by chronic bilateral carotid artery occlusion (BCCAo) and in the hippocampus of chronic BCCAo normalized MAPKs (mitogen-activated protein kinase) signaling. *S. baicalensis* also attenuated activated spatial memory impairments and inflammatory responses induced by chronic lipopolysaccharide (LPS) infusions [29]. In another study, flavonoids isolated from *S. baicalensis* stem-leaf showed inhibitory effects on tau phosphorylation in ischemia-induced VaD (vascular dementia) rat model. These flavonoids were shown to decreased oxidative stress, counteract neuronal death, and improve learning and memory. The protective effects of flavonoids in disease most probably related to regulating kinases-triggered phosphorylation and PP2A-catalyzed dephosphorylation [30]. Taken together, *S. baicalensis* could be candidate for the prevention of vascular dementia and Alzheimer's disease.

3.2. Scutellaria and cerebral ischemia

The third most common cause of death and adult disability is stroke or cerebral ischemia that results in subsequent loss of neuronal function and irreversible brain damage [31]. A promising approach to treatment of acute stroke is neuroprotection. Effective neuroprotection may need the inhibition of pathological actions activated by ischemia [32]. Despite several studies exist to develop neuroprotective treatment for brain injury; the present way for acute stroke therapy is accomplished *via* the administration of the thrombolytic agent and tissue-plasminogen activator (t-PA) [33].

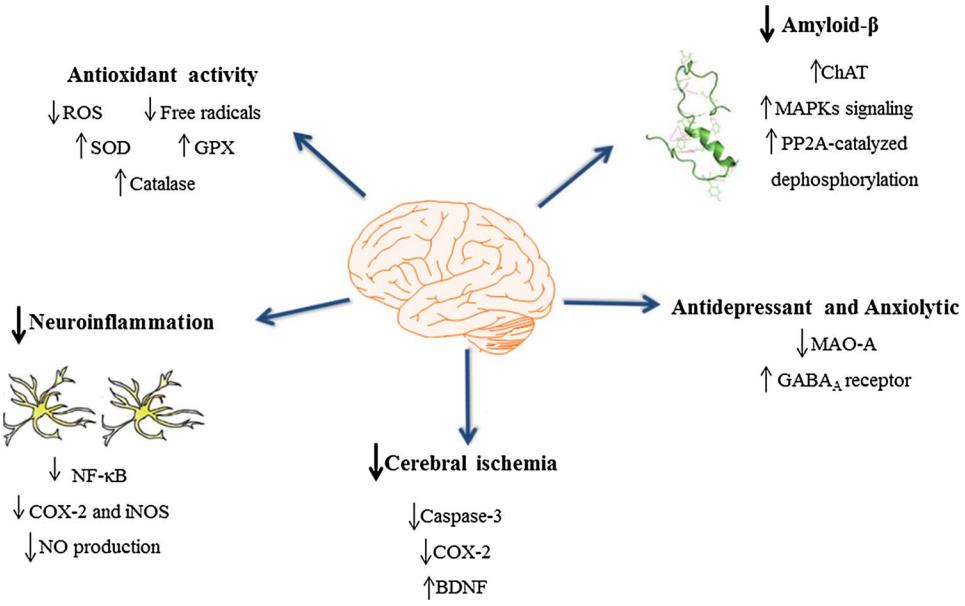


Fig. 1. Pharmacodynamic Influences of Scutellaria on the Brain.

In an *in vitro* model of ischemia, *S. litwinowii* Extract on deacreased the ROS level in serum/glucose-deprived cultured PC12 cell [34]. Piao et al. showed wogonin isolated from *S. baicalensis* radix significantly decreased the cerebral hypoxic/ischemic injury in a rat focal ischemic model. Wogonin notably inhibited inflammatory activation of microglial cells (proinflammatory cytokines and generation of NO) and decreased the infarct volume *via* suppression of activated microglial cells. In summary, this study may suggest that wogonin during cerebral ischemic insults is a candidate for attenuate inflammatory responses [35].

In a study conducted by Cao et al., baicalin (a main flavonoid extracted from the roots of *S. baicalensis* Georgi) has neuroprotective effects against cerebral ischemic injury in rats [36]. Baicalin could inhibit global ischemic reperfusion injury through decreasing oxidative stress, up-regulating BDNF expression and reducing the caspase-3 activity. Neuroprotective effect of baicalin in global cerebral ischemia in gerbils has been consistent with its anti-oxidative and anti-apoptotic activities. In another research, baicalin had significant neuroprotective activity against global cerebral ischemia injury. It reduced apoptosis of hippocamp alpyramidal cells and prevented cognitive dysfunction in rats after ischemic insult. The anti-inflammatory activity and inhibition of COX-2 expression following global ischemia is the mechanism of neuroprotective activity of baicalin [37].

It also reported, flavonoids from *S. baicalensis* have a significant protective effect on ischemia reperfusion and cerebral ischemia induced brain injury. In middle cerebral artery occlusion (MCAO) procedure, infarction areas were decreased, the neurological impairment was improved, the water content in brain was reduced and flavonoids protect brain tissues from cerebral ischemia and reperfusion injury. A basic and important mechanism of the protective effect of *Scutellaria* flavonoids related to its anti-free radical properties [38,101,102]. *Scutellaria baicalensis* showed neuroprotective effect through inhibition of caspase-3 activity [104]. Also, *S. baicalensis* in C17.2 cell reduced damage in the cortex and exerts neuroprotective effects by modulating oxidative stress

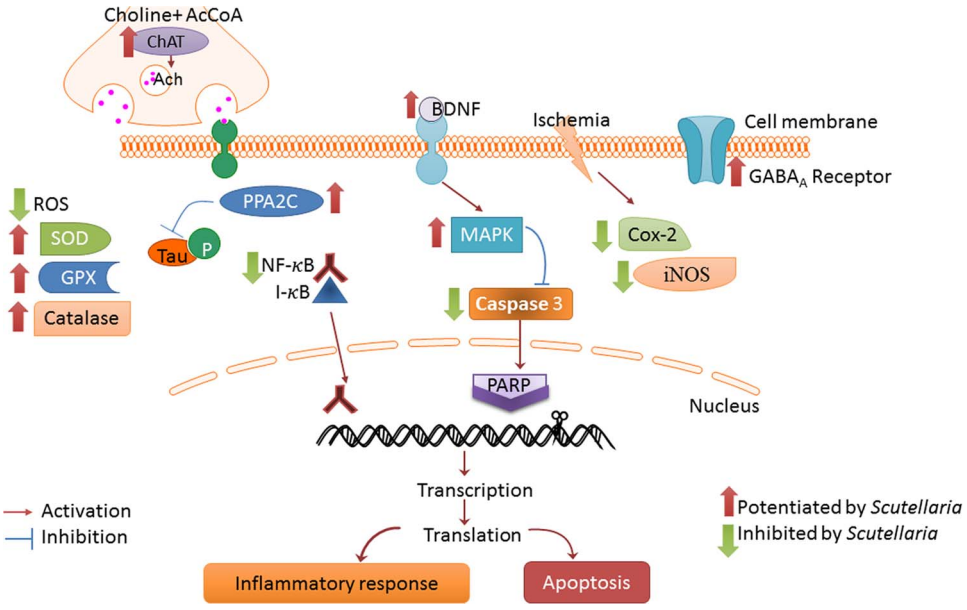


Fig. 2. Pathway: Molecular mechanism of *Scutellaria* in the neural cells.

Table 2
Neuroprotective effect of the genus *Scutellaria*.

Species	Extract/Active component	Subject/ assay	Dose	Mechanism	Ref.
S. baicalensis	Xiao-Xu-Ming decoction (XXMD)	Human Ischemic neuronal injury	Maximal neuroprotective effect 77.0%	Inhibition of caspase-3 activity and up-regulation of Bcl-2 expression	[104]
S. baicalensis	HT008-1, a prescription of traditional korean medicine	Animal study Transient focal cerebral ischemia model in rats	300 mg/kg	Anti-inflammatory mechanism and reducing damage in the cortex and caudoputamen	[105]
S. baicalensis	Wogonin	Animal study Focal cerebral ischemia rat model	50 mg/kg	By inactivating NF-κB signaling pathway	[35]
S. baicalensis	Baicalin	Animal study Gerbils subjected to transient global cerebral ischemic–reperfusion injury	200 mg/kg	By minimizing oxidative stress, up-regulating BDNF expression and decreasing the caspase 3 activity	[36]
S. baicalensis	Ethyl acetate extract	*In vivo* Cerebral ischemia injury	SOD (NU/g): 1486	Anti-free radical appears to be a basic and important mechanism of the protective effect	[38]
S. baicalensis	Water extract	Animal study Rescue of memory impairments in male Wister rats	100 mg/kg	By chronic cerebral infusion and microglial activation by chronic LPS	[29]
S. baicalensis	Baicalein	Cell culture C17.2 neural progenitor cells	10 μM	By modulating oxidative stress and elevating BDNF-pCREB signaling	[106]
S. baicalensis	Stem-leaf total flavonoids (SSTFs) extract	Animal study Chronic cerebral ischemia-induced vascular dementia of rats	100 mg/kg of SSTF for 60 days	SSTF reduced the activity of glycogen synthase kinase 3β and cyclin-dependent kinase 5 in VaD rats	[30]
S. baicalensis	Scutelarin	*In vitro* aggregated β-amyloid	Not stated	Not stated	[107]
S. baicalensis	Ethanol extract	Animal study Neuronal cells in model rats	30 mg/kg	Not stated	[28]
S. baicalensis	Water extract (SSF)	Animal study Permanent global ischemia in rats	35 mg/kg, 19-20 days	SSF is beneficial for ameliorating cognitive deficit, protecting neuronal injury and reduced density of Nissl bodies in the neuron	[2]
S. baicalensis	Ethanol extract / baicalein, baicalin, wogonin, wogonoside, scutellarin, and Oroxylin A	Animal study Excitotoxic neuronal cell in rat	35.1 μg/mL	Interaction with the glycine binding site of the NMDA receptor	[108]
S. baicalensis	Ethanol extract	Animal study Spinal cord injury in rats	100 mg/kg	Inhibition of lipopolysaccharide-induced expression of inflammatory mediators as TNF-α, IL-1β, IL-6, COX-2, and i-NOS	[109]
S. baicalensis	Oroxylin A	Animal study Rat cerebral cortical membrane	IC_{50}:1.09 ± 0.07 μM	Inhibition of [3H]flunitrazepam binding to rat cerebral cortical membrane	[45]
S. baicalensis	Favonoids	*In vitro/In vivo* Ischemia or stroke-induced neuronal cell death	3–9 g of dried roots	Not stated	[110]
S. baicalensis	Baicalein	Animal study Nigrostriatal dopaminergic system of rat brain *in vivo*	30 mg/kg/day	Inhibition of α-synuclein aggregation, inflammasome activation and cathepsin B production	[57]
S. baicalensis	S/B remedy (water extract)	Animal study Nigrostriatal dopaminergic system of rat brain	20 mg/kg	Inhibitiion of iron-induced oxidative injury, -synuclein aggregation, Neuro-inflammation and apoptosis.	[60]
S. baicalensis and *S. indica*	Aqueous extract	Human Cyclic nucleotides in the brain	Not stated	Inhibition of PDE	[111]
S. lateriflora	Baicalin	Animal study Global ischemia/reperfusion rats	100 mg/kg	Reduction of hippocampal apoptosis *via* the inhibition of COX-2 expression	[37]
S. baicalensis	Apigetrin	Cell culture HT22 Hippocampal Cells/ hydrogen peroxide (H_2O_2)	100 μM/ 10 μM	Through the inter-regulation of neuroinflammation, oxidative stress, and neuronal injury	[112]

Table 3
Antidepressant and Anxiolytic effects of the genus *Scutellaria*.

Species	Extract/Active component	Subject/ assay	Dose	Mechanism	Ref.
S. baicalensis	Baicalin	Animal study Mice and Rats	25 mg/kg for 5 weeks	Inhibition of MAO A and B in rat brain	[40]
S. baicalensis	Wogonin	Animal study Rat dorsal root ganglion neurons	7.5 to 30 mg/kg	Positive allosteric modulation of the GABAA receptor complex *via* interaction at the BZD-S	[41]
S. baicalensis	Baicalin	Animal study Adult female Swiss mice	0.02, 0.2 pmol	Not stated	[43]
S. lateriflora	Baicalin baicalein amino acids GABA glutamine	Animal study cytochrome P450 3A4	> 84% inhibition (in 25% ethanol, 40% glycerin extract)	Binding to benzodiazepine site of the GABAA receptor.	[42,44]

and elevating BDNF-pCREB signaling both *in vitro* and *in vivo* [105–107]. In another study, ethanol extract of *S. baicalensis* by reduced the expression of inflammatory mediators as TNF-α, IL-1β, IL-6, COX-2, and i-NOS exhibited neuroprotective activity [108,109]. In addition, flavonoids extracted from *S. baicalensis* indicated protective activity through inter-regulation of neuroinflammation, oxidative stress, and neuronal injury [110–112].

3.3. Scutellaria and antidepressant and anxiolytic effects

Depression and chronic stress affects the cognitive activities. In fact, the major symptoms of depressive and anxiety disorders are cognitive deficits including impairments in memory, attention and learning [39]. The memory loss in Alzheimer's disease always accompanies with different comorbidities. It has been proved that most Alzheimer's disease affected patients suffer from major depressive disorder [40]. Interferences that have positive effects on depression and anxiety are so likely to have beneficial effects on cognitive activities. Baicalin, a flavone isolated from *S. baicalensis* has an antidepressant-like effect in behavioral models in mice and rats [40,78]. The antidepressant activity of baicalin may be related to inhibition of MAO-A (monoamine oxidase) and B in rat brain. Also there are some reports on anxiolytic effect wogonin from *S. baicalensis* and positive allosteric modulation of the $GABA_A$ receptor complex *via* interaction at the benzodiazepine site BZD-S [41]. Additionally, in rats, *S. lateriflora* has been shown to reduce the anxiety levels. The authors suggested baicalin and baicalein, as two neuroactive flavonoids interacting with $GABA_A$ receptor complex with anxiolytic activity [42–44].

Despite baicalin and baicalein, oroxylin A has been introduced as selective antagonist of the benzodiazepine binding site (BDS) in rat cerebral cortical membrane [45].

3.4. Scutellaria and anti-inflammatory effects

Inflammation is a response to injury, stress, infection and is an important part of the pathogenesis of immune-mediated disease. The acute inflammation is a self-terminating and rapid process and can be harmful to the host and lead to the chronic inflammation if it continues [46]. During the inflammatory response, macrophages generate various mediators including nitric oxide (NO), pro-inflammatory cytokines and prostaglandins (PGs) [47]. Lipopolysaccharide as initiators of inflammatory response modulates macrophage and induces fever, septic shock and microbial invasion [48]. However, inflammation in many neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and multiple sclerosis plays a key role [49].

The anti-inflammatory activity of the plant belongs to *Scutellaria* genus has been referenced in multiple studies. Flavonoids and phenolic acids present in the extract of *S. barbata* have been reported to show anti-inflammatory activity toward RAW 264.7 cells by inhibition of NF-??B (nuclear factor-kappa B) activity [50]. Moreover, *S. baicalensis* (water extract) has been shown to have anti-inflammatory activity *via* the inhibition of the NF-κB activation [51]. In one study butanol and water extract of *S. baicalensis* both have shown anti-inflammatory activity [52,53]. Hong et al., showed the flavonoids isolated from *S. baicalensis* Georgi have anti-inflammatory effects in RAW264.7 cells. *Scutellaria baicalensis* and the isolated flavonoids (baicalin, baicalensis, wogonin, and wogonoside) could regulate the expression of inflammatory mediators (COX-2 and iNOS) and inhibit the activation of NF-??B and MAPK (mitogen activated protein kinases) [54,86]. Among of the active flavonoids responsible for the anti-inflammatory activity Tsai et al., introduced baicalein from *S. baicalensis* as an active compound [55]. The rich polyhydroxyflavonoids extract of *S. baicalensis* which mainly contains baicalein, oroxylin A and wogonin had anti-inflammatory effects by inhibition of nitric oxide (NO) production. In respect to the inhibition of NO, wogonin was the superior compounds among all other flavonoids [56].

In one study, baicalein significantly decreased the toxicity of MPP +, a parkinsonian neurotoxin, in the nigrostriatal dopaminergic system of rat brain by inflammasome activation, cathepsin B production and the inhibition of α-synuclein aggregation [57]. The administration of UP446, standardized extracts from *S. baicalensis* and *Acacia catechu*, into beagle dogs and rats has been shown anti-inflammatory effect with no pharmaco-toxicological effect on the central nervous systems compared to the cyclooxygenase-2 (COX-2) inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) [58]. Also baicalin showed strong anti-inflammatory property in the treatment of multiple sclerosis (MS) [59]. Moreover, S/B remedy, a mixture from *S.baicalensis* Georgi and *Bupleurum scorzonerifolfium*, exhibited a potential therapeutic benefit for the CNS neurodegenerative diseases in rat brain [60]. In another study, baicalein indicated anti-inflammatory effects *via* inhibition of TNF- α, IL-8 and NF-κB [79–82]. Additionally, *S. baicalensis* exert strong anti-inflammatory activity in both *in vitro* and *in vivo* [83–88].

Wogonin one of plant flavones of the *Scutellariae* radix showed anti-inflammatory activity in different animal models of inflammation in rats. Wogonin was found to be one of the most potent suppressors of COX-2 and iNOS (inducible nitric oxide synthase) expression in the macrophages. Modulation in the expression of proinflammatory gene is one of the proposed mechanisms of anti-inflammation of wogonin [61]. In another study, wogonin was shown to suppress iNOS expression and exert anti-inflammatory activity [62].

4. *Scutellaria* and antioxidant effects

The production of free radicals and decreased antioxidant defenses creates a state of oxidative stress. Free radicals involving singlet oxygen ($_1O^2$), superoxide ion (O_2^-), hydroxyl ion (·OH), peroxyl radical (ROO ·) were very reactive and toxic molecules which cause oxidative damage to lipids, proteins, enzymes and DNA [63]. The reactive oxygen species play an imperative role in the pathogenesis of many human diseases such as Crohn's, cancer, liver injury, aging and a number of neurological disorders [64]. In order to decrease damage to the human body, antioxidants are often used to scavenge the free radicals or to

Table 4
Anti- inflammatory effects of the genus *Scutellaria*.

Species	Extract/Active component	Subject/ assay	Dose	Mechanism	Ref.
S. baicalensis	Baicalin	Animal study Animal model of multiple sclerosis (MS)	100 mg/kg/day	*Via* STAT/NFκB signaling pathways.	[79]
S. baicalensis	Wogonin	Animal study Carrageenan induced rat hind paw edema	IC_{50} (μM) 43.5	Not stated	[56]
S. agrestis	Aqueous extract	Animal study In mice	30, 100 and 300 mg/kg	Not stated	[80]
S. baicalensis	Baicalein	Animal study Lipopolysaccha ride-induced acute lung injury in rats	20 mg/kg	Inhibition of NF-κB mediated inflammatory responses and up regulation of Nrf2/HO-1 pathway	[55]
S. baicalensis	Water extract	Animal study Lung injury	125 mg/kg	Inhibition of NF-κB activation pathways	[51]
S. baicalensis	Baicalin	Animal study Levels of TNF-α and IL-6 for the model rat	0.104 ± 0.011 and 1.079 ± 0.013 resp.	Not stated	[81]
S. baicalensis	Water extract	Cell culture HMC-1 cells	IL-8 Secrition (μg/ml): 1200 at 10 μg/mL sb	Inhibition of both TNF- and IL-8 expression in HMC-1 cells	[82]
S. baicalensis	Radix water extract	Cell culture 264.7 cells	25, 50, 100, 200 μg/mL	Inhibition of NO, cytokine, chemokine, and growth factor production in macrophages	[53]
S. baicalensis	Butanol fraction	Animal study Mouse air-pouch model	300 μg/mL	Inhibition of iNOS, COX-2, PGE2, IL-1β, IL-2, IL-6, IL-12 and TNF-α expression	[52]
S. baicalensis	Wogonin	*In vivo* Inflammation associated genes	1000 μg/ear/3 days	Increase in COX-1 and fibronectin mRNA	[61]
S. baicalensis	Baicalein	Human Eotaxin production by IL-4 plus TNF-α-stimulated human fibroblasts	IC_{50}: 1.8 μg/mL.	Inhibition of human eotaxin mRNA expression in IL-4 plus TNF-α-stimulated human fibroblasts	[14]
S. baicalensis	Wogonin	Cell culture RAW 264.7 cells	IC_{50}: 0.3 μM	Inhibition of inducible nitric oxide synthase (iNOS) expression	[62]
S. baicalensis	Flavonoids	Cell culture RAW 264.7 Cells	No cytotoxicity at 100 μg/mL	Inhibition of NF-κB and MAPK	[54]
S. baicalensis	Combination of *S. baicalensis, Encephalartos. senticosus*, and vitamin C	Human Ex Vivo Human Mucosal Tissue Model	0.2 μg/mL and 2 μg/mL	The combination of *S. baicalensis* and *E. senticosus* significantly block allergic early-and late-phase mediators and substAnti-ally suppress the release of proinflammatory	[83]
S. baicalensis	Dimethoxyflavone, Pentahydroxyflavanone	Animal study Acute UVB-irradiated hairless mice	50 mg/kg, for 14 consecutive days	Increase in skin thickness, levels of MMP-2, MMP-9 and VEGF	[84]
S. baicalensis	Water extract	Animal study Forty subjects (20 per group)	Gingival Index (GI):1.585 ± 0.218 (day 21)	Toothpaste formulation was able to significantly reduce the extent of gingivitis, plaque development, and vital flora	[85]
S. baicalensis	Mixed extract/baicalin (*S. baicalensis*) and catechin (*Acacia catechu*)	*In vitro* COX-1 and COX-2 peroxidase enzyme	15 μg/mL	Not stated	[86]
S. barbata	Ethanol and ethyl acetate extracts/ phenolics, flavonoids, chlorophylls, and carotenoids	Cell culture RAW 264.7 cells	at < 500 mg/mL and < 200 mg/mL respectively	Inhibition of NF-κB activity and reduction in the expressions of iNOS, COX-2, p-ERK, and p-JNK, as well as in the production of NO, PGE2, IL-1b, and IL-6	[50]
S. baicalensis	Ethanol extract	Human/ *In vitro* Human fibroblasts/ DPPH	0.5 mg/mL of nanoparticles/ 58.62%	Using a nanoencapsulation process	[87]
S. baicalensis	Ethanol extract	*In vitro* Inhibition of NO production/ DPPH	IC_{50} 0.04 mg/mL/ 201.9 ± 0.71	Not stated	[88]
S. baicalensis	UP446	Animal study Central nervous systems in Beagle dogs and rats	5000 mg/kg	Not stated	[58]

Table 5
Anti-oxidant effects of the genus *Scutellaria*.

Species	Extract/Active component	Subject/ assay	Dose	Mechanism	Ref.
S. baicalensis	Ethanol extract	Human/ *In vitro* Human fibroblasts/ DPPH	0.5 mg/mL of nanoparticles/ 58.62%	Using a nanoencapsulation process	[87]
S. baicalensis	Ethanol extract	*In vitro* Inhibition of NO production/DPPH	IC_{50}:0.04 mg/mL/ 201.9 ± 0.71	Not stated	[88]
S. altissima L	Methanol extracts from shoots and root	*In vitro* ABTS	$EC_{50:}$ 30 μg/mL	Not stated	[67]
S. baicalensis	Baicalin Wogonin	*In vitro* On DPPH radical	IC_{50} (μM) 7.9	Catechol group in ring B remains the major determinant for OHR scavenging capability	[75]
S. baicalensis	Baicalein	*In vitro* DPPH	EC_{50} 14.49 mg/mL	Radical scavenging and reducing power	[89]
S. baicalensis	Ethanol extracts	Animal study U14 tumor-bearing mice	1000 mg/kg	Enhance the level of SOD to eliminate excessive free radicals and reducing the lipid peroxidation	[90]
S. baicalensis	Water extract	*In vitro* Scavenging ROS	100 μg/mL	H_2O_2/$FeSO_4$ for hydroxyl radicals, xanthine/ xanthine oxidase for suproxide	[91]
S. baicalensis	Baicalein, Baicalin, Wogonin and Wogonoside	*In vitro* DPPH	10 μM	Baicalein was the most effective Anti-oxidant due to itso-tri-hydroxyl structure in the ring	[92]
S.baicalensis *S.racemosa* *S.lateriflora*	Baicalin Wogonin Scutellarin Melatonin Serotonin	*In vitro* DPPH	*S.baicalensis* and *S.racemosa*: 0.058 mg/g; *S.lateriflora*: 0.054 mg/g	*S.racemosa* as a potential source of important phytopharmaceuticals for treatment of human disease.	[93]
S. baicalensis	Baicalin	*In vitro* DPPH	16.4 μg/mL	Not stated	[74]
S. baicalensis	Flavone extract	*Cell culture* Neuronal HT-22 cells	Viability 85 ± 5%	Increase in Bcl-2 content in the cell, resulted in its phosphorylation, and in contrast decrease the Bax levels	[77]
S. baicalensis	Acetone extract	*In vitro* DPPH radical scavenging activity	IC_{50}:0.16 ± 0.00	Not stated	[94]
S. baicalensis	Wogonin 7-O-b-D-ethylglucuronide	*In vitro* $FeSO_4$ –Cys-induced liver homogenate lipid peroxidation	IC_{50}18.2 mM	Not stated	[76]
S. baicalensis	Baicalein and Baicalin	Cell culture SH-SY5Y cell lines	10 μM	*Via* inhibition hydrogen peroxide-induced oxidative stress	[73]
S. baicalensis	Water extract (Huangqin)	Cell culture H_2O_2-induced H9C2 cells	Cell viability (%): 92.33 ± 2.19	Not stated	[95]
S. barbata	Polysaccharides	*In vitro* BHT	0.48 mg/mL	Not stated	[96]
S. barbata	Polysaccharides	*In vitro* DPPH radical, hydroxyl radical and superoxide radicals	IC_{50}(mg/mL):DPPH radical: 0.57 hydroxyl radical: 0.3 superoxide radicals: 0.17	Polysaccharides had significant Anti-oxidant activity and free radical-scavenging activity	[70]
S. colebrookiana S. violacea	Chloroform extract	Human 2,2′ azobis (2-amidinopropane) hydrochloride (AAPH) induced oxidative damage in human erythrocyte	IC_{50}: 92 and 70 μg/mL resp.	Not stated	[72]
S. colebrookiana and S. violacea	Chloroform extract	*In vitro* ABTS DPPH	IC_{50} (μg/mL) 24.5 and 28.0 (ABTS) 76.25 and 69.75 (DPPH)	Inhibition of membrane peroxidation and scavenging free radicals	[71]
S. litwindowii	Baicalin, baicalein, wogonin	Cell culture NIH 3T3 cells	Co-treatment protocol: methanolic extract at 1000 μg/ mL	Not stated	[68]
S. pinnatifida	Phenolic compound (using perculation and pressurized liquid extraction, PLE)	*In vitro* FRAP and DPPH	IC_{50}:34.9 mmol/g and 0.86 mg/mL resp.	Not stated	[97]
S. ramosissima	Eugenol	*In vitro* FRAP assay	IC_{50}:2476.92 ± 15.8 mM Fe(II)/g	Not stated	[69]
S. rehderiana	Acetone extract	*In vitro* BHT	100 ppm	Not stated	[98]
S. baicalensis	Baicalin Wogonoside, Baicalein, Wogonin	*In vitro* DPPH	IC_{50}: ranged from 68.81 to 73.88 μg/mL	Not stated	[99]
S. hastifolia	Phenylethanoid glycoside (hastifolioside)	*In vitro* DPPH	10%	DPPH radical scavenging capability	[100]

inhibit the activity or to enhance the expression of antioxidant enzymes such as superoxide dismutase, peroxiredoxin-6, glutathione peroxidase and catalase [65].

Scutellaria lindbergii and its individual constituents possess strong antioxidant activity. In the study conducted by Ehtesham-Gharaee et al., flavonoids and phenolics present in *S. lindbergii* act as antioxidant and prevent against oxidative DNA damage which determined with MTT assay [66]. In another study, high phenolic and flavonoid compounds isolated from shoots and roots of *S. altissima* showed potent antioxidant activity and free radical scavenging that evaluated using ABTS radical scavenging, the lipid peroxidation and FRAP metal reduction power test [67]. Also *Scutellaria litwinowii* indicated strong antioxidant activity which has been attributed to high levels of phenolic and flavonoids in the methanol extract [68]. The monoterpenes, thymol and eugenol identified in *S. immaculata*, *S. ramosissima* and *S. schachristanica* showed moderate antioxidant activity by inhibiting ROS generation and increasing the endogenous antioxidant compounds including ascorbic acid (vitamin C) and glutathione [69]. It is also reported that polysaccharides from *S. barbata* indicated potent antioxidant activity that measured using DPPH method [70].

Analysis of *Scutellaria* species of Western Ghats, confirmed that all the species exhibited significant antioxidant and cytotoxic activity. The extent of the antioxidant activity varied across different species and the methods used for extraction which the extract of *S. colebrookiana* and *S. violacea* exhibited the highest activity [71]. Moreover, *S. colebrookiana* and *S. violacea* protected erythrocytes from AAPH (2,2′ azobis (2-amidinopropane) hydrochloride) caused oxidative damage. The cytoprotective effect of extract of *S. colebrookiana and S. violacea* is probably related to its antioxidant activity [72].

Baicalein and baicalin isolated from *S. baicalensis* Georgi had protective effects on the oxidative injury in neuronal cells and inhibited lipoxygenase or phospholipase C and scavenged H_2O_2 produced free radicals [73]. Also baicalin could scavenge the diphenylpicrylhydrazyl radical (DPPH) and possess strong antioxidant activity [74]. The antioxidant effects of baicalin were suggested that significantly is better than BHT and ascorbic acid. The majority of antioxidant effects are attributed to *Scutellaria* flavonoids such as baicalein, baicalin, wogonin and glucuronideas as they exhibit strong radical scavenging activity. In facts, baicalin showed the strong scavenging activity against DPPH [75]. A new flavone glycoside, wogonin 7-O-b-D-ethylglucuronide and wogonoside are also introduced as powerful antioxidants [76]. There is also a report on antioxidant activity of the flavone rich extract of *S. baicalensis* which scavenge of ROS assayed *via* Formazan assay kit [77]. The extracts of *S. baicalensis* possess antioxidant activity through radical scavenging, enhance the level of SOD and reduce the lipid peroxidation [89–95]. Also, *S. barbata*, *S. pinnatifida*, *S. rehderiana* and *S. hastifolia* indicated potent antioxidant activity [96–100,103].

5. Conclusion

The genus of *Scutellaria* exhibited pleiotropic activities such as antioxidant and anti-inflammatory effects, as well as an inhibitory action on the progression of neurodegenerative diseases, supporting the promising action of the plants for the development in the treatment of neuropsychiatric problems. Phenols and terpenes as the two main chemical compounds have been identified in different species of the genus of *Scutellaria*. Among them, baicalin, baicalein, wogonin and scutebarbatine B are one of the most abundant compounds in *Scutellaria* and indicated strong neuroprotective effects against various neurotoxic agents. In this review, we summarize the neuroprotective efficacy of the genus of *Scutellaria* in various *in vitro* and *in vivo* models and the related molecular mechanisms of the plant in protection against both neurologic and psychiatric disorders. Additionally, the scientific studies reveal that due to multi-targeted actions, *Scutellaria* may be used as a novel therapeutic agent for the treatment of neurodegenerative diseases. However, more investigation is essential to help us elucidate the potential activity of the plant to enhance the cognitive health and wellbeing.

6. Strengths and limitations

In the field of neuroscience, the effect of the *Scutellaria* genus has been extensively evaluated on different aspects of pathogenesis of the related disease including neuroprotection, antidepressant and anxiolytic, anti-inflammation and anti-oxidant activity. In this regard extracts and active components were studied and the mechanism of the protection against neural disease has been proposed. In spite of the evidence for potential activity, it seems the exact component responsible for the biologic activity of the plant has not been stated when the extract has been studied.

Although the safety and efficacy of the genus *Scutellaria* have been shown in clinical studies as for cancer treatment, but the lack of clinical trials in the field of neuroscience made it difficult to use the plant in patients with neuropsychiatric problems.

7. Perspective

Due to the lack of clinical studies on *Scutellaria* in the field of neuroscience authors are encouraged to work on the safety and efficacy of the plant on human subjects. Interestingly extracts and active components were both studied and showed therapeutic potential in *in vitro* and animal model of neuropsychiatric diseases. Since synergism or antagonism between active component change the activity of the extracts, study on the related mechanism would be a good topic for future studies.

Authors' contributions

Z. Tayarani-Najaran has attributed to study concepts, design also manuscript editing and review; S. EghbaliFeriz and A. Taleghani conducted data acquisition, manuscript preparation and review.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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References

[1] J. Willis, A Dictionary of the Flowering Plant and Ferns, Cambridge University Press, 1966.
[2] Y. Shang, J. Cheng, J. Qi, H. Miao, Scutellaria flavonoid reduced memory dysfunction and neuronal injury caused by permanent global ischemia in rats, Pharmacol. Biochem. Behav. 82 (1) (2005) 67–73.
[3] M. Bruno, F. Piozzi, A.M. Maggio, M.S. Simmonds, Antifeedant activity of neoclerodane diterpenoids from two Sicilian species of Scutellaria, Biochem. Syst. Ecol. 30 (8) (2002) 793–799.
[4] R. Tiwari, M. Trivedi, Z.C. Guang, G.Q. Guo, G.C. Zheng, Agrobacterium rhizogenes mediated transformation of Scutellaria baicalensis and production of flavonoids in hairy roots, Biol. Plantarum 52 (1) (2008) 26–35.
[5] K. Patel, R.B. Singh, D.K. Patel, Medicinal significance, pharmacological activities, and analytical aspects of solasodine: a concise report of current scientific literature, J. Acute. Dis. 2 (2) (2013) 92–98.
[6] X. Shang, X. He, X. He, M. Li, R. Zhang, P. Fan, Q. Zhang, Z. Jia, The genus Scutellaria an ethnopharmacological and phytochemical review, J. Ethnopharmacol. 128 (2) (2010) 279–313.
[7] F. Tomás-Barberán, E. Wollenweber, Flavonoid aglycones from the leaf surfaces of someLabiatae species, Plant. Syst. Evol. 173 (3-4) (1990) 109–118.

[8] Y. Xu, L. Guo, J. Chen, Separation and purification polysaccharides from Scutellaria bartata D. Don, Nat. Prod. Res. Dev. 4 (1992) 1–5.
[9] S.-C. Ma, J. Du, P.P.-H. But, X.-L. Deng, Y.-W. Zhang, V.E.-C. Ooi, H.-X. Xu, S.H.-S. Lee, S.F. Lee, Antiviral Chinese medicinal herbs against respiratory syncytial virus, J. Ethnopharmacol. 79 (2) (2002) 205–211.
[10] Y. Miyaichi, T. Morimoto, K. Yaguchi, H. Kizu, Studies on the constituents of Scutellaria species (XXI): constituents of the leaves of Scutellaria strigillosa Hemsley, J. Nat. Med. 60 (2) (2006) 157–158.
[11] K. Kitamura, M. Honda, H. Yoshizaki, S. Yamamoto, H. Nakane, M. Fukushima, K. Ono, T. Tokunaga, Baicalin, an inhibitor of HIV-1 production in vitro, Antivir. Res. 37 (2) (1998) 131–140.
[12] D.-e. Shieh, L.-T. Liu, C.-C. Lin, Antioxidant and free radical scavenging effects of baicalein, baicalin and wogonin, Anticancer Res. 20 (5A) (1999) 2861–2865.
[13] S. Ikemoto, K. Sugimura, N. Yoshida, R. Yasumoto, S. Wada, K. Yamamoto, T. Kishimoto, Antitumor effects of Scutellariae radix and its components baicalein, baicalin, and wogonin on bladder cancer cell lines, Urology 55 (6) (2000) 951–955.
[14] T. Nakajima, M. Imanishi, K. Yamamoto, J.-C. Cyong, K. Hirai, Inhibitory effect of baicalein, a flavonoid in Scutellaria root, on eotaxin production by human dermal fibroblasts, Planta. Med. 67 (02) (2001) 132–135.
[15] M. Boozari, A. Mohammadi, J. Asili, S.A. Emami, Z. Tayarani-Najaran, Growth inhibition and apoptosis induction by Scutellaria pinnatifida A. Ham. on HL-60 and K562 leukemic cell lines, Environ. Toxicol. Pharmacol. 39 (1) (2015) 307–312.
[16] M. Motaez, S.A. Emami, Z. Tayarani-Najaran, Growth inhibition and apoptosis induction of Scutellaria luteo-coerulea Bornm. & Sint. on leukemia cancer cell lines K562 and HL-60, Avicenna J. Phytomed. 5 (6) (2015) 553–559.
[17] Z. Tayarani-Najaran, S.A. Emami, J. Asili, A. Mirzaei, S.H. Mousavi, Analyzing cytotoxic and apoptogenic properties of Scutellaria litwinowii root extract on cancer cell lines, Evid. Based. Complement. Altern. Med. 2011 (2011) 160682.
[18] Z. Tayarani-Najaran, S.H. Mousavi, J. Asili, S.A. Emami, Growth-inhibitory effect of Scutellaria lindbergii in human cancer cell lines, Food. Chem. Toxicol. 48 (2) (2010) 599–604.
[19] Z. Tayarani-Najaran, S.H. Mousavi, N. Vahdati-Mashhadian, S.A. Emami, H. Parsaee, Scutellaria litwinowii induces apoptosis through both extrinsic and intrinsic apoptotic pathways in human promyelocytic leukemia cells, Nutr. Cancer 64 (1) (2012) 80–88.
[20] H. Lee, Y.O. Kim, H. Kim, S.Y. Kim, H.S. Noh, S.S. Kang, G.J. Cho, W.S. Choi, K. Suk, Flavonoid wogonin from medicinal herb is neuroprotective by inhibiting inflammatory activation of microglia, FASEB. J. 17 (13) (2003) 1943–1944.
[21] S. Gafner, C. Bergeron, L.L. Batcha, J. Reich, J.T. Arnason, J.E. Burdette, J.M. Pezzuto, C.K. Angerhofer, Inhibition of [3H]-LSD binding to 5-HT7 receptors by flavonoids from Scutellaria l ateriflora, J. Nat. Prod. 66 (4) (2003) 535–537.
[22] D. Goh, Y.H. Lee, E.S. Ong, Inhibitory effects of a chemically standardized extract from Scutellaria barbata in human colon cancer cell lines, LoVo, J. Agric. Food Chem. 53 (21) (2005) 8197–8204.
[23] B. Pouzet, SB-258741: A 5-HT7 receptor antagonist of potential clinical interest, CNS. Drug Rev. 8 (1) (2002) 90–100.
[24] S.V. More, H. Kumar, D.-Y. Cho, Y.-S. Yun, D.-K. Choi, Toxin-induced experimental models of learning and memory impairment, Int. J. Mol. Sci. 17 (9) (2016) 1447.
[25] D.J. Selkoe, Alzheimer's disease: a central role for amyloid, J. Neuropathol. Exp. Neurol. 53 (5) (1994) 438–447.
[26] L.M. Bierer, V. Haroutunian, S. Gabriel, P.J. Knott, L.S. Carlin, D.P. Purohit, D.P. Perl, J. Schmeidler, P. Kanof, K.L. Davis, Neurochemical correlates of dementia severity in Alzheimer's disease: relative importance of the cholinergic deficits, J. Neurochem. 64 (2) (1995) 749–760.
[27] A. Ueki, C. Miwa, K. Miyoshi, Impairment in the acquisition of passive and active avoidance learning tasks due to bilateral entorhinal cortex lesions, J. Neurol. Sci. 125 (1) (1994) 14–21.
[28] H. Heo, Y. Shin, W. Cho, Y. Choi, H. Kim, Y.K. Kwon, Memory improvement in ibotenic acid induced model rats by extracts of Scutellaria baicalensis, J. Ethnopharmacol. 122 (1) (2009) 20–27.
[29] Y.K. Hwang, M. Jinhua, B.-R. Choi, C.-A. Cui, W.K. Jeon, H. Kim, H.Y. Kim, S.-H. Han, J.-S. Han, Effects of Scutellaria baicalensis on chronic cerebral hypoperfusion-induced memory impairments and chronic lipopolysaccharide infusion-induced memory impairments, J. Ethnopharmacol. 137 (1) (2011) 681–689.
[30] Y. Cao, L. Liang, J. Xu, J. Wu, Y. Yan, P. Lin, Q. Chen, F. Zheng, Q. Wang, Q. Ren, The effect of Scutellaria baicalensis stem-leaf flavonoids on spatial learning and memory in chronic cerebral ischemia-induced vascular dementia of rats, Acta. Biochimica. et. Biophysica. Sinica. 48 (5) (2016) 437–446.
[31] K.-S. Hong, J.L. Saver, Quantifying the value of stroke disability outcomes, Stroke 40 (12) (2009) 3828–3833.
[32] M. Fisher, Characterizing the target of acute stroke therapy, Stroke 28 (4) (1997) 866–872.
[33] M.D. Ginsberg, Neuroprotection for ischemic stroke: past, present and future, Neuropharmacology 55 (3) (2008) 363–389.
[34] M. Afsharzadeh, Z. Tayarani-Najaran, A. Zare, S.H. Mousavi, Protective effect of Scutellaria litwinowii extract on serum/glucose-deprived cultured PC12 cells and determining the role of reactive oxygen species, J. Toxicol. 2012 (2012) 413279.
[35] H.Z. Piao, S.A. Jin, H.S. Chun, J.-C. Lee, W.-K. Kim, Neuroprotective effect of wogonin: potential roles of inflammatory cytokines, Arch. Pharm. Res. 27 (9) (2004) 930.
[36] Y. Cao, X. Mao, C. Sun, P. Zheng, J. Gao, X. Wang, D. Min, H. Sun, N. Xie, J. Cai, Baicalin attenuates global cerebral ischemia/reperfusion injury in gerbils via anti-oxidative and anti-apoptotic pathways, Brain. Res. Bull. 85 (6) (2011) 396–402.
[37] O. Cheng, Z. Li, Y. Han, Q. Jiang, Y. Yan, K. Cheng, Baicalin improved the spatial learning ability of global ischemia/reperfusion rats by reducing hippocampal apoptosis, Brain. Res. 1470 (2012) 111–118.
[38] Y. Zhang, X. Wang, X. Wang, Z. Xu, Z. Liu, Q. Ni, X. Chu, M. Qiu, A. Zhao, W. Jia, Protective effect of flavonoids from Scutellaria baicalensis Georgi on cerebral ischemia injury, J. Ethnopharmacol. 108 (3) (2006) 355–360.
[39] M. Scult, A. Paulli, E. Mazure, T. Moffitt, A. Hariri, T. Strauman, The association between cognitive function and subsequent depression: a systematic review and meta-analysis, Psychol. Med. 47 (1) (2017) 1.
[40] S. Bennett, A.J. Thomas, Depression and dementia: cause, consequence or coincidence? Maturitas 79 (2) (2014) 184–190.
[41] K.M. Hui, M.S. Huen, H.Y. Wang, H. Zheng, E. Sigel, R. Baur, H. Ren, Z.W. Li, J.T.-F. Wong, H. Xue, Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from Scutellaria baicalensis Georgi, Biochem. Pharmacol. 64 (9) (2002) 1415–1424.
[42] R. Awad, J. Arnason, V. Trudeau, C. Bergeron, J. Budzinski, B. Foster, Z. Merali, Phytochemical and biological analysis of skullcap (Scutellaria lateriflora L.): a medicinal plant with anxiolytic properties, Phytomedicine 10 (8) (2003) 640–649.
[43] R.S.M. de Carvalho, F.S. Duarte, T.C.M. de Lima, Involvement of GABAergic non-benzodiazepine sites in the anxiolytic-like and sedative effects of the flavonoid baicalein in mice, Behav. Brain. Res. 221 (1) (2011) 75–82.
[44] F. Wang, M. Shing, Y. Huen, S.Y. Tsang, H. Xue, Neuroactive flavonoids interacting with GABAA receptor complex, CNS Neurol. Disord. Drug Targets 4 (5) (2005) 575–585.
[45] M.S. Huen, J.W. Leung, W. Ng, W. Lui, M.N. Chan, J.T.-F. Wong, H. Xue, 5, 7-Dihydroxy-6-methoxyflavone, a benzodiazepine site ligand isolated from Scutellaria baicalensis Georgi, with selective antagonistic properties, Biochem. Pharmacol. 66 (1) (2003) 125–132.
[46] E.M. Shin, H.Y. Zhou, G.H. Xu, S.H. Lee, I. Merfort, Y.S. Kim, Anti-inflammatory activity of hispidol A 25-methyl ether, a triterpenoid isolated from Ponciri immaturus fructus, Eur. J. Pharmacol. 627 (1) (2010) 318–324.
[47] W. Hu, X. Yang, C. Zhe, Q. Zhang, L. Sun, K. Cao, Puerarin inhibits iNOS, COX-2 and CRP expression via suppression of NF-κB activation in LPS-induced RAW264.7 macrophage cells, Pharmacol. Rep. 63 (3) (2011) 781–789.
[48] S.-Y. Cho, S.-J. Park, M.-J. Kwon, T.-S. Jeong, S.-H. Bok, W.-Y. Choi, W.-I. Jeong, S.-Y. Ryu, S.-H. Do, C.-S. Lee, Quercetin suppresses proinflammatory cytokines production through MAP kinases and NF-κB pathway in lipopolysaccharide-stimulated macrophage, Mol. Cell. Biochem. 243 (1) (2003) 153–160.
[49] T. Chitnis, H.L. Weiner, CNS inflammation and neurodegeneration, J. Clin. Invest. 127 (10) (2017) 3577–3587.
[50] H.-L. Liu, T.-H. Kao, C.-Y. Shiau, B.-H. Chen, Functional components in Scutellaria barbata D. Don with anti-inflammatory activity on RAW 264.7 cells, J. Food. Drug. Anal. (2017).
[51] J.-J. Chen, C.-C. Huang, H.-Y. Chang, P.-Y. Li, Y.-C. Liang, J.-S. Deng, S.-S. Huang, G.-J. Huang, Scutellaria baicalensis ameliorates acute lung injury by suppressing inflammation in vitro and in vivo, Am. J. Chin. Med 45 (01) (2017) 137–157.
[52] E.H. Kim, B. Shim, S. Kang, G. Jeong, J.-s. Lee, Y.-B. Yu, M. Chun, Anti-inflammatory effects of Scutellaria baicalensis extract via suppression of immune modulators and MAP kinase signaling molecules, J. Ethnopharmacol. 126 (2) (2009) 320–331.
[53] S.-B. Yoon, Y.-J. Lee, S.K. Park, H.-C. Kim, H. Bae, H.M. Kim, S.-G. Ko, H.Y. Choi, M.S. Oh, W. Park, Anti-inflammatory effects of Scutellaria baicalensis water extract on LPS-activated RAW 264.7 macrophages, J. Ethnopharmacol. 125 (2) (2009) 286–290.
[54] G.E. Hong, J.A. Kim, A. Nagappan, S. Yumnam, H.J. Lee, E.H. Kim, W.S. Lee, S.C. Shin, H.S. Park, G.-S. Kim, Flavonoids identified from Korean Scutellaria baicalensis Georgi inhibit inflammatory signaling by suppressing activation of NF-κB and MAPK in RAW 264.7 cells, Evid. Based. Complement. Altern. Med. 2013 (2013).
[55] C.L. Tsai, Y.C. Lin, H.-M. Wang, T.C. Chou, Baicalein, an active component of Scutellaria baicalensis, protects against lipopolysaccharide-induced acute lung injury in rats, J. Ethnopharmacol. 153 (1) (2014) 197–206.
[56] W.H. Huang, A.R. Lee, C.H. Yang, Antioxidative and anti-inflammatory activities of polyhydroxyflavonoids of Scutellaria baicalensis GEORGI, Biosci. Biotechnol. Biochem. 70 (10) (2006) 2371–2380.
[57] K.C. Hung, H.J. Huang, Y.T. Wang, A.M.Y. Lin, Baicalein attenuates α-synuclein aggregation, inflammasome activation and autophagy in the MPP++-treated nigrostriatal dopaminergic system in vivo, J. Ethnopharmacol. 194 (2016) 522–529.
[58] M. Yimam, Y.C. Lee, Q. Jia, Effect of a botanical composition, UP446, on respiratory, cardiovascular and central nervous systems in beagle dogs and rats, Regul. Toxicol. Pharmacol. 77 (2016) 184–191.
[59] L. Zhang, Q. Cai, J. Lin, Y. Fang, Y. Zhan, A. Shen, L. Wei, L. Wang, J. Peng, Chloroform fraction of Scutellaria barbata D. Don promotes apoptosis and suppresses proliferation in human colon cancer cells, Mol. Med. Rep. 9 (2) (2014) 701–706.
[60] A.M. Lin, Y. Ping, G. Chang, J. Wang, J. Chiu, C. Kuo, C. Chi, Neuroprotective effect of oral S/B remedy (Scutellaria baicalensis Georgi and Bupleurum scorzonerifolfium willd) on iron-induced neurodegeneration in the nigrostriatal dopaminergic system of rat brain, J. Ethnopharmacol. 134 (3) (2011) 884–891.
[61] Y.S. Chi, H. Lim, H. Park, H.P. Kim, Effects of wogonin, a plant flavone from Scutellaria radix, on skin inflammation: in vivo regulation of inflammation-associated gene expression, Biochem. Pharmacol. 66 (7) (2003) 1271–1278.
[62] Y.S. Chi, B.S. Cheon, H.P. Kim, Effect of wogonin, a plant flavone from Scutellaria radix, on the suppression of cyclooxygenase-2 and the induction of inducible nitric oxide synthase in lipopolysaccharide-treated RAW 264.7 cells, Biochem. Pharmacol. 61 (10) (2001) 1195–1203.

[63] B. Halliwell, J. Gutteridge, Protection against oxidants in biological systems: the superoxide theory of oxygen toxicity, Free. Radic. Biol. Med. (1989) 86.
[64] S.A. Aherne, J.P. Kerry, N.M. O'brien, Effects of plant extracts on antioxidant status and oxidant-induced stress in Caco-2 cells, Br. J. Nutr. 97 (02) (2007) 321–328.
[65] Y.F. Sasaki, S. Kawaguchi, A. Kamaya, M. Ohshita, K. Kabasawa, K. Iwama, K. Taniguchi, S. Tsuda, The comet assay with 8 mouse organs: results with 39 currently used food additives, Mutat. Res. Genet. Toxicol. Environ. Mutagen. 519 (1) (2002) 103–119.
[66] M. Ehtesham-Gharaee, A. Eshaghi, S. Shojaee, J. Asili, S.A. Emami, J. Behravan, F. Mosaffa, Protective effects of Scutellaria lindbergii root extract against oxidative-induced cell and DNA damage in mouse fibroblast-like cells, Drug. Chem. Toxicol. 38 (3) (2015) 293–299.
[67] I. Grzegorczyk-Karolak, Ł. Kuźma, H. Wysokińska, Study on the chemical composition and antioxidant activity of extracts from shoot culture and regenerated plants of Scutellaria altissima L, Acta. Physiologiae. Plantarum 37 (1) (2015) 1736.
[68] S. Shojaee, H. Parhiz, A. Eshaghi, S.A. Emami, J. Asili, J. Behravan, F. Mosaffa, In vitro protective effects of Scutellaria litwinowii root extract against H2O2-induced DNA damage and cytotoxicity, J. Complement. Integr. Med. 11 (2) (2014) 121–127.
[69] N.Z. Mamadalieva, F. Sharopov, P. Satyal, S.S. Azimova, M. Wink, Composition of the essential oils of three Uzbek Scutellaria species (Lamiaceae) and their antioxidant activities, Nat. Prod. Res. 31 (10) (2017) 1172–1176.
[70] C.-L. Ye, Q. Huang, Extraction of polysaccharides from herbal Scutellaria barbata D. Don (Ban-Zhi-Lian) and their antioxidant activity, Carbohydr. Polym. 89 (4) (2012) 1131–1137.
[71] S. Salini, T. Chubicka, N. Sasidharan, E. Sindhu, T. Babu, Cytotoxic and antioxidant properties of selected Scutellaria species from the Western Ghats of Peninsular India, Pharm. Biol. 51 (2) (2013) 152–159.
[72] S. Salini, M.K. Divya, T. Chubicka, N. Meera, D.P. Fulzele, A.C. Ragavamenon, T.D. Babu, Protective effect of Scutellaria species on AAPH-induced oxidative damage in human erythrocyte, J. Basic. Clin. Physiol. Pharmacol. 27 (4) (2016) 403–409.
[73] Z. Gao, K. Huang, H. Xu, Protective effects of flavonoids in the roots of Scutellaria baicalensis Georgi against hydrogen peroxide-induced oxidative stress in HS-SY5Y cells, Pharmacol. Res. 43 (2) (2001) 173–178.
[74] L. Peng-Fei, H. Fu-Gen, D. Bin-Bin, D. Tian-sheng, H. Xiang-lin, Z. Ming-qin, Purification and antioxidant activities of baicalin isolated from the root of huangqin (Scutellaria baicalensis gcorsi), J. Food. Sci. Technol. 50 (3) (2013) 615–619.
[75] H. Bochořáková, H. Paulová, J. Slanina, P. Musil, E. Táborská, Main flavonoids in the root of Scutellaria baicalensis cultivated in Europe and their comparative antiradical properties, Phytother. Res. 17 (6) (2003) 640–644.
[76] M.-H. Wang, L.-Z. Li, J.-B. Sun, F.-H. Wu, J.-Y. Liang, A new antioxidant flavone glycoside from Scutellaria baicalensis Georgi, Nat. Prod. Res. 28 (20) (2014) 1772–1776.
[77] J. Choi, C.C. Conrad, C.A. Malakowsky, J.M. Talent, C.-S. Yuan, R.W. Gracy, Flavones from Scutellaria baicalensis Georgi attenuate apoptosis and protein oxidation in neuronal cell lines, Biochim. Biophys. Acta. 1571 (3) (2002) 201–210.
[78] W. Zhu, S. Ma, R. Qu, D. Kang, Y. Liu, Antidepressant effect of baicalin extracted from the root of Scutellaria baicalensis. In mice rats, Pharm. Biol. 44 (7) (2006) 503–510.
[79] Y. Zhang, X. Li, B. Ciric, C.-g. Ma, B. Gran, A. Rostami, G.-X. Zhang, Therapeutic effect of baicalin on experimental autoimmune encephalomyelitis is mediated by SOCS3 regulatory pathway, Sci. Rep. 30 (5) (2015) 17407.
[80] A. Oliveira, G. Barbosa, M. Verdam, D. Ohana, M. Mendonça, R. Meira, Analgesic and anti-inflammatory effect of the aqueous extract of" trevo-roxo"(Scutellaria agrestis A. St.-Hil. ex Benth.-Lamiaceae) leaves in rodents, Rev. Bras. Plantas Med. 16 (2) (2014) 174–181.
[81] Z. Jue, Q. Fan, Z. HangJun, Z. XiaoHong, C. LiangZhong, Comparison of anti-inflammatory and anti-nociceptive activities of Curcuma wenyujin YH Chen et C. Ling and Scutellaria baicalensis Georgi, Afr. J. Trad. BMC. Complement. Altern. Med. 7 (4) (2010) 339–349.
[82] H.-S. Jung, M.H. Kim, N.-G. Gwak, Y.-S. Im, K.-Y. Lee, Y. Sohn, H. Choi, W.M. Yang, Antiallergic effects of Scutellaria baicalensis on inflammation in vivo and in vitro, J. Ethnopharmacol. 141 (1) (2012) 345–349.
[83] N. Zhang, K. Van Crombruggen, G. Holtappels, C. Bachert, A herbal composition of Scutellaria baicalensis and Eleutherococcus senticosus shows potent anti-inflammatory effects in an ex vivo human mucosal tissue model, Evid. Based. Complement. Altern. Med. 2012 (2012).
[84] Y. Kimura, M. Sumiyoshi, Effects of various flavonoids isolated from Scutellaria baicalensis roots on skin damage in acute UVB-irradiated hairless mice, J. Pharm. Pharmacol. 63 (12) (2011) 1613–1623.
[85] N.B. Arweiler, G. Pergola, J. Kuenz, E. Hellwig, A. Sculean, T.M. Auschill, Clinical and antibacterial effect of an anti-inflammatory toothpaste formulation with Scutellaria baicalensis extract on experimental gingivitis, Clin. Oral. Investig. 15 (6) (2011) 909–913.
[86] B. Burnett, Q. Jia, Y. Zhao, R. Levy, A medicinal extract of Scutellaria baicalensis and Acacia catechu acts as a dual inhibitor of cyclooxygenase and 5-lipoxygenase to reduce inflammation, J. Med. Food. 10 (3) (2007) 442–451.
[87] W. Choi, R.H. No, H.-S. Kwon, H.Y. Lee, Enhancement of skin anti-inflammatory activities of Scutellaria baicalensis extract using a nanoencapsulation process, J. Cosmet. Laser. Ther. 16 (6) (2014) 271–278.
[88] L. Zhang, A.S. Ravipati, S.R. Koyyalamudi, S.C. Jeong, N. Reddy, P.T. Smith, J. Bartlett, K. Shanmugam, G. Münch, M.J. Wu, Antioxidant and anti-inflammatory activities of selected medicinal plants containing phenolic and flavonoid compounds, J. Agric. Food. Chem. 59 (23) (2011) 12361–12367.
[89] D. Woźniak, A. Dryś, A. Matkowski, Antiradical and antioxidant activity of flavones from Scutellariae baicalensis radix, Nat. Prod. Res. 29 (16) (2015) 1567–1570.
[90] Y. Peng, C.-S. Guo, P.-X. Li, Z.-Z. Fu, L.-M. Gao, Y. Di, Y.-K. Ju, R. Tian, J.-J. Xue, Immune and anti-oxidant functions of ethanol extracts of Scutellaria baicalensis Georgi in mice bearing U14 cervical cancers, Asian. Pac. J. Cancer. Prev. 15 (10) (2013) 4129–4133.
[91] Z.-H. Shao, T.L. Vanden Hoek, C.-Q. Li, P.T. Schumacker, L.B. Becker, K.C. Chan, Y. Qin, J.-J. Yin, C.-S. Yuan, Synergistic effect of Scutellaria baicalensis and grape seed proanthocyanidins on scavenging reactive oxygen species in vitro, Am. J. Chin. Med. 32 (01) (2004) 89–95.
[92] Z. Gao, K. Huang, X. Yang, H. Xu, Free radical scavenging and antioxidant activities of flavonoids extracted from the radix of Scutellaria baicalensis Georgi, Biochim. Biophys. Acta. 1472 (3) (1999) 643–650.
[93] I.B. Cole, J. Cao, A.R. Alan, P.K. Saxena, S.J. Murch, Comparisons of Scutellaria baicalensis, Scutellaria lateriflora and Scutellaria racemosa: genome size, antioxidant potential and phytochemistry, Planta Med. 74 (04) (2008) 474–481.
[94] J.-H. Park, R.-Y. Kim, E. Park, Antioxidant and α-glucosidase inhibitory activities of different solvent extracts of skullcap (Scutellaria baicalensis), Food. Sci. Biotechnol. 20 (4) (2011) 1107–1112.
[95] E. Chan, C.Y.-K. Wong, C.-W. Wan, C.-Y. Kwok, J.-H. Wu, K.-M. Ng, C.-H. So, A.L.-S. Au, C.C.-W. Poon, S.-W. Seto, Evaluation of anti-oxidant capacity of root of Scutellaria baicalensis Georgi, in comparison with roots of Polygonum multiflorum thunb and Panax ginseng CA Meyer, Am. J. Chin. Med. 38 (04) (2010) 815–827.
[96] J. Gao, X. Yang, P. Liu, W. Yin, Short communication optimization of ultrasonic-assisted extraction of polysaccharides from Scutellaria barbata and determination of their anticancer and antioxidant activities, Int. J. Pharmacol. 12 (7) (2016) 754–759.
[97] E. Golmakani, A. Mohammadi, T.A. Sani, H. Kamali, Phenolic and flavonoid content and antioxidants capacity of pressurized liquid extraction and perculation method from roots of Scutellaria pinnatifida A. Hamilt. subsp alpina (Bornm) Rech. f, J. Supercrit. Fluids. 95 (2014) 318–324.
[98] Y.-L. Su, L.K. Leung, Y.-R. Bi, Y. Huang, Z.-Y. Chen, Antioxidant activity of flavonoids isolated from Scutellaria rehderiana, J. Am. Oil Chem. Soc. 77 (8) (2000) 807–813.
[99] H. Li, S. Luo, J. Su, H. Ke, W. Wang, B. Yang, Optimization of extraction conditions for flavonoid composition and antioxidant activity of radix scutellariae, Anal. Lett. 48 (8) (2015) 1234–1244.
[100] H. Bardakci, H. Skaltsa, T. Milosevic-Ifantis, D. Lazari, D. Hadjipavlou-Litina, E. Yeşilada, H. Kırmızıbekmez, Antioxidant activities of several Scutellaria taxa and bioactive phytoconstituents from Scutellaria hastifolia L, Ind. Crops. Prod. 77 (2015) 196–203.
[101] S. Zhao, W. Kong, S. Zhang, M. Chen, X. Zheng, X. Kong, Pretreatment with *scutellaria baicalensis* stem-leaf total flavonoid prevents cerebral ischemia-reperfusion injury, Neural Regen. Res. 8 (34) (2013) 3183.
[102] Y.-Z. Shang, H. Miao, J.-J. Cheng, J.-M. Qi, Effects of amelioration of total flavonoids from stems and leaves of Scutellaria baicalensis Georgi on cognitive deficits, neuronal damage and free radicals disorder induced by cerebral ischemia in rats, Biol. Pharm. Bull. 29 (4) (2006) 805–810.
[103] F. Şenol, I. Orhan, G. Yilmaz, M. Cicek, B. Şener, Acetylcholinesterase, butyrylcholinesterase, and tyrosinase inhibition studies and antioxidant activities of 33 Scutellaria L. taxa from Turkey, Food. Chem. Toxicol. 48 (3) (2010) 781–788.
[104] X.-H. Zhu, S.-J. Li, H.-H. Hu, L.-R. Sun, M. Das, T.-M. Gao, Neuroprotective effects of Xiao-Xu-Ming decoction against ischemic neuronal injury in vivo and in vitro, J. Ethnopharmacol. 127 (1) (2010) 38–46.
[105] Y. Bu, S. Kwon, Y.T. Kim, M.Y. Kim, H. Choi, J.G. Kim, N. Jamarkattel-Pandit, S. Doré, S.H. Kim, H. Kim, Neuroprotective effect of HT008-1, a prescription of traditional Korean medicine, on transient focal cerebral ischemia model in rats, Phytother. Res. 24 (8) (2010) 1207–1212.
[106] S.B. Oh, H.R. Park, Y.J. Jang, S.Y. Choi, T.G. Son, J. Lee, Baicalein attenuates impaired hippocampal neurogenesis and the neurocognitive deficits induced by γ-ray radiation, Br. J. Pharmacol. 168 (2) (2013) 421–431.
[107] S.L. Xu, K.Y. Zhu, C.W. Bi, L. Yan, S.W. Men, T.T. Dong, K.W. Tsim, Flavonoids, derived from traditional Chinese medicines, show roles in the differentiation of neurons: possible targets in developing health food products, Birth Defects Res. 99 (4) (2013) 292–299.
[108] J. Yang, X. Wu, H. Yu, X. Liao, L. Teng, NMDA receptor-mediated neuroprotective effect of the Scutellaria baicalensis Georgi extract on the excitotoxic neuronal cell death in primary rat cortical cell cultures, Sci. World J. 2014 (2014).
[109] T.Y. Yune, J.Y. Lee, C.M. Cui, H.C. Kim, T.H. Oh, Neuroprotective effect of Scutellaria baicalensis on spinal cord injury in rats, J. Neurochem. 110 (4) (2009) 1276–1287.
[110] B.P. Gaire, S.-K. Moon, H. Kim, Scutellaria baicalensis in stroke management: nature's blessing in traditional Eastern medicine, Chin. J. Integr. Med. 20 (9) (2014) 712–720.
[111] A. Kumar, V. Sharma, V.P. Singh, M. Kaundal, M.K. Gupta, J. Bariwal, R. Deshmukh, Herbs to curb cyclic nucleotide phosphodiesterase and their potential role in Alzheimer's disease, Mech. Ageing. Dev. 149 (2015) 75–87.
[112] H.-S. Lim, O.-S. Kim, B.-Y. Kim, S.-J. Jeong, Apigetrin from Scutellaria baicalensis Georgi inhibits neuroinflammation in BV-2 microglia and exerts neuroprotective effect in HT22 hippocampal cells, J. Med. Food 19 (11) (2016) 1032–1040.