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Review Article

The food and medicine homologous Chinese Medicine from Leguminosae species: A comprehensive review on bioactive constituents with neuroprotective effects on nervous system

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Abstract: The food and medicine homologous traditional Chinese medicines (FMHCMs) have attracted great attention for their high nutritional and broad medicinal value, especially for the neuroprotective effects on nervous system. In this review, the neuroprotective constituents of FMHCMs from Leguminosae species, including *Astragalus membranaceus* (*Astragalus membranaceus* (Fisch.) Bge.), *Glycyrrhiza uralensis* Fisch. (*Glycyrrhiza inflata* Bat. or *Glycyrrhiza glabra* L.), *Cassia obtusifolia* L. (*Cassia tora* L.), *Vigna umbellata* Ohwi et Ohashi (*Vigna angularis* Ohwi et Ohashi), *Glycine max* (L.) Merr., *Sophora japonica* L., *Canavalia gladiata* (Jacq.) DC., *Pueraria lobata* (Willd.) Ohwi, and *Dolichos lablab* L. are summarized. As a result, 25 bioactive constituents are found to exert neuroprotective effects on nervous system through reducing oxidative stress and neuroinflammation responses, protecting nerve cell from apoptosis, and improving mitochondrial function and blood flow to the brain. The purpose of the review is to provide comprehensively and systematically information about the neuroprotective constituents of FMHCMs from Leguminosae species, and lay the basis for the future developments of FMHCMs from Leguminosae species.

Keywords: neuroprotective effect; nervous system; food and medicine homologous Chinese Medicine; Leguminosae; bioactive constituents

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1 Introduction

The nervous system plays a vital role in mastering the physiological and bodily functions. Once the nervous system injured by diseases or neurotoxic substances, the body will be in dysfunction and the health of human will be threatened. With the increasing population aging, the neurological diseases, especially those happened in the central nervous system (CNS), will become a heavy burden in worldwide[1, 2]. The most common CNS diseases include neurodegenerative diseases, such as Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Alzheimer's disease (AD). Although the pathogenesis of these diseases was different, the neurological function was all impaired. Hence, a variety of neuroprotective therapeutic strategies have been carried out to reduce brain damage and preserve or restore neurological function in PD, HD, AD, ALS, and stroke disease model[3-5]. It demonstrated that the neuroprotective mechanism exerted through reducing oxidative stress, inhibiting neuroinflammation response, protecting nerve cell from apoptosis, and improving mitochondrial function and blood flow to the brain[6, 7].

Food and Medicine Homologous Chinese Medicines (FMHCMs) can be used as medicine and food, which play a vital role in improving human's health. To date, there are 110 kinds of FMHCMs recorded in Chinese pharmacopoeia. Numerous studies have revealed that various types of components have been isolated and identified from FMHCMs, including triterpenoids, flavonoids, polyphenols, polysaccharides, and so on. Modern biological studies have indicated that these components exhibited diverse bioactivities including neuroprotective, nephroprotective, antitumor, and anti-inflammatory activities. FMHCMs are from 40 families, including Leguminosae, Cornaceae, Zingiberaceae, and so on. *Gastrodia elata*, as one of the commonly used FMHCMs, showed significant anti-inflammatory, neuroprotective

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and analgesic effects[8-12]. Moreover, *Cornus officinalis*, a member of Cornaceae, exhibited the rheumatoid arthritis, and diabetic nephropathy, and possess neuroprotective effect[13-17]. In addition, *Zingiber officinale* which was from Zingiberaceae had the gastroprotective, anti-obesity and weight lowering, and neuroprotective effects[18-20]. Leguminosae contained the largest number of FMHCMs, including *Astragalus membranaceus* (*Astragalus membranaceus* (Fisch.) Bge.), *Glycyrrhiza uralensis* Fisch. (*Glycyrrhiza inflata* Bat. or *Glycyrrhiza glabra* L.), *Cassia obtusifolia* L. (*Cassia tora* L.), *Vigna umbellata* Ohwi et Ohashi (*Vigna angularis* Ohwi et Ohashi), *Glycine max* (L.) Merr., *Sophora japonica* L., *Canavalia gladiata* (Jacq.) DC., *Pueraria lobata* (Willd.) Ohwi, and *Dolichos lablab* L. Evidence showed that a lot of constituents from FMHCMs of Leguminosae with neuroprotective effects exhibit potential in prevention and curing of nervous system diseases.

The present review summarized the neuroprotective effect of chemical constituents from FMHCMs in Leguminosae and lay the foundation for further research on the treatment of neurological diseases.

2 The ethnobotany of FMHCMs from Leguminosae species

There are 9 kinds of FMHCMs from Leguminosae. *A. membranaceus* (also named "huang qi"), had a long history of medicinal use as Chinese herbal medicine. It was first recorded in Shen Nong's Herbal Classic, and traditionally used to tonify Qi. *G. uralensis*, also known as "Gancao" in Chinese, was firstly recorded in Shen Nong's Herbal Classic. It was traditionally used to harmonize the effect of other herbal medicines in TCM prescriptions. *P. lobata,* widely known as "Gegen", which was traditionally used to treat fever, diarrhea, emesis, cardiac dysfunctions, liver injury, weight loss, and toxicosis. *G. max* was traditionally used to nourish the heart. Traditionally, *C. obtusifolia* was used to clear heat, brighten eyes, and moisten bowel. *V. umbellate* was traditionally used to enrich the blood. *S. japonica* was used in traditional medicine to cool the blood and stop bleeding. *C. gladiate and D. lablab* could all tonify the stomach, intestines, and spleen.

3 Methodology

The literatures for this review were carried out by searching both English and Chinese electronic databases including PubMed, Google Scholar, Web of Science, ACS, ScienceDirect, and CNKI. All related literatures were downloaded, and the full text of the literatures was read to pick the related information.

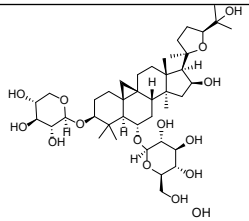
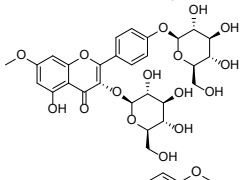
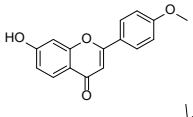
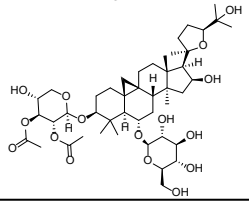
4 Chemical constituents from FMHCMs of Leguminosae species with neuroprotective effects on nervous system

In the present review, 25 small molecules with neuroprotective effect in different nerve system disease model were summarized. Of them, astragaloside IV, complanatuside A, formononetin, astragaloside I, astragaloside III, astragaloside, calycosin are from *A. membranaceus* or *A. membranaceus* (Fisch.) Bge. Puerarin and daidzein are from *P. lobata* (Willd.) Ohwi. Isoliquiritigenin, glycyrrhizic acid, liquiritigenin, licochalcone E, licochalcone A, licopyranocoumarin, glycyrurol, dehydroglyasperin C, licochalcone B, liquiritin, and glabridin are from *G. uralensis* Fisch., *G. inflata* Bat., or *G. glabra* L. Genistein, cyanidin-3-glucoside, soyasaponin I, glyceollins, and 3-*O*-[*β*-*D*-glucopyranosyl(1-2)-*β*-*D*-galactopyranosyl(1-2)-*β*-*D*-glucuronopyranosyl]olean-12-en-3*β*, 22*β*, 24-triol are from *G. max* (L.) Merr (Table 1).

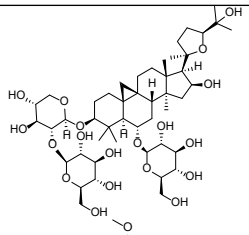
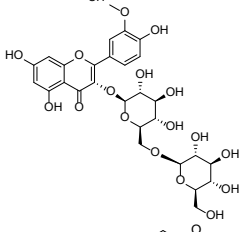
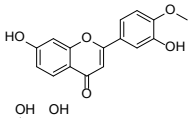
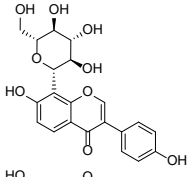
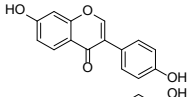
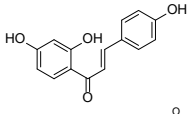
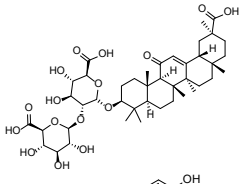
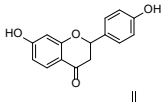
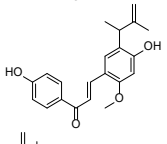
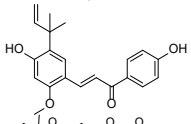
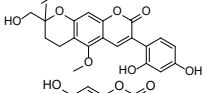
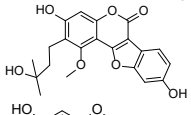
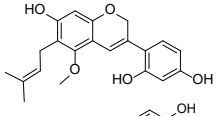
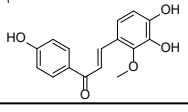
4.1 Neuroprotective effects of constituents on Alzheimer's Disease model

AD is one of the most common neurodegenerative diseases.

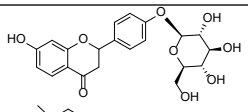
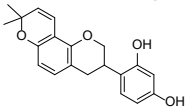
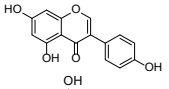
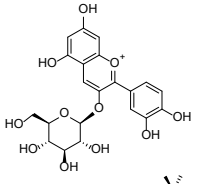
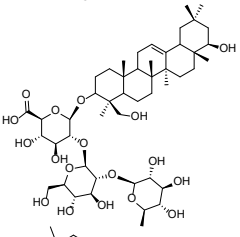
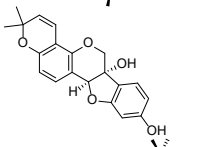
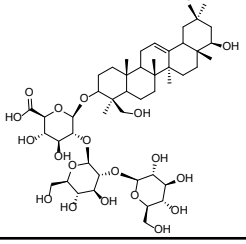
Table 1 Summary of the neuroprotective effects of constituents from medicine food homologous Chinese Medicine in Leguminosae

No.	Compound name	Molecular formula	Structure	Source	Neuroprotective effect in different disease model
1	Astragaloside IV	$C_{41}H_{68}O_{14}$		*Astragalus membranaceus*; *Astragalus membranaceus*(Fisch.) Bge.	AD [24-25] PD [39-41] Stroke [51, 56-57, 58-61] AE [74] SAH [77-78] Others [89-92]
2	Complanatuside A	$C_{28}H_{32}O_{16}$		*Astragalus membranaceus*; *Astragalus membranaceus*(Fisch.) Bge.	SCI [81]
3	Formononetin	$C_{16}H_{12}O_4$		*Astragalus membranaceus*; *Astragalus membranaceus*(Fisch.) Bge.	DPN [88]
4	Astragaloside I	$C_{45}H_{72}O_{16}$		*Astragalus membranaceus*; *Astragalus membranaceus*(Fisch.) Bge.	Stroke [62]

(Continued)

No.	Compound name	Molecular formula	Structure	Source	Neuroprotective effect in different disease model
5	Astragaloside III	$C_{47}H_{78}O_{19}$		*Astragalus membranaceus*; *Astragalus membranaceus*(Fisch.) Bge.	Stroke [62]
6	Astragaloside	$C_{28}H_{32}O_{17}$		*Astragalus membranaceus*; *Astragalus membranaceus*(Fisch.) Bge.	Others [93]
7	Calycosin	$C_{16}H_{12}O_5$		*Astragalus membranaceus*; *Astragalus membranaceus*(Fisch.) Bge.	PD [42]
8	Puerarin	$C_{21}H_{20}O_9$		*Pueraria lobata*(Willd.) Ohwi	AD [27-32] PD [43-46] Stroke [64-65] SAE [85] Others [94-97]
9	Daidzein	$C_{15}H_{10}O_4$		*Pueraria lobata*(Willd.) Ohwi; *Glycine max* (L.) Merr.	Stroke [63]
10	Isoliquiritigenin	$C_{15}H_{12}O_4$		*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza inflata* Bat.; *Glycyrrhiza glabra* L.	AD [34] PD [47] Others [98, 102-104]
11	Glycyrrhizic acid	$C_{42}H_{62}O_{16}$		*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza inflata* Bat.; *Glycyrrhiza glabra* L.	Stroke [66] Others [98-100]
12	Liquiritigenin	$C_{15}H_{12}O_4$		*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza inflata* Bat.; *Glycyrrhiza glabra* L.	Others [98, 102-103]
13	Licochalcone E	$C_{21}H_{22}O_4$		*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza inflata* Bat.; *Glycyrrhiza glabra* L.	PD [48]
14	Licochalcone A	$C_{21}H_{22}O_4$		*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza inflata* Bat.; *Glycyrrhiza glabra* L.	AD [33]
15	Licopyranocoumarin	$C_{21}H_{20}O_7$		*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza inflata* Bat.; *Glycyrrhiza glabra* L.	PD [49]
16	Glycyrurol	$C_{21}H_{20}O_7$		*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza inflata* Bat.; *Glycyrrhiza glabra* L.	PD [49]
17	Dehydroglyasperin C	$C_{21}H_{22}O_5$		*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza inflata* Bat.; *Glycyrrhiza glabra* L.	AD [26]
18	Licochalcone B	$C_{16}H_{14}O_5$		*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza inflata* Bat.; *Glycyrrhiza glabra* L.	Others [107]

(Continued)

No.	Compound name	Molecular formula	Structure	Source	Neuroprotective effect in different disease model
19	Liquiritin	$C_{21}H_{22}O_9$		*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza inflata* Bat.; *Glycyrrhiza glabra* L.	Stroke [67]
20	Glabridin	$C_{20}H_{20}O_4$		*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza inflata* Bat.; *Glycyrrhiza glabra* L.	Stroke [68]
21	Genistein	$C_{15}H_{10}O_5$		*Glycine max* (L.) Merr.	AD [35] Stroke [69]
22	Cyanidin-3-glucoside	$C_{21}H_{21}O_{11}^+$		*Glycine max* (L.) Merr.	Stroke [70]
23	Soyasaponin I	$C_{48}H_{78}O_{18}$		*Glycine max* (L.) Merr.	Others [100]
24	Glyceollins	$C_{20}H_{18}O_5$		*Glycine max* (L.) Merr.	Others [106]
25	3-*O*-[*β*-*D*-glucopyranosyl(1-2)-*β*-*D*-galactopyranosyl(1-2)-*β*-*D*-glucuronopyranosyl]olean-12-en-3*β*,22*β*,24-triol	$C_{48}H_{78}O_{19}$		*Glycine max* (L.) Merr.	Others [105]

The aggregation of amyloid β (Aβ) and hyperphosphorylation of tau are known to be the major pathogenic factors, which will aggravate neuro-inflammation response, impair synaptic plasticity, and induce neuronal cell death[21-23]. Constituents from medicine food homologous Chinese Medicine in Leguminosae with neuroprotective effects on AD were summarized and shown in Table 2 and Fig. 1.

Astragaloside IV could suppresses the Aβ-induced neuronal cell death and apoptosis, whereas, increased BDNF (brain-derived neurotrophic factor) and PPARγ expression in HT22 cells. Moreover, astragaloside IV improved Aβ-induced memory impairment and reduced apoptosis of hippocampal neurons. In addition, astragaloside IV suppressed the Aβ-induced reduction in BDNF by promoting PPARγ activation in the hippocampus[24]. Pretreatment of astragaloside IV significantly increased the viability of neuronal cells, reduced apoptosis, decreased the generation of intracellular reactive oxygen species (ROS) and decreased mitochondrial superoxide in Aβ(1-42)-induced neurotoxicity of SK-N-SH cells[25]. Dehydroglyasperin C could significantly reduce cytotoxicity and ROS generation in glutamate-induced HT22 cells[26]. Puerarin treatment ameliorated cognitive impairment and decreased the neuronal apoptosis in the hippocampus of Aβ(1-42)-induced rats. Besides, puerarin inhibited the expression of Bad and caspase-9, the key proteins related to apoptosis[27]. It was also found that puerarin could inhibit oxidative-stress-induced apoptosis through down-regulation of Bax/Bcl-2 ratio and caspase-3. Therefore, puerarin may act as an intracellular ROS scavenger, and protect neurons against oxidative-stress-induced apoptosis[28,29]. Puerarin also displayed neuroprotective effect through suppressing the Aβ-induced cytotoxicity in primary hippocampal neurons and attenuating Aβ-induced ROS production[30]. In the Aβ(25-35)-induced apoptosis in PC12 cells, puerarin could increase the cell viability through suppress the expression of proapoptotic proteins such as cytochrome c, Bax, and the production of ROS[31,32]. Licochalcone A and liquiritigenin could suppress neuronal apoptosis through increasing the expression of Bcl-2 and decreasing the expression of IGFBP2, Bad, Bax and cleaved caspase 3. The neuroprotective effect of licochalcone A and liquiritigenin might decrease oxidative stress and microglia-mediated inflammation[33]. Isoliquiritigenin could prevent Aβ(25-35)-induced neuronal apoptotic death by interfering with the increases of $[Ca^{2+}]_i$ and ROS[34]. Genistein could alleviate Aβ(25-35)-induced cell apoptosis and prevent Aβ(25-35)-induced TNF-α and IL-1β release in C6 cells[35].

Table 2 The suggested neuroprotective mechanisms of constituents from medicine food homologous Chinese Medicine in Leguminosae

Disease type	Bioactive constituents	Suggested Mechanism	Cell or animal models	References
AD	Astragaloside IV	BDNF and PPARγ ↑, memory ability ↑, apoptotic hippocampal neurons ↓	HT22 cells and Aβ(1-42) oligomers-induced mice	[24]
		The viability of neuronal cells ↑, cell apoptosis ↓, intracellular reactive oxygen species ↓, mitochondrial superoxide ↓	SK-N-SH cells induced by Aβ(1-42)	[25]
	Dehydroglyasperin C	Cytotoxicity and reactive oxygen species ↓	Glutamate-induced HT22 cells	[26]
	Puerarin	Cognitive ability ↑ of Aβ(1-42)-induced rats, apoptotic hippocampal neurons ↓, Bad and caspase-9 ↓	Aβ(1-42)-induced rats	[27]
		Bax↓, Bcl-2 ↑, caspase-3 ↓	Neurons induced by oxidative-stress-	[28-29]
		Cytotoxicity ↓, reactive oxygen species ↓	Primary hippocampal neurons induced by Aβ	[30]
		Cell viability ↑, cytochrome c ↓, Bax ↓, reactive oxygen species ↓	PC12 cells induced by Aβ(25-35)	[31-32]
	Licochalcone A	Neuronal apoptosis ↓, Bcl-2 ↑, IGFBP2 ↓, Bad ↓, Bax ↓, cleaved caspase 3 ↓	Hippocampal neurons in low pH	[33]
	Liquiritigenin	Neuronal apoptosis ↓, Bcl-2 ↑, IGFBP2 ↓, Bad ↓, Bax ↓, cleaved caspase 3 ↓	Hippocampal neurons in low pH	[33]
	Isoliquiritigenin	Neuronal apoptosis ↓ induced by Aβ(25-35), $[Ca^{2+}]_I$ ↓, reactive oxygen species ↓	Neurons induced by Aβ(25-35)	[34]
	Genistein	Cell apoptosis ↓, TNF-α and IL-1β ↓	C6 cells induced by Aβ(25-35)	[35]
PD	Astragaloside IV	Motor behavior ↑, dopaminergic neurons degeneration ↓, neuroinflammation and oxidative stress response ↓	MPTP-induced PD mice	[39]
		Cell viability ↑, microtubule associated protein 2 ↑, cell apoptosis ↓, inflammation and oxidative stress response ↓	6-OHDA-treated SH-SY5Y cells	[40]
		The loss and apoptosis of SH-SY5Y cells ↓, α-synuclein ↓, tyrosine hydroxylase ↑	Hydrogen peroxide induced SH-SY5Y cells	[41]
	Calycosin	Cytotoxicity ↓, motor behavior ↑, dopamine levels ↑	MPTP-induced PD mice	[42]
	Puerarin	Cell viability ↑ of SH-SY5Y, tyrosine hydroxylase ↑, vesicular monoamine transporter 2 ↑, dopamine levels ↑, motor behavior ↑	Rotenone-induced PD cells and rats	[43]
		Cell apoptosis↓, cytochrome c and caspase-3 ↓, loss of mitochondrial membrane potential ↓	PC12 induced by MPP+	[44]
		GDNF ↑, reactive oxygen species ↓, dopaminergic neuron degeneration and dopamine depletion ↓	MPTP-induced PD mice	[45]
		Neuronal apoptosis and death ↓, Bax ↓, dopamine and dihydroxyphenylacetic acid ↑, GDNF ↑	6-OHDA-induced rats	[46]
	Isoliquiritigenin	Neurotoxicity ↓, Bax and caspase 3 ↓, Bcl-2 and BNDF ↑	A dopaminergic SN4741 cell line induced by 6-OHDA	[47]
	Licochalcone E	Cell viability ↑	SH-SY5Y induced by 6-OHDA	[48]
	Licopyranocoumarin	Cell viability ↑, loss of mitochondrial membrane potential ↓, reactive oxygen species ↓	PC12 induced by MPP+	[49]
	Glycyrurol	Cell viability ↑, loss of mitochondrial membrane potential ↓, reactive oxygen species ↓	PC12 induced by MPP+	[49]
Stroke	Astragaloside IV	NLRP3 inflammasome activation ↓, reactive oxygen species ↓, inflammatory cytokines ↓	Cerebral ischemic mice	[56]
		Neurological function ↑, cerebral infarction and neuronal apoptosis ↓, Fas, FasL, Caspase-8, and Bax/Bcl-2 ↓	Ischemia reperfusion injured rat	[57]
		Infarct volume ↓, behavioral function ↑, BNDF ↑	MCAO rats	[58]
		Neuronal apoptosis ↓, mitochondrial integrity ↑,	Neuronal cell induced by OGD	[59]
		Proliferative ability of splenic cells ↑, activation of hypothalamic-pituitary-adrenal ↓	MCAO mice	[60]
		Neurological deficits ↓, neuronal death ↓	MCAO rats	[51]
		Aldolase C ↑, dihydrolipoamide dehydrogenase and triose-phosphate isomerase ↑	Ischemia-reperfusion injury rat	[61]
	Astragaloside I	Proliferative ability of neural stem cells ↑, neurological and motor function ↑	MCAO mice	[62]
	Astragaloside III	Proliferative ability of neural stem cells ↑, neurological and motor function ↑	MCAO mice	[62]
	Daidzein	Neurological function ↑, infarct volume ↓, cleaved caspase-3 ↓, BDNF ↑	Ischemia-reperfusion injury rat	[63]
	Puerarin	Hippocampal cell death ↓	Hippocampal neuron	[64]
		Infarct volume ↓, apoptosis and necrosis in the dorsolateral cortex ↓	MCAO rats	[65]
	Glycyrrhizic acid	Infarct volume ↓, neurological function ↑	MCAO rats	[66]
	Liquiritin	Brain injury ↓, cell apoptosis ↓	Ischemia-reperfusion injury mouse	[67]
	Glabridin	Cortical neurons survival ↑, Bcl-2 ↑, Bax ↓, caspase 3 ↓	Rat cortical neurons induced by staurosporine	[68]
	Genistein	Lactate dehydrogenase ↓, cleaved caspase-3 ↓	Cortical cells induced by OGD	[69]
	Cyanidin-3-glucoside	Neuronal cell death ↓, reactive oxygen species ↓, loss of mitochondrial membrane potential ↓	Primary neurons induced by OGD	[70]

(Continued)

Disease type	Bioactive constituents	Suggested Mechanism	Cell or animal models	References
AE	Astragaloside IV	Changed astrocytes from A1 to a neuroprotective A2 phenotype in the spinal cord, neurons apoptosis ↓	EAE mice	[74]
SAH	Astragaloside IV	Antioxidant capacity ↑, lipid peroxides ↓, Nrf2/HO-1 signaling pathway ↑, ferroptosis ↓	SAH-induced early brain injury in rats	[77]
		Neuronal death and injury ↓, cleaved caspase 3 ↓	SAH-induced early brain injury in rats	[78]
SCI	Complanatuside A	Proinflammatory mediators ↓, neuronal cell apoptosis ↓, motor function ↑	BV2 cell and spinal cord injury in mice	[81]
SAE	Puerarin	Neurobehavioral scores ↑, survival rate ↑, pathological damage ↓, NSE and S100β ↓	SAE rats	[85]
DPN	Formononetin	Oxidative stress ↓, mitochondrial dysfunction ↓, NGF ↑	RSC96 Schwann cells induced by high glucose	[88]
		Number and diameter of myelinated nerve fibers ↑, motor nerve conduction velocity and action potential amplitude ↑	Sciatic nerve injury mouse	[89]
	Astragaloside IV	Neurotoxicity ↓, cell apoptosis ↓	RGC-5 cells induced by H_2O_2	[90-91]
		Protect the integrity of blood-brain barrier, zo-1 ↑, occluding ↑, claudin-5 ↑, inflammatory responses ↓, reactive oxygen species ↓, Nrf2 ↑	LPS stimulated bEnd.3 cells and mice	[92]
	Astragaloside	Learning and memory ability ↑, protected morphological structure of neurons	Microwave exposure induced rat	[93]
		Neuronal injury ↓,	Cadmium-induced neuronal injury rat	[94]
	Puerarin	Cells damage ↓, PARP, Bax and caspase-3 ↓, Bcl-2 ↑	Schwann cells induced by glucose fluctuation	[95]
		Caspase-3, cytochrome c, and Bax ↓, Bcl-2 ↑, GABA, dopamine, 5-serotonin and norepinephrine ↑	3-Nitropropionic-acid induced rats	[96-97]
Others		Hippocampus injury ↓, cell apoptosis ↓, oxidative stress ↓	*Semen Strychni*-induced rats	[98]
	Glycyrrhizic acid	Neuronal death ↓	Hippocampus neurons induced by kainic acid	[99]
		Cell viability ↑, ameliorate abnormal alterations in mitochondria, Bax, cleaved caspase 3 and cytochrome C ↓	PC12 cells induced by glutamate	[100]
		Hippocampus injury ↓, cell apoptosis ↓, oxidative stress ↓	*Semen Strychni*-induced rats	[98]
	Liquiritigenin	Neuronal cells damage ↓, reactive oxygen species ↓, Bax ↓, Bcl-2 ↑	HT22 hippocampal neuronal cells induced by glutamate	[102-103]
		Hippocampus injury ↓, cell apoptosis ↓, oxidative stress ↓	*Semen Strychni*-induced rats	[98]
	Isoliquiritigenin	Neuronal cells damage ↓, reactive oxygen species ↓, Bax ↓, Bcl-2 ↑	HT22 hippocampal neuronal cells induced by glutamate	[102-103]
		Reactive oxygen species ↓, mitochondrial fission ↓, neuronal cell death ↓	HT22 hippocampal neuronal cells induced by glutamate	[104]
	Soyasaponin I	Learning and memory ability ↑, neurogenesis and neurite outgrowth ↑	Memory deficient model rats	[101]
	3-*O*-[*β*-*D*-glucopyranosyl(1-2)-*β*-*D*-galactopyranosyl(1-2)-*β*-*D*-glucuronopyranosyl]oleanan-12-en-3*β*, 22*β*, 24-triol	Cell toxicity ↓	Rat cortical cell induced by glutamate	[105]
	Glyceollins	Cell cytotoxicity ↓, reactive oxygen species ↓, cognitive function ↑	Primary cortical neuron induced by glutamate and scopolamine-induced mice	[106]
	Licochalcone B	Cell cytotoxicity and apoptosis ↓, caspase-3 ↓	PC-12 cells induced by H_2O_2	[107]

4.2 Neuroprotective effects of constituents on Parkinson's Disease model

PD is another common neurodegeneration disease. The pathological characteristic of the diseases is the progressive loss of dopaminergic neurons in substantia nigra compacta and striatum[36-38]. Constituents from medicine food homologous Chinese Medicine in Leguminosae with neuroprotective effects on PD were summarized and shown in Table 2 and Fig. 1.

Astragaloside IV could alleviate motor impairment, protect dopaminergic neurons degeneration, and inhibit neuroinflammation and oxidative stress in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced PD mice[39]. Astragaloside IV also significantly increased the cell viability and microtubule associated protein 2 (MAP2) expression, and repaired the morphological damage of SH-SY5Y cells induced by 6-hydroxydopamine (6-OHDA). In addition, astragaloside IV decreased apoptosis rate, the production of ROS and Bax/Bcl-2 ratio induced by 6-OHDA. The reported results showed that astragaloside IV had neuroprotective effect through enhancing the cell viability, and inhibiting apoptosis, inflammation and oxidative stress of 6-OHDA-treated SH-SY5Y cells[40]. In another study, astragaloside IV could suppress the loss and apoptosis of human neuronal cells (SH-SY5Y cells) induced by hydrogen peroxide (H_2O_2). Besides, it decreased the expression of α-synuclein and increased the expression of tyrosine hydroxylase (TH)[41]. Calycosin decreased microglia-mediated cytotoxicity *in vitro*, and improved motor behavior, suppressed the loss of dopamine

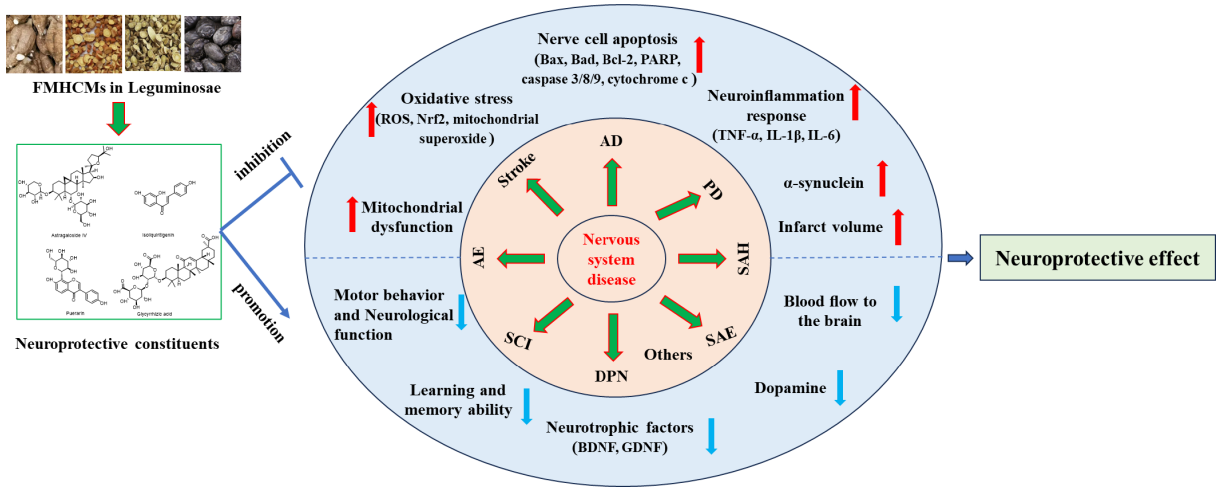


Figure 1 Schematic diagram of the potential neuroprotective mechanism of constituents from medicine food homologous Chinese Medicine in Leguminosae against nervous system disease.

(DA) neurons and inhibited the activation of microglial cells in MPTP-induced PD mice[42]. Puerarin could protect SH-SY5Y cells from rotenone toxicity, and up-regulated TH and vesicular monoamine transporter 2 (VMAT2) expression and dopamine levels in dopaminergic cells. Besides, it alleviated behavioral defects of rotenone-induced parkinsonian animals. Thus, puerarin could protect the dopaminergic neurons against rotenone toxicity by alleviating the oxidative stress and apoptosis in a PD cellular model[43]. Puerarin also could protect PC12 cells against 1-methyl-4-pehenylpyridinium (MPP+)-induced apoptosis, inhibit the release of cytochrome c and the activity of caspase-3, and prevent loss of mitochondrial membrane potential (MMP). These findings suggested that puerarin could block MPP+-mediated apoptosis by mitochondria-dependent caspase cascade[44]. In another study, puerarin could up-regulates GDNF (glial-cell-line-derived neurotrophic factor) expression and down-regulated the production of ROS against MPTP-induced PD model in mice. Moreover, it could ameliorate MPTP-induced motor dysfunctions, dopaminergic neuron degeneration and dopamine depletion[45]. In addition, puerarin could prevent neuronal apoptosis and death, reduce the expression of Bax, reverse the decrease of dopamine and dihydroxyphenylacetic acid levels, and increase the GDNF in striatum in the 6-OHDA-induced rats[46]. Isoliquiritigenin could protect 6-OHDA-induced neurotoxicity, inhibit the expression of Bax and caspase 3, the cytochrome c release, and increase the expression of Bcl-2 and BNDF (brain-derived neurotrophic factor) in a dopaminergic SN4741cell line induced by 6-OHDA. These results suggested that isoliquiritigenin could protect dopaminergic cells under oxidative stress conditions by regulating the apoptotic process[47]. Licochalcone E could protect dopaminergic SH-SY5Y cells against 6-OHDA-induced cell death[48]. Licopyranocoumarin and glycyrurol markedly blocked MPP+-induced differentiated PC12 cell death and disappearance of mitochondrial membrane potential, and inhibited the production of ROS[49].

4.3 Neuroprotective effects of constituents on Stroke model

Stroke, especially, ischemic stroke accounted for about 85%, remains the leading cause of death in China and a second major cause of death worldwide[50]. The pathophysiology of ischemic stroke is characterized by the overproduction of ROS, neural cell apoptosis, occurrence of oxidative stress and neuroinflammation[51-55]. Constituents from medicine food homologous Chinese Medicine in Leguminosae with neuroprotective effects on stroke were summarized and shown in Table 2 and Fig. 1.

It was found that astragaloside IV possessed neuroprotective effects against transient cerebral ischemia and reperfusion through suppressing NLRP3 inflammasome activation and ROS production, and reducing overactivation of microglia and the overexpression of inflammatory cytokines in the hippocampus[56]. In another study, astragaloside IV could significantly attenuate the neurological deficit in rats with ischemia reperfusion injury, and reduce cerebral infarction and neuronal apoptosis. Furthermore, the molecular mechanism study showed that astragaloside IV inhibited the mRNA level of Fas, FasL, caspase-8, and Bax/Bcl-2, and the protein expression of caspase-8, Bid, cleaved caspase 3 and cytochrome c after ischemia reperfusion[57]. Astragaloside IV could reduce the infarct volume, improve behavioral function and enhance neurogenesis and the expression of BNDF in MCAO (middle cerebral artery occlusion) rats. Therefore, astragaloside IV might be a promising therapeutic agent for ischemic stroke[58]. Astragaloside IV also could protect neuronal survival against oxygen glucose deprivation (OGD) and reduce neuronal apoptosis. Besides, it maintained the mitochondrial integrity, and prevented AIF release from mitochondria[59]. Astragaloside IV enhanced proliferative ability of splenic cells, inhibited apoptosis and activation of hypothalamic-pituitary-adrenal (HPA) axis in MCAO mice[60]. In the other study, astragaloside IV could improve delayed ischemic neurological deficits and decrease neuronal death[51]. Moreover, astragaloside IV acted as neuroprotectors through regulating the expression of aldolase C, dihydrolipoamide dehydrogenase and triose-phosphate isomerase in ischemia-reperfusion injury rat model[61]. Astragaloside I and astragaloside III could promote the proliferation of neural stem cells (NSCs) *in vitro* and *in vivo*. In addition, astragaloside I and III improved neurological and motor function of MCAO mice. These findings suggested that astragaloside I and III could provide a protective effect on experimental stroke mainly by enhancing proliferation of neural stem cells[62]. Daidzein could down-regulated neurological impairment scores and volume of infarct in rat after ischemia-reperfusion (I/R). Besides, daidzein also attenuated activation of cleaved caspase 3, and enhanced the activation of BDNF in I/R-treated mice[63]. Puerarin could prevent hippocampal cell death during extracellular low pH[64]. In another

study, puerarin markedly decreased the infarct volume, the percentages of apoptosis and necrosis in the dorsolateral cortex in MCAO rats. These findings revealed that the neuroprotection of puerarin against cerebral ischemia is associated with anti-apoptosis[65]. Glycyrrhizic acid could inhibit infarct formation in the postischemic brain with an extended therapeutic window, and ameliorate motor impairment and neurological deficits after MCAO[66]. Liquiritin could protect mouse brain from I/R injury, and suppressed the cell apoptosis[67]. Glabridin could promote cell survival and the expression of Bcl-2, whereas suppress the expression of Bax protein and caspase 3 induced by staurosporine in cultured rat cortical neurons[68]. Genistein and daidzein significantly reduced lactate dehydrogenase (LDH) release and the expression of cleaved caspase-3 after OGD in cortical cells[69]. Cyanidin-3-glucoside could markedly prevent neuronal cell death and excessive production of ROS, and preserve mitochondrial membrane potential in primary neurons induced by OGD[70].

4.4 Neuroprotective effects of constituents on autoimmune encephalomyelitis model

Multiple sclerosis (MS) is an inflammatory demyelinating disease caused by immune system disorders, genetic susceptibility, and environmental exposures[71]. The experimental autoimmune encephalomyelitis (EAE) is a commonly used animal model for MS, characterized by the progressive enlargement of an area of demyelination, accompanied by the infiltration of inflammatory cells, activation of glial cells, and the loss of axons[72-74]. Constituents from medicine food homologous Chinese Medicine in Leguminosae with neuroprotective effects on autoimmune encephalomyelitis were summarized and shown in Table 2 and Fig. 1.

Astragaloside IV inhibited the neurotoxic M1 microglia/macrophage phenotype, accelerated the change of astrocytes from A1 to a neuroprotective A2 phenotype in the spinal cord, and protected neurons from apoptosis in EAE mice. These results showed that astragaloside IV could improve paralysis and pathology of EAE, and might be a potential and promising drug for multiple sclerosis treatment[74].

4.5 Neuroprotective effects of constituents on subarachnoid hemorrhage model

Subarachnoid hemorrhage (SAH) is a severe type of stroke with high morbidity and mortality rate[75-77]. Early brain injury (EBI) refers to the direct injury in the whole brain that occurs within 72 h after the induction of SAH and is regarded as the major cause of the dismal prognosis of SAH patients[77]. Constituents from medicine food homologous Chinese Medicine in Leguminosae with neuroprotective effects on SAH were summarized and shown in Table 2 and Fig. 1.

Astragaloside IV could enhance the antioxidant capacity, suppress the accumulation of lipid peroxides, stimulate Nrf2/HO-1 signaling pathway and attenuate ferroptosis after SAH-induced early brain injury[77]. The other study showed that astragaloside IV could down-regulate the protein expression of cleaved caspase 3, inhibit neuronal death, and attenuate neuronal injury in the cortex at 24 h after SAH-induced early brain injury[78].

4.6 Neuroprotective effects of constituents on spinal cord injury model

Spinal cord injury (SCI) is a catastrophic condition commonly observed in clinic[79]. It often causes permanent motor and sensory dysfunction, which can cause serious physiological, psychological, and economical issues[80,81]. Constituents from medicine food homologous Chinese Medicine in Leguminosae with neuroprotective effects on SCI were summarized and shown in Table 2 and Fig. 1.

Complanatuside A could inhibit the release of proinflammatory mediators, and prevent neuronal cell apoptosis caused by activated BV2 cells. Besides, it could accelerate the restoration of motor function in mice after SCI[81].

4.7 Neuroprotective effects of constituents on sepsis-associated encephalopathy model

Sepsis-associated encephalopathy (SAE) is one of the most common complications in the acute stage of sepsis and up to 70% of sepsis patients eventually develop SAE[82]. SAE may even lead to long-term cognitive impairment in the later stage[83-85]. Constituents from medicine food homologous Chinese Medicine in Leguminosae with neuroprotective effects on SAE were summarized and shown in Table 2 and Fig. 1.

Puerarin could improve the signs, neurobehavioral scores, and survival rate of SAE rats. In addition, it alleviated pathological damage and reduced the release of brain injury markers NSE and S100β in SAE rats. Thus, puerarin might play a role in brain protection and provide a novel strategy for the treatment of SAE[85].

4.8 Neuroprotective effects of constituents on diabetic peripheral neuropathy model

Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes, which is characterized by spontaneous pain, hyperalgesia, and abnormal pain[86-88]. Constituents from medicine food homologous Chinese Medicine in Leguminosae with neuroprotective effects on DPN were summarized and shown in Table 2 and Fig. 1.

Formononetin could inhibit oxidative stress, alleviate mitochondrial dysfunction, and increase the nerve growth factor (NGF) release in high glucose-induced RSC96 Schwann cells. Formononetin might become a SIRT3 (a member of NAD^+-dependent deacetylase enzymes located in the mitochondrial) activator for treatment of peripheral nerve regeneration related diseases, such as diabetic peripheral neuropathy[88].

4.9 Neuroprotective effects of constituents on other neurological diseases model

In a mouse model of sciatic nerve injury, the treatment of astragaloside IV could increase the number and diameter of myelinated nerve fibers, motor nerve conduction velocity and action potential amplitude. The result revealed that astragaloside IV contributed to sciatic nerve regeneration and functional recovery in mice[89]. Astragaloside IV also protected RGC-5 cells against H_2O_2-induced neurotoxicity and PC12 cells against glutamate-induced neurotoxicity, respectively, and reduced apoptosis of RGC-5 cells induced by H_2O_2[90,91]. Astragaloside IV also could protect the integrity of blood-brain barrier (BBB) through increasing the expression of tight junction proteins such as zo-1, occludin and claudin-5, inhibiting the inflammatory responses, alleviating ROS level and activating Nrf2 antioxidant pathway in LPS stimulated bEnd.3 cells or in brain microvessels of LPS induced mice[92]. In rat model of microwave exposure,

astragaloside promoted recovery of learning and memory ability, and protected morphological structure of neurons in hippocampus[93]. In rat model of cadmium-induced neuronal injury, puerarin protected neuronal from injury *in vitro* and *in vivo*[94]. In the glucose fluctuation-induced cell injury model, puerarin could protect Schwann cells from damage, suppress activation of apoptosis related proteins including PARP and caspase-3, up-regulate the expression of Bcl-2, and down-regulate the intracellular distribution of Bax[95]. In rat model of 3-nitropropionic-acid induced neurotoxicity, puerarin could down-regulate the activity of caspase-3, cytochrome c, and Bax, up-regulate the expression of Bcl-2, and increase the levels of neurotransmitters of GABA, dopamine, 5-serotonin and norepinephrine[96, 97]. In the rat model of *Semen Strychni*-induced hippocampus injury, glycyrrhizic acid, liquiritigenin, and isoliquiritigenin could ameliorate the hippocampus injury and attenuate cell apoptosis and oxidative stress in brains[98]. In the model of kainic acid (KA)-induced neuronal death in the hippocampus, glycyrrhizic acid could decrease the neuronal death[99]. Glycyrrhizic acid could improve cell viability, ameliorate abnormal alterations in mitochondria, down-regulate the expressions of Bax and cleaved caspase 3 and the release of cytochrome c release in differentiated PC12 cells induced by glutamate[100]. In the ibotenic acid-treated rat model, soyasaponin I could improve learning and memory impairment of rats, promote neurogenesis and neurite outgrowth[101]. In glutamate-induced cytotoxicity and oxidative stress model, isoliquiritigenin and liquiritigenin could protect HT22 hippocampal neuronal cells from damage and decrease the ROS production and the ratio of Bax/Bcl-2[102, 103]. Similar study showed that isoliquiritigenin could decrease the ROS production and mitochondrial fission and protect neuronal cell from death[104]. 3-*O*-[*β*-*D*-glucopyranosyl (1-2)-*β*-*D*-galactopyranosyl(1-2)-*β*-*D*-glucuronopyranosyl]olean-12-en-3*β*, 22*β*, 24-triol exhibited significant neuroprotective activities against glutamate-induced toxicity in rat cortical cell[105]. Glyceollins could attenuate glutamate-induced cytotoxicity in primary cortical neuron and inhibit the ROS production. Moreover, glyceollins attenuated scopolamine-induced cognitive impairment of mice[106]. Licochalcone B was found to reduce cell cytotoxicity and apoptosis of PC-12 cells induced by H_2O_2 and to suppress the level of cleaved caspase-3[107].

5 Conclusion and discussion

In this review, 25 bioactive constituents from FMHCMs of Leguminosae were summarized. These compounds showed neuroprotective effects on nerve system diseases, such as Parkinson's disease, Huntington's disease, Alzheimer's disease, ischemia-reperfusion injury, autoimmune encephalomyelitis, subarachnoid hemorrhage, spinal cord injury, sepsis-associated encephalopathy, and diabetic peripheral neuropath. The review firstly summarized the constituents from FMHCMs of Leguminosae with anti-neuroinflammation, anti-oxidative stress effects, anti-apoptosis of nerve cells, and regulation of mitochondrial function and blood flow to the brain. These findings showed that the bioactive constituents from FMHCMs of Leguminosae possessed neuroprotective effects. On the basis, the review will provide guide for the future developments of FMHCMs of Leguminosae.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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