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A review on recent advances on nobiletin in central and peripheral nervous system diseases

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Abstract

In recent years, the role of nobiletin in neuronal disorders has received extensive attention. However, the study of nobiletin in the peripheral nervous system is limited. Nobiletin, as a compound with high fat solubility, high bioavailability and low toxicity, has been extensively studied. Accumulating scientific evidence has shown that nobiletin has a variety of biological functions in the nervous system, such as inhibiting the expression of inflammatory factors, reducing the neurotoxic response, improving the antioxidant capacity, promoting the survival of nerve cells, promoting axon growth, reducing blood–brain barrier permeability, reducing brain oedema, promoting cAMP response element binding protein expression, improving memory, and promoting mild depolarization of nerve cell mitochondria to improve antioxidative stress capacity. Accumulating studies have shown that nobiletin also protects enteric nervous system, spinal cord and sciatic nerve. To explore the new therapeutic potential of nobiletin in the nervous system, recent and relevant research progress is reviewed in this article. This will provide a new research idea for nobiletin in the nervous system.

Keywords Nobiletin, Polymethoxyflavones, Central nervous system (CNS), Enteric nervous system (ENS), Neuroprotection

Background

The advantage of natural products is that they already exist in the human diet and can avoid the adverse reactions caused by some synthetic drugs. Citrus peel, as a byproduct of fruit and a traditional Chinese herb, has been widely used since ancient times. Nobiletin, a natural extract of citrus peel, has been widely studied in nervous system diseases, such as Alzheimer's disease (AD) [12], depression [32], stroke [60, 62], amyotrophic lateral sclerosis [18], and even enteric nervous system disease [16, 46]. However, its specific molecular mechanisms are still unclear. While there are a few reviews on the effects of citrus peel or nobiletin on the nervous system, there is still no systematic description of the absorption, distribution, effect and mechanisms of nobiletin in the central and peripheral nervous systems. Therefore, we reviewed nobiletin in in the context of central and peripheral nervous system diseases. Such work may provide a state-of-the-art reference and prospective intervention strategy for central and peripheral nervous disorders.

Search strategy

We searched relevant studies by using databases including PubMed, Embase, and Web of Science restricted to April 24, 2023. The Medical Subject Headings and Embase Subject Headings resources were used for selecting the keywords and free words. Our search strategies

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included the following terms: 1# the keywords "nobiletin", "methoxyflavones", "hexamethoxyflavoneor", "polymethoxylated flavones", "citrus folium", "citrus peel" and "tangerine peel" were combined with their free words, and the Boolean logic word "OR" was used; 2# the keywords "nervous system disorders", "enteric nervous system", "central nervous system", "peripheral nervous system", "brain diseases" and "brain" were combined with their free words, and the Boolean logic word "OR" was used. The Boolean logic word "and" was used between search strategies #1 and #2. Furthermore, a manual search of reference lists in the selected articles was performed. Four additional studies were included in the original article search. Yueshan Pang and Juan Xiong independently reviewed all the identified studies and selected full papers for analysis according to the inclusion and exclusion criteria. The inclusion criteria for selecting the articles were as follows: research content related to keywords or free words. The exclusion criteria were as follows: (1) articles belonging to meeting abstracts, reviews, letters, editorials, expert opinions, and case reports; (2) literature written in a language other than English; and (3) content not related to keywords. Any discrepancies between the two investigators were determined independently by the third investigator (You Wu). The study process is shown in Fig. 1. The mechanism maps were drawn using ScienceSlides.

Absorption and distribution patterns of nobiletin

The biotransformation of nobiletin in the intestine. There are three main pathways for the entry of nobiletin into the body: oral administration, intravenous injection and intraperitoneal injection. After oral administration, nobiletin is metabolized by intestinal microbiota into more active products [29, 79]. The intestinal microbiota of healthy individuals can cause demethylation of nobiletin [7, 29]. After demethylation, flavonoids with stronger solubility and biological activity can be produced [7, 14].

The metabolism and absorption of nobiletin. Nobiletin has a higher intestinal absorption rate than other flavonoids [43]. A permeability test with an artificial membrane showed that the permeability of nobiletin was very high at both pH 4.0 and pH 7.0 [55], which indicates that nobiletin may be absorbed in the entire intestinal tract. There is a first-pass effect after nobiletin is absorbed by the intestinal tract [28]. Liver P450 reductases such as CYP2C11, CYP2C12, CYP2D1, CYP3A1 and CYP3A2 are responsible for demethylation at the 6-, 7-, 3- and 4-positions in rings A and B, whereas CYP1A1 and CYP1A2 preferentially catalyse demethylation at the 3- and 4-positions in ring B [28]. Studies have shown that almost all nobiletin undergoes demethylation after oral administration, and only a small amount of nobiletin itself was identified in the urinary metabolites [34, 35, 72]. 4'-Demethylated nobiletin is the main metabolite of nobiletin, and 24-h urine excretion only accounts for 13.19 ± 1.43% of the total amount of oral nobiletin [72]. Moreover, this secondary metabolite of nobiletin has a stronger anti-inflammatory effect [34]. Nobiletin can bind to serum proteins but does not affect the overall conformation of serum proteins [73], which reduces the toxicological properties and increases bioavailability.

The distribution of nobiletin in vivo. Nobiletin can be detected in brain tissues 5 min after intravenous injection [4, 50, 69]. After oral administration of nobiletin (50 mg/kg), the concentrations in the blood and brain peaked at 1.78 μg/mL and 4.20 μg/mL, respectively [55]. The half-lives of nobiletin in the plasma and brain are 1.80 h and 11.42 h, respectively [55]. The concentration of nobiletin in the brain is higher when taken intravenously than when taken orally [4], which means that intravenous administration is the preferred method for central nervous system diseases. Nobiletin has high lipid solubility and permeability in the blood–brain barrier [54]. The preparation of nobiletin into nanoscale amorphous dispersed solids can further increase its concentration in the brain and increase its bioavailability [44], which is conducive to the treatment of central nervous system diseases. In brief, these characteristics of nobiletin make it an ideal candidate for drug research and development.

Effect and mechanisms of nobiletin in the CNS

AD model

Molecular docking studies have also shown that nobiletin can stably bind to beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), inhibit BACE1 activity, and suppress Aβ protein production [40, 76]. Nobiletin can promote Aβ degradation by activating neprilysin [10, 27, 45]. In addition, nobiletin suppresses inflammation via the TLR4/NF-kB/Nrf2 [12] and JNK [75] pathways and suppresses iNOS and COX-2 expression and neuronal apoptosis in an Aβ-induced AD model [75].

After treatment with nobiletin, the expression of HMGB1 and pyroptosis-related proteins (nucleotide-binding oligomerization domain-like receptor 3, ASC, cleaved caspase-1, and N-terminal fragment of gasdermin D) was inhibited in an AD model [8]. Nobiletin can significantly inhibit AChE activity [30], increase ChAT expression and alleviate cognitive dysfunction [23, 41].

Pathways related to nobiletin in cognitive dysfunction. Nobiletin protects hippocampal neurons through the cAMP/PKA/ERK/CREB signalling pathways and improves learning and memory ability [11, 24, 38, 39, 58]. Nobiletin and nerve growth factor act together to increase the phosphorylation level of ERK and activate CRE-dependent transcription [58]. Intraperitoneal

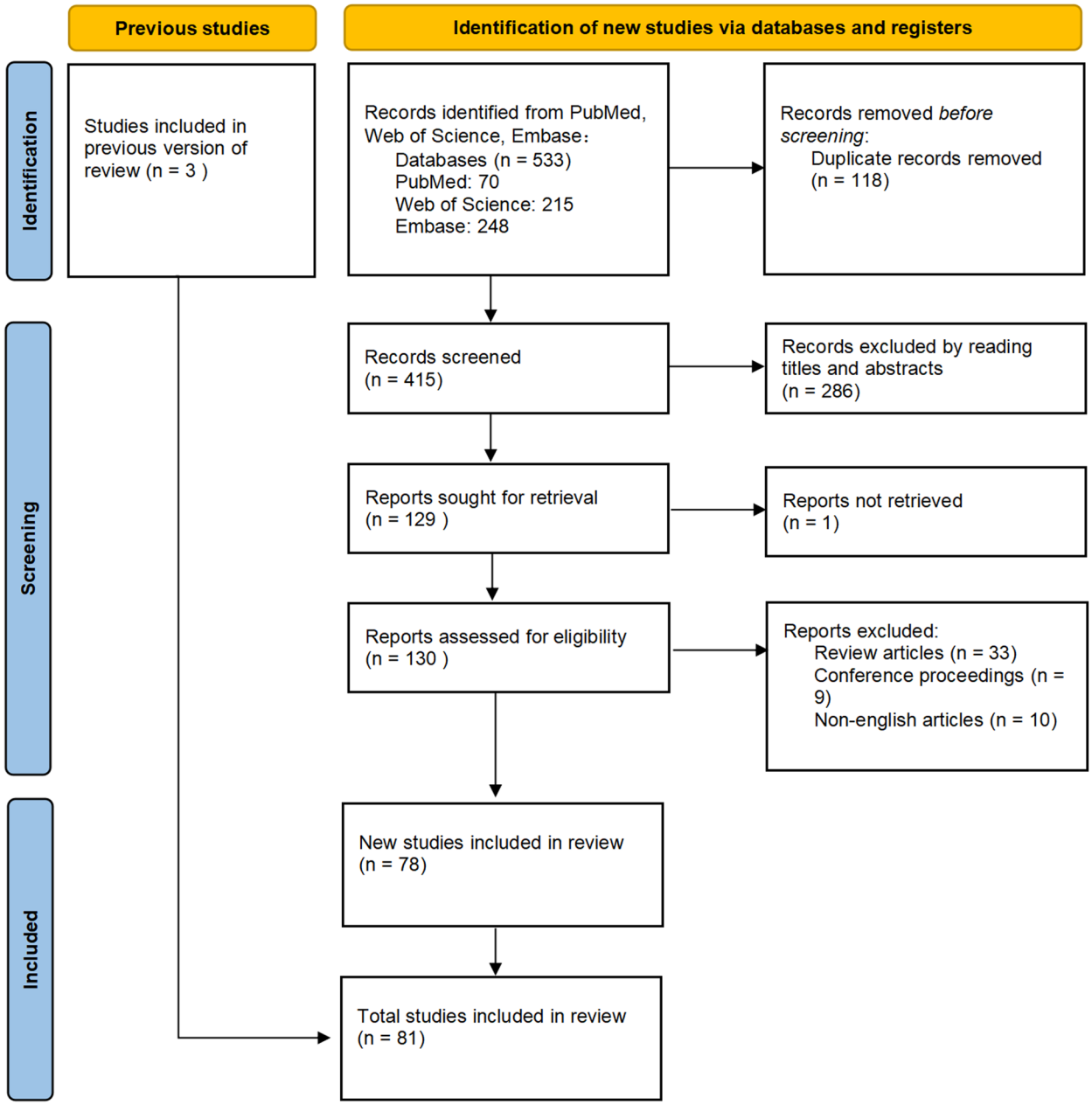

Fig. 1 The flow of the literature search. A total of 536 articles were retrieved. Among the retrieved articles, 455 articles were excluded for the following reasons: (1) articles belonging to meeting abstracts, reviews, letters, editorials, expert opinions, and case reports; (2) literature written in a language other than English; and (3) content not related to keywords. A total of 81 articles were ultimately included in this review

injection of 10 or 50 mg/kg 4-demethylnobiletin can improve NMDA receptor dysfunction-induced cognitive dysfunction via the PKA/ERK/CREB pathway [2]. PKA is a key enzyme in the formation of memory. After treatment with nobiletin, the expression level of PKA and the phosphorylation level of the AMPA receptor subunit GluR1 were significantly increased, thereby regulating local postsynaptic potentials [37]. Isoflurane-induced cognitive disorder can also be improved by nobiletin by promoting the expression of Akt, Bax, p-CREB and BDNF in the brain [5]. The mechanisms of nobiletin are shown in Fig. 2, and the treatment-related information for nobiletin is described in Table 1.

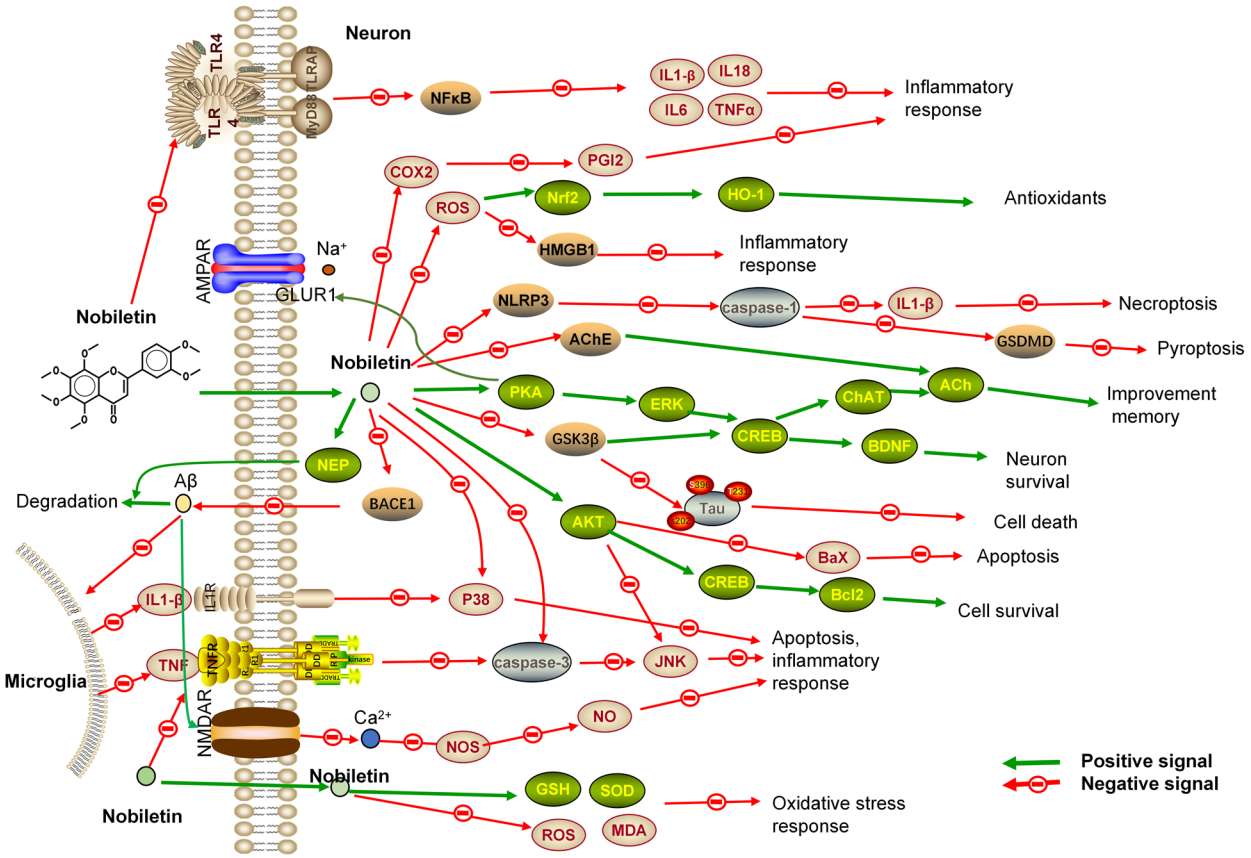

Fig. 2 The mechanisms of nobiletin. Nobiletin inhibits microglial activation and inflammatory factor production to reduce apoptosis in neuronal cells. Nobiletin inhibits apoptosis, inflammation and oxidative stress action directly on the neuronal cells. Nobiletin also promotes neuronal cell survival and improves memory impairment

In summary, nobiletin can inhibit BACE1 activity, suppress the production of Aβ protein and ameliorate cognitive dysfunction in AD.

Stroke model

Nobiletin improved stroke-induced learning and memory impairment by promoting the expression of Ca2 + /calmodulin-dependent protein kinase II (CaMKII), microtubule-associated protein 2 and glutamate receptor 1 and increasing ERK and CREB phosphorylation levels [67]. In an in vitro glial cell hypoxia model, nobiletin promoted Nrf2 nuclear translocation and haem oxygenase-1 (HO-1) expression and inhibited the hypoxia-induced oxidative stress response [60]. Nobiletin reduces the permeability of the blood–brain barrier and cerebral oedema by increasing the expression of claudin-5 [78]. After intravenous injection of nobiletin, nobiletin rapidly accumulates in the infarcted area to protect against nerve damage by activating the Akt/CREB pathway [71, 78], increasing the expression of BDNF [30, 62, 71, 78], and reducing neutrophil infiltration and neuronal apoptosis [71]. Nobiletin reduces local inflammation after stroke by inhibiting NF-κB/MMP9 signalling [77]. Nobiletin also improves the antioxidant capacity after stroke by increasing the activity of SOD1 and GSH and reducing MDA content [77]. Nobiletin can reduce the expression of NO, IL-1β, IL-6, Bax, caspase-3 and TNF-α inflammatory cytokines [62, 80] and increase IL-10 expression through the TLR4/NF-κB and MAPK signalling pathways after stroke [62]. Nobiletin also promotes cell survival and reduces apoptosis by activating the Akt/mTOR/GSK-3β pathway in stroke [80]. In the oxygen–glucose deprivation–reperfusion model of PC12 cells, it was also confirmed that nobiletin activated PI3K/Akt and reversed endoplasmic reticulum (ER) stress (ERS)-induced apoptosis to reduce neuronal injury [36]. The treatment-related information of nobiletin is described in Table 1.

In brief, nobiletin inhibits inflammation and oxidative/nitrosative stress to protect neurons and facilitate neurological recovery in stroke.

Table 1 Treatment-related information of nobiletin

Dose and route of administration	Time	Model	Effects	References
10, 50 or 100 μM	/	Cell-derived AD model	BACE1 inhibitory	[76]
10 – 50 mg/kg (i.p.)	7 d	AD model mice	Soluble $A\beta_{1-40}$↓ learning and memory impairment ↓	[40]
0, 10, 50, 30 or 100 μM	72 h	Cell-derived AD model (SK-N-SH cells)	Neprilysin activity ↑	[10]
3, 10 or 30 μM	24 h	Cell-derived AD or normal neurons model	Neprilysin mRNA ↑ $A\beta_{1-42}$ ↓	[27]
10 mg/kg (i.p.)	4 m	AD model mice	Guanidine-soluble $A\beta_{1-40}$ and $A\beta_{1-42}$ ↓	[45]
1, 10, 25 or 50 μM	1 h	Cell-derived AD or normal neurons model	Oxidative stress ↓ Interleukin-1 ↓ Tumour necrosis factor-α↓ Nitric oxide (NO)↓ Prostaglandin E2↓ Cyclooxygenase-2↓ c-Jun N-terminal kinase and p38 ↓	[75]
25, 50 or 75 mg/kg (p.o.)	90 d	AD model mice	Apoptosis↓ IL-1β↓, TNF-α↓, and IL-18 levels ↓ HMGB-1↓, NLRP3↓, ASC↓ Cleaved Caspase-1↓, GSDMD-N ↓	[8]
30 mg/kg (p.o.)	4 w	Aβ 1–42 injection mice model	AchE activity↑ Bax and cleaved caspase-3 ↓ Bcl-2 and Bcl-2/Bax ↑	[30]
50 mg/kg	11 d	AD model mice	ChAT ↑	[23]
30 or 100 μM	18 h	PC12D cells and hippocampal neurons	ChAT ↑, AchE ↑ Cholinergic neurodegeneration ↓	[41]
30 μM	5 h	PC12D cells	CRE-mediated transcriptional Activity ↑ ERK phosphorylation level ↑	[11]
25 mg/kg	7 d	AD Model mice	CRE-mediated transcriptional activity ↑	[24]
10 μM	/	PC12 cells	CRE-dependent transcriptional activity ↑ Erk phosphorylation ↑	[58]
10 or 50 mg/kg	7 d	AD Model mice	CREB phosphorylation ↑ Learning ability ↑	[38]
100 μM	8 h	PC12D cells	Neurite outgrowth ↑ Improve impaired memory ↑ CRE-dependent transcription ↑	[39]
10 or 50 mg/kg (i.p.)	7 d	AD model mice	PKA/ERK/CREB signalling ↑ learning impairment ↓	[2]
100 μM	15 min	PC12D cells	protein kinase A phosphorylation ↑ GluR1 receptor phosphorylation ↑	[37]
10 or 25 mg/kg (i.p.)	3 d	AD model mice	phosphorylated -Akt ↑ CREB ↑, BDNF ↑ Bax ↓	[5]
25 or 50 mg/kg (i.p.)	7 d	Stroke model mice	Calcium/calmodulin-dependent protein kinase II ↑ Microtubule-associated protein 2 ↑ Glutamate receptor 1 ↑	[67]
1 μM	48 h	Cell hypoxia model	Astrocytes activation↓ Nrf2 nuclear translocation ↑ HO-1 expression ↑ GFAP ↓ ROS and MDA ↓ Mitochondrial dysfunction ↓	[60]
10 or 25 mg/kg(i.p.)	3 d	Stroke model rat	Brain oedema ↓ Infarct volume ↓ p-Akt↑, CREB↑, BDNF↑, Bcl-2 ↑ Claudin-5 ↑	[78]
15 mg/kg (i.p.)	1 d	Stroke model rat	Infarct volume ↓ Brain oedema ↓ Neutrophil invasion ↓ Apoptotic ↓	[71]

Table 1 (continued)

Dose and route of administration	Time	Model	Effects	References
10 or 25 mg/kg(i.p.)	3 d	Stroke model rat	Neurological deficits ↓ Brain oedema ↓ Infarct volume ↓ Nrf2 ↑, HO-1↑, SOD1↑, GSH ↑ NF-κB ↓, MMP-9↓, MDA ↓	[77]
100 or 200 mg/kg (p.o.)	9 d	Stroke model rat	TNF-a↓, IL-1β↓, IL-6↓, NO ↓ TLR4↓, NF-κB ↓	[80]
1, 10, 20 or 50 μM	24 h	Stroke cell model	Endoplasmic reticulum (ER) stress(ERS) -induced apoptosis ↓ Dehydrogenase ↓ Cellular viability ↑ PI3K/AKT pathway ↑	[36]
0,10,50 or 100 μM	24 h	LPS-stimulated BV-2 microglia	TNF-a, IL-1β ↓ NF-kB ↓, ERK ↓, p38 ↓, JNK phosphorylation ↓	[9]
25 or 100 μg/ml	24 h	LPS-stimulated microglia	NO↓, iNOS↓, NF-κB↓, MAPK phosphorylation ↓	[19]
3–10 μM	24 h	BV-2 cells	IL-1β↓	[17]
40 μM	20 h	LPS-stimulated BV-2 microglia	NO ↓, TNF-a ↓, IL-1β↓, IL-6 ↓	[1]
100 mg/kg (p.o)	10 d	LPS intrahippocampal challenge	Memory deficit ↓ COX-2 ↓, IL-1β ↓, TNF-α ↓, and iNOS↓	[48]
100 or 200 mg/kg (p.o.)	6 w	LPS-induced neuroinflammation	iNOS↓, IL-6 ↓, JAK2↓, TNF↓, IL-1↓, and NF-κB↓ STAT3 phosphorylation ↓	[63]
6.25, 12.5, 25 or 50 μg/ml	24 h	LPS-stimulated BV-2 microglia	NO↓, iNOS↓, IL-6↓, JAK2↓, TNFα↓, IL-1β↓, and NF-κB ↓	[57]
10, 20 or 40 μM	24 h	H2O2-induced oxidative stress in astrocytes	Ose-regulated protein(GRP) 78 ↑, Cell death ↓ Endoplasmic reticulum (ER) stress lead ↓	[21]
30, 50, 100 or 200 μM	10 min	Glutamate-stimulated neurons	Calcium overload ↓ ROS ↓ Mitochondrial depolarization ↑	[31]
1, 10 or 30 μM	5 min	Neurons	ROS↓, apoptotic signalling↓, ATP production ↑, Neuronal viability↑, Nrf2↓, HO-1↓	[3]
10 mg/kg (i.p.)	9 d	Cisplatin-induced nerve injury	Peroxide↓, apoptotic↓	[25]
50 μM	96 h	Sodium arsenate-induced neural progenitor cells toxic	Neuronal degeneration ↓, Oedema ↓, caspase-3↓ BDNF ↑, G6PD activity ↑ Antioxidant ↑, Antiapoptotic ↑ Neuroprotective effects ↑	[42]

Parkinson's disease (PD) model

PD is associated with the progressive degeneration of dopaminergic cells. However, increasing evidence suggests that PD may be associated with inflammation and a reduction in glial cell line-derived neurotrophic factor (GDNF) [22, 66]. Nobiletin (50 mg/kg, i.p.) can increase the CaMKII autophosphorylation level, increase the activity of tyrosine hydroxylase and reduce the loss of dopamine neurons to improve 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson-like symptoms [22, 66]. Nobiletin (1, 10 or 20 mg/kg, i.p.) also inhibits microglial activation, promotes GDNF expression, and reduces neurodegenerative lesions in PD [22]. Although the number of studies on nobiletin in PD is small, further research should be conducted in this area.

Anxiodepressive model

A study has shown that citrus peel extract produced has a strong antidepressant effect [32]. The antidepressant effect of nobiletin (10 mg/kg, p.o.) is achieved through the serotonergic, dopaminergic and noradrenergic systems [74]. In addition, the antidepressant effects of nobiletin (20 or 40 mg/kg, p.o.) were also shown to increase

the expression of BDNF, TrkB and synapsin I in the hippocampus [33]. Nobiletin can improve behavioural symptoms by reducing iNOS, IL-1β, IL-6, COX-2 and inflammasome expression through the AMPK pathway in a lipopolysaccharide-induced depression model [61]. Nobiletin (100 μM) also increases autophagy by increasing LC3-II and Beclin-1 expression through activating the AMPK pathway to improve LPS-induced depressive symptoms in a BV2 cell model [61]. In conclusion, the antianxiodepressive effect of nobiletin is associated with anti-inflammatory effects and improves the expression of nerve growth factor.

Epilepsy model

Epilepsy is a complex disease that may be the result of increased excitability of neurons in several regions of the brain. Nobiletin (12.5, 25 or 50 mg/kg, p.o.) may inhibit neuronal apoptosis by increasing Bcl-2 and Bcl-xL expression and reducing caspase-3, Bad, and Bax expression in epilepsy models [68]. The BDNF–TrkB signalling pathway is critical for the development of epilepsy, and nobiletin also inhibits seizures by inhibiting the BDNF–TrkB pathway [68]. Nobiletin also reduces the incidence of seizures by reducing Glu/GABA levels [6, 68]. In addition, nobiletin can increase GSK-3β, mTORc-1, and mTORc-2 levels through the PI3K/Akt pathway to inhibit epileptic seizures [68]. In conclusion, the effect of nobiletin in epilepsy is associated with the apoptotic, BDNF-TrkB and PI3K/Akt signalling pathways.

Disordered circadian clock model

In recent years, the function of PMFs in regulating the biological clock has gradually attracted attention. A clinical study of AD showed that nobiletin, which is enriched in orange peels, can improve abnormal mental behaviour. Midazolam can induce circadian rhythm disorders by reducing PER2 in the hippocampus; however, this can be alleviated by nobiletin (1 mg/kg, i.p.) through enhancing the amplitude of PER2 [13]. Another study also suggested that nobiletin (containing 0.1% diets) can significantly increase the temporal changes in the expression of Clock, Bmal1 and Npas2 [26, 64]. Nobiletin (1, 10, 30 or 50 mg/kg, i.p.) improved surgery-induced neurocognitive decline by preserving the expression of the clock genes Bmal and Rors [56]. A disordered central circadian clock is related to many diseases. In this review, nobiletin improved the disordered central circadian clock by regulating clock genes. It would be interesting to investigate this further.

Brain tumour model

Although brain tumours rarely metastasize to distant sites, their diffuse and invasive growth in the brain usually directly affects the success of therapy. Therefore, finding new adjuvant therapy drugs has always been the eternal topic of antitumour therapy. Nobiletin (425 μM or 4 mg/ml) can inhibit the expression of MMP-2 and MMP-9 in glioma cells and reduce the motility, adhesion and invasion ability of glioma cells [49, 51]. The antitumour effect of nobiletin in the brain is associated with reducing adhesion and invasion of glioma cells, and more mechanistic studies deserve to be further explored.

Neuroinflammation and neurotoxicity model

Nobiletin can suppress lipopolysaccharide-stimulated BV-2 glial cell activation by inhibiting the phosphorylation levels of ERK, p38 and JNK [9, 19] and NO, TNF-a, IL-1β, IL-6 and iNOS expression through NF-κB signalling [1, 9, 17, 48, 63]. Nobiletin also inhibits IL-1β, IL-6, and TNF-α expression by inhibiting the JAK2/STAT3 pathway [63].

After injection of nobiletin, the expression of GRP78 was increased, and endoplasmic reticulum stress and neurotoxicity were decreased in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity model [57]. Excessive glutamate has been considered an excitotoxic agent in neural cells, and glutamate receptors have become targets for the treatment of this neurotoxicity. Molecular docking studies showed that nobiletin could stably bind to glutamate receptors, indicating that nobiletin is a potential therapeutic drug for glutamate-induced neurotoxicity [21]. Nobiletin also increased mitochondrial K^+ influx to mildly depolarize mitochondria and reduce mitochondrial calcium overload to protect nerves [31].

There are two effects of nobiletin treatment on rotenone-induced neurotoxicity. When complex I is in the activated state and binds to nobiletin, complex I can be inhibited, thereby inhibiting oxidative stress defence and increasing cell viability; when complex I is in the inhibited state and binds to nobiletin, the brain mitochondrial oxygen consumption rate can be improved [3]. Through binding to the mitochondrial complex I subunit NDUFV1, nobiletin can decrease complex I activity and inhibit ROS production, thereby reducing mitochondrial apoptosis-inducing factor (AFI) nuclear translocation and suppressing nerve cell apoptosis [3]. Nobiletin can also promote ATP production, activate the mitochondrial α-ketoglutarate dehydrogenase complex, cause mild mitochondrial depolarization, and accelerate the phosphorylation of the matrix substrate level to protect nerves from neurotoxic effects [3, 53]. The neuroprotective mechanisms of nobiletin in mitochondria are shown in Fig. 3.

Nobiletin increased BDNF concentration and glucose-6-phosphate 1-dehydrogenase activity and reduced

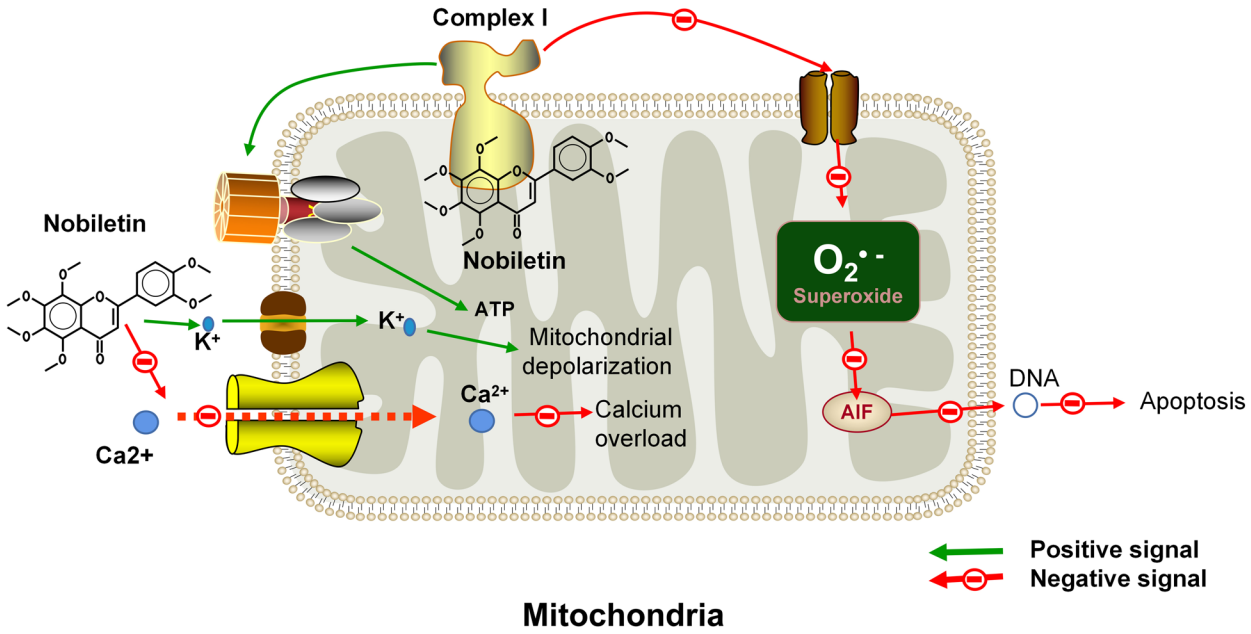

Fig. 3 Mechanisms of nobiletin in mitochondria. Nobiletin inhibits mitochondrial calcium overload by blocking calcium influx. Nobiletin promotes mitochondrial depolarization by increasing potassium influx and ATP production. Nobiletin inhibits oxidative stress and apoptosis via complex I

caspase-3 expression to protect against chemotherapeutic drug cisplatin-induced neurotoxicity [25]. Nobiletin has therapeutic effects on sodium arsenate-induced neurotoxicity [20]. Nobiletin can restore morphological damage (neurite damage), restore the levels of stress granule ras-GTPase-activating protein (SH3 domain)-binding protein and T cell-restricted intracellular antigen, and increase the expression of the neural marker proteins β tubulin, Nestin, and Pax6 [20]. Nobiletin also restores arsenic-induced mitochondrial membrane potential damage [20]. The treatment-related information of nobiletin is described in Table 1.

In summary, nobiletin reduces neuroinflammation and neurotoxicity. Nobiletin reduces neuroinflammation and is associated with suppressing microglial activation. Mitochondria is one of targets for nobiletin in neuroinflammation and neurotoxicity model and that deserves further investigation.

Effect and mechanisms of nobiletin in the peripheral nervous system

ENS

The enteric nervous system is known as the second brain. Nobiletin has a bidirectional regulatory effect on jejunal movement. Low doses of nobiletin (1.25–5.0 μM) showed a promoting effect, and high doses of nobiletin (10.0–40.0 μM) showed an inhibitory effect on normal contractility in the jejunum [65]. Nobiletin stimulates low contractility jejunum movement while inhibiting high contractility jejunum movement [15, 65]. The inhibitory effect of nobiletin on the jejunum is related to NO secretion by nitrergic neurons, and the contraction-promoting effect on the jejunum is related to Cajal cells [65]. The Ca^{2+} channel is another indispensable factor for the bidirectional regulatory effect of nobiletin [65]. Nobiletin can increase epinephrine-induced low [Ca2+]i and reduce ach-induced high [Ca2+]i status [65]. Nobiletin (100 μM) can significantly reduce the expression of LPS-induced inflammatory factors, such as TNF-α, NF-κB, COX-2 and iNOS, in RAW264.7 cells [15]. A recent study also suggested that nobiletin (100 or 200 mg/kg, p.o.) inhibited HFD-induced colon inflammation and improved colon motor function by increasing Trem2 expression [46]. The ENS has been a focus of research in recent years. The ENS has been implicated in the development of various diseases. This review suggests that nobiletin protects the ENS and regulates intestinal motor functions. Nobiletin in ENS is deserving of further research and development.

Spinal cord diseases

Amyotrophic lateral sclerosis is a degenerative disease of motor neurons distributed in the cortex, brain stem, and spinal cord. Superoxide dismutase type 1 (SOD1) mutations lead to protein aggregation and reduced protein stability, which is associated with amyotrophic lateral sclerosis. Nobiletin (2 or 10 μM) significantly alleviates autoimmune encephalomyelitis symptoms by inhibiting Th17 cell differentiation and interleukin-17A

production [42]. Nobiletin (25 or 50 mg/kg, i.p.) also significantly reduces the expression of TNF-α, IL-1β and IL-6 in the brain and spinal cord and increases the expression of IL-10, TGF-β and interferon γ to reduce the inflammatory response in the brain and spinal cord in encephalomyelitis [70]. In brief, nobiletin also suppresses neuroinflammation in the spinal cord.

Other peripheral nerves

Sciatic nerve injury leads to sensory and motor impairment. Nobiletin can inhibit H_2O_2-induced sciatic nerve cell toxicity [52]. Nobiletin (50 or 100 μM) can significantly promote synaptic growth of sciatic nerve cells, which is associated with the BDNF-ERK1/2 and AKT pathways [52]. At present, the clinical treatment effect of sciatic nerve injury caused by long-term chronic compression is poor. However, a study has shown that the administration of nobiletin (30, 60, 120 mg/kg) for 8 days can significantly improve the pain of the long-term compressed sciatic nerve, which was associated with inhibition of the IRF5/P2X4R/BDNF signalling pathway in spinal microglia [81]. In conclusion, nobiletin had a protective effect on the sciatic nerve.

Conclusions

The major effects of nobiletin on the nervous system are inhibiting inflammatory cytokine expression [1, 48, 63], reducing neurotoxicity [20, 21, 25], promoting the survival of nerve cells and axon outgrowth [52], reducing blood–brain barrier permeability and cerebral oedema [36, 59, 60, 77], promoting mild depolarization of nerve cell mitochondria and increasing capacity against oxidative stress [3, 53]. The biological roles of nobiletin are inseparable from its basic mechanism. Nobiletin has two or more methoxy groups, has no glycosidic bonds, is more hydrophobic than hydroxyl compounds, and has a higher intestinal absorption rate than other flavonoids [43]. Nobiletin also has high permeability in the blood–brain barrier due to its high lipophilicity [54]. The hydroxyl groups at the C-3 and C-4 positions of nobiletin are necessary for its antioxidative capacity and radical scavenging capacity [47]. Nobiletin has a native structure for scavenging free radicals, high lipophilicity and high bioavailability and is worthy of further development and research as a drug.

There are many studies of nobiletin in the CNS, and the effect of nobiletin on the peripheral nervous system has gradually attracted attention in recent years [15, 42, 46, 65, 70], especially in the ENS [46]. Many risk factors cause ENS damage. However, there are few effective drugs for ENS damage. The intestinal microbiota can cause nobiletin demethylation [29]. After demethylation, nobiletin has a stronger solubility and biological activity [14]. A study has shown that nobiletin protects against HFD-induced ENS damage [46]. However, further studies are necessary to deeply elucidate the mechanism of nobiletin in the ENS. After nobiletin treatment, whether there are also alterations in neuroinflammation, apoptosis and neurogenesis in the ENS is still unclear. Hence, this is an intriguing direction for future research. Therefore, we reviewed the effects and mechanisms of nobiletin in the nervous system to provide a state-of-the-art literature and prospective intervention strategy for nervous disorders by nobiletin.

Abbreviations

CREB	CAMP response element binding protein
PMFs	Polymethoxy flavonoids
AD	Alzheimer's disease
ENS	Enteric nervous system
CYP2C11	Cytochrome P450 2C11 precursor
CYP2C12	Cytochrome P450 2C12 precursor
CYP2D1	Cytochrome P450 2D1
CYP3A1	Cytochrome P450 3A1
CYP3A2	Cytochrome P450 3A2
CYP1A1	Cytochrome P450 family 1 subfamily A1
CYP1A2	Cytochrome P450 family 1 subfamily A2
PI3K/Akt	Phosphatidylinositol 3'-kinase/serine/threonine-protein kinase
MMP	Matrix metalloproteinase
CYP3A4	Cytochrome P450 family 3 subfamily A4
Aβ	β-Amyloid
GSK-3β	Glycogen synthase kinase 3β
cAMP	Cyclic AMP
DCX	Neuronal migration protein doublecortin
GFAP	Glial fibrillary acidic protein
TNF-α	Tumour necrosis factor superfamily-α
COX-2	Cyclooxygenase-2
NF-κB	Nuclear factor-kappa B
TLR4	Toll-like receptor4
VEGF	Vascular endothelial growth factor
BACE1	Beta-site amyloid precursor protein cleaving enzyme 1
CNS	Central nervous system
HMGB-1	High mobility group protein B1
ASC	Apoptosis-associated speck-like protein containing a CARD
Nrf2	Nuclear factor erythroid 2-related factor 2
AChE	Acetylcholinesterase
ChAT	Choline O-acetyltransferase
BDNF	Brain-derived neurotrophic factor
PKA	Protein kinase A
ERK	Mitogen-activated protein kinase 1/3
CaMKII	Ca2 + /calmodulin-dependent protein kinase II
iNOS	Inducible NO synthase
MDA	Monochrome display adapter
SOD	Superoxide dismutase
HO-1	Heme oxygenase 1
GSH	Glutathione
MAPK	Mitogen-activated protein kinase
IL-1β	Interleukin-1β
IL-6	Interleukin-6
TrkB	Neurotrophic tyrosine kinase receptor type 2
IL-10	Interleukin-10
PER2	Period circadian protein 2
NDUFV1	NADH dehydrogenase (ubiquinone) flavoprotein 1
JAK2/STAT3	Janus kinase 2/signal transducers 3
GRP78	Heat shock protein family A (Hsp70) member 5
NMDA	N Methyl-D-aspartate

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Author contributions
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