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Review

From bench to beside: luteolin's therapeutic promise in neurological disorders

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ABSTRACT

Luteolin (3′,4′,5,7-tetrahydroxyflavone) is a naturally occurring flavonoid found in diverse plant families, including Apiaceae, Brassicaceae and Lamiaceae, and is a major bioactive component of Chinese medicines such as *Chrysanthemum morifolium* and *Perilla frutescens*. It possesses antidepressant, anti-inflammatory, antioxidant and neuroprotective activities, and has shown therapeutic potential in depression, Alzheimer's disease (AD) and Parkinson's disease (PD). Based on a comprehensive PubMed search, this review examines the shared pathological features—neuroinflammation, oxidative stress and synaptic dysfunction—across these three disorders and elucidates the pharmacological actions of luteolin. Clinical trial data were retrieved from NIH and ICTRP registries. We critically analyze current research limitations, including the lack of validated direct targets beyond PPARγ, the predominance of pathway-based evidence without orthogonal validation, and significant pharmacokinetic defects (low oral bioavailability, rapid glucuronidation, poor BBB penetration). While luteolin holds promise for central nervous system (CNS) disorders, its clinical translation requires advanced drug delivery systems (e.g., nano-formulations, brain-region-specific prodrugs), combination therapies or structural modification, and future cohort studies for prophylactic use. Addressing these priorities will be essential for its therapeutic development.

1. Introduction

Central nervous system (CNS) disorders encompass a wide range of conditions that disrupt sensory perception, emotional regulation and behavior. Alzheimer's disease (AD), Parkinson's disease (PD) and depression are among the most prevalent and debilitating neurological disorders worldwide [1]. Their incidence continues to rise. Depression increased sharply during the COVID-19 pandemic [2]. AD affects about 50 million people globally, a number expected to double by 2050 [3]. PD affects more than six million people globally, with motor symptoms such as rigidity, slowness and tremor [4]. These disorders often co-occur, highlighting the need for broad-spectrum treatments [5, 6]. However, success with synthetic compounds remains limited, leading researchers to explore natural products.

Luteolin (3′,4′,5,7-tetrahydroxyflavone; $C_{15}H_{10}O_6$) is a naturally occurring flavonoid with a diphenylpropane (C6–C3–C6) backbone [7]. It belongs to the flavone subclass and carries hydroxyl groups on both aromatic rings [8, 9]. First isolated from *Reseda odorata* L., luteolin is found in diverse plant families, including Apiaceae (e.g., carrots), Brassicaceae (e.g., broccoli) and Lamiaceae (e.g., thyme, peppermint and *Perilla frutescens*) [8, 10, 11]. In East Asia, *Chrysanthemum morifolium* (Juhua) is consumed as a herbal tea, with its antioxidant properties partly ascribed to luteolin [12]. The compound has well-documented anti-inflammatory, antioxidant and anti-apoptotic activities [13, 14]. It is also a major bioactive component of several traditional Chinese medicines, including Xiaoyaosan [15, 16]. Preclinical evidence indicates that luteolin exerts neuroprotective effects, making it a candidate for depression, Alzheimer's disease and Parkinson's disease [17].

Several recent reviews have summarized the neuroprotective effects of luteolin [18, 19]. However, none systematically compared luteolin across depression, AD and PD within an integrated framework linking shared pathological features to disease-specific mechanisms. Our review fills this gap. We provide disease-stratified summary tables, critically discuss direct molecular targets, compare luteolin with approved drugs, and analyze pharmacokinetic limitations, BBB penetration, formulation strategies, toxicology, clinical trial status, patent barriers and competition from emerging biologics. Finally, we offer actionable recommendations for future research.

2. Methods

2.1. Literature search strategy

A structured literature search was conducted using the PubMed database to identify studies related to luteolin and its po-

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tential roles in neurological diseases. Relevant articles published between 2000 and 2025 were systematically retrieved using combinations of the keywords (Fig. 1). In addition, the reference lists of selected studies were manually screened to identify potentially relevant publications that were not captured during the initial database search.

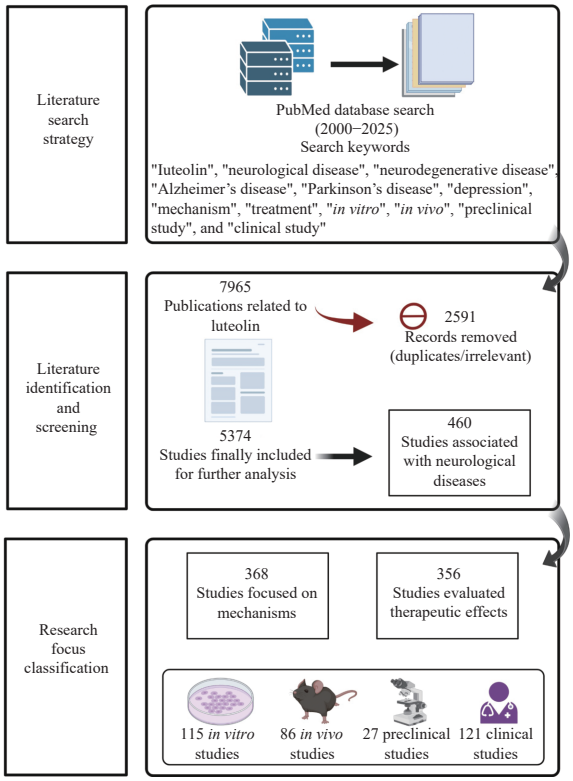


Fig. 1 Flowchart illustrating the development of luteolin for neurological diseases over the past 25 years.

2.2. Inclusion and exclusion criteria

Studies were included according to the following criteria: original research articles and review articles published in English that focused on luteolin and its biological functions, pharmacological activities, therapeutic effects, or mechanisms associated with neurological diseases. The exclusion criteria were as follows: (1) editorials, conference abstracts, letters, and book chapters; (2) duplicate publications; (3) studies unrelated to luteolin; and (4) preprint articles that had not undergone peer review.

2.3. Data classification and quantitative analysis

To provide a comprehensive overview of current research trends, the included studies were further categorized according to research focus and experimental design (Fig. 1). Specifically, a total of 7965 publications related to luteolin published between 2000 and 2025 were initially identified through the PubMed database search. After removal of 2591 duplicate or irrelevant records, 5374 studies were finally included for further analysis. Among these, 460 studies were associated with neurological diseases. Furthermore, 368 studies focused on molecular or cellular mechanisms, and 356 evaluated therapeutic effects, with some overlap between the two categories. According to study type, 115 studies were classified as *in vitro* investigations, 86 as *in vivo* studies, 27 as preclinical studies, and 121 as clinical studies.

3. Potential common pathological basis of depression, AD, and PD

Depression, AD, and PD represent distinct central nervous system disorders; however, their frequent co-occurrence suggests the existence of overlapping pathogenic mechanisms and convergent therapeutic targets [20-22]. This shared pathological framework provides a mechanistic basis for the broad neuroprotective potential of luteolin. Current evidence indicates that neuroinflammation, oxidative stress (OS), and synaptic dysfunction constitute three major pathological intersections among these disorders.

Neuroinflammation is a central driver. Activated microglia release interleukin (IL)-1β, IL-18, and tumor necrosis factor-α (TNF-α), impairing synaptic plasticity and contributing to depressive behaviors [23]. In AD, amyloid β (Aβ) deposition triggers sustained chronic microglial activation, leading to synaptic injury and neuronal loss [3]. In PD, microglia and peripheral immune cells promote dopaminergic neuron degeneration in the substantia nigra [24]. Thus, modulating neuroinflammation may represent a shared therapeutic strategy.

OS also plays a pivotal role. Reduced brain-derived neurotrophic factor (BDNF) signaling impairs the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway in depression [25]. Nrf2 deficiency aggravates Aβ accumulation and cognitive decline in AD [26]. Mitochondrial dysfunction and oxidative damage are strongly linked to PD onset [27].

Synaptic dysfunction is another convergence. Depression involves reduced synaptic connectivity in the prefrontal cortex (PFC) and hippocampus (HPC) [28]. Synaptic loss is also closely associated with cognitive decline in human and animal models of AD. The Aβ and abnormally phosphorylated microtubule-associated protein tau induce synaptic toxicity, propagate through neural circuits, and trigger phenotypic alterations in neuroglial cells, culminating in neuronal damage and synaptic degeneration [29]. Neuroglial cells engulf abnormal synapses, disrupting synaptic vesicle endocytosis and leading to the loss of synaptic homeostasis, a pivotal element in the pathogenic mechanisms of PD [30].

Luteolin mitigates these shared processes. It reduces oxidative stress, inflammatory signaling and neuronal injury in zebrafish models [31-32]. Thus, luteolin may exert broad protective effects across these disorders. As detailed in the following sections, luteolin alleviates depressive-like behaviors by restoring BDNF signaling, reduces Aβ and tau pathology in AD, and protects dopaminergic neurons in PD.

4. Luteolin and depression

Depression involves neuroinflammation, OS and impaired synaptic plasticity. Luteolin exerts antidepressant effects by inhibiting neuroinflammation, reducing neuronal injury and apoptosis, modulating neurotrophic factors and neurotransmitters, and regulating gut microbiota (Fig. 2, Table 1).

4.1. L Luteolin blocks NLRP3 inflammasome activation

In neuroinflammation, activated glial cells release inflammatory mediators that drive depression [45]. Luteolin suppresses NLRP3 activation *via* Sirt1/NF-κB or PPARγ pathways [16, 35, 46]. However, the anti-NLRP3 effect varies: acute LPS challenge induces stronger IL-1β reduction than chronic stress models. Most evidence is rodent-based; human data are lacking, and long-term safety of NLRP3-targeted intervention remains unexplored.

4.2. Luteolin limits neuronal injury and apoptosis

OS triggers pro-inflammatory signals and apoptosis. Luteolin

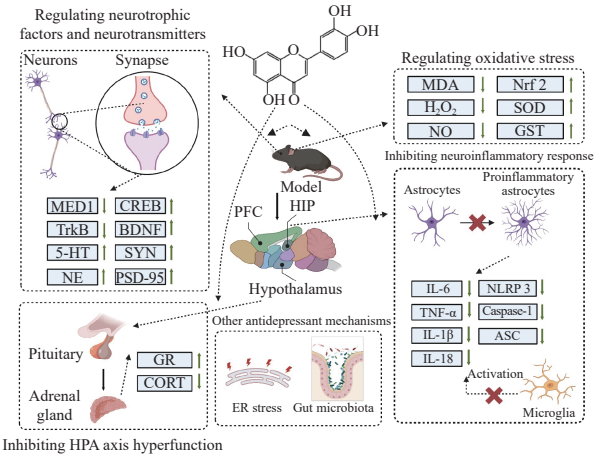


Fig. 2 The mechanism and influence site of luteolin on depression. Luteolin exerts its antidepressant effects by inhibiting neuroinflammation, reducing OS levels, modulating neurotrophic factors, neurotransmitter content, synaptic function, and regulating intestinal microecology.

normalizes Bax/Bcl-2 ratios and reduces oxidative markers [38, 41]. The effect of luteolin on neuronal injury depends on the model: combination with gallic acid rescued chemical hypoxia-induced neuronal loss, whereas luteolin alone reversed neuropathic pain-induced apoptosis. No study has examined direct binding of luteolin to apoptosis regulators, and all experiments used male animals - sex differences are unexplored.

4.3. Luteolin boosts BDNF and monoamines

Luteolin upregulates BDNF *via* MED1/TrkB and restores 5-HT and NE through BDNF-mTOR signaling [33, 35, 37]. It also regulates the HPA axis [39]. BDNF elevation occurs faster in some models (7 days) than others (14 days). Most measurements come from tissue homogenates, missing cell-type resolution. Clinical evidence is lacking.

4.4. other mechanisms

Luteolin also modifies gut microbiota (enriching beneficial bacteria) and glycerophospholipid metabolism, affecting autophagy and ER stress [36, 42, 44]. These findings are preliminary. Different mouse strains and stress protocols hinder direct comparison. Causal links need validation through faecal transplantation or genetic approaches.

As discussed earlier, neuroinflammation, OS and synaptic dysfunction are shared across depression, AD and PD. Luteolin targets all three pathways, indicating that its antidepressant actions are part of a broader neuroprotective strategy.

5. Luteolin and AD

Luteolin has notable neuroprotective effects and is being investigated for anti-AD properties [47-50]. It alleviates neuroinflammation, OS and autophagy dysregulation, reduces Aβ and tau pathology, and protects synaptic function (Fig. 3, Table 2).

5.1. Luteolin lowers Aβ and tau burden

Aβ and tau aggregation drive AD pathology [61–62]. Luteolin pretreatment reduced Aβ plaques by about 50% in a TBI-accelerated model and nearly prevented cognitive decline after acute Aβ injection [50, 57]. Efficacy varies with intervention timing, administration route and model type (traumatic *vs* amyloid-based). Most studies used young or middle-aged animals. Data from aged animals (over 18 months) are scarce. Direct binding of luteolin to Aβ or tau has not been shown by biophysical methods, and long-term efficacy in large animals remains untested.

5.2. Luteolin suppresses glial activation via ER stress relief

Luteolin inhibits astrocyte and microglial activation and lowers ER stress-driven inflammation [49, 51, 55, 58]. Whether microglia or astrocytes contribute more is unclear. One study found strong astrocyte inhibition with a luteolin formulation, whereas another reported effects on both cell types [51, 58]. No study has used genetic tools to confirm that ER stress sensors are required for luteolin's action. Moreover, effective in vitro concentrations (10–50 μmol·L^{-1}) far exceed achievable plasma levels, raising questions about physiological relevance.

5.3. Luteolin improves mitochondrial function and regulates autophagy

Luteolin reduces oxidative stress markers, boosts antioxidant enzymes, and restores mitochondrial function *via* PPARγ activation [53, 59–60]. Autophagy regulation appears paradoxical, with one study reporting restored autophagy and another finding bidirectional changes depending on brain region [53, 36]. Bulk measurements obscure cell-type-specific flux; tandem fluorescent reporters would provide better resolution. No clinical study has tested whether luteolin enhances mitochondrial bioenergetics or auto-

Table 1 The main mechanism and influence site of luteolin on depression.

Animal or cell line	Model	Main mechanism	Reference
Male CD1 mice	Thalamic hemorrhage-induced pain	Restores BDNF *via* MED1/TrkB pathway	33
Male C57BL/6 mice	Sleep deprivation	Activates BDNF signaling	34
Male ICR mice + primary AS	LPS injection	Reduces inflammation; upregulates BDNF, dopamine, NE	35
Male Wistar rats	CUMS	Modulates glycerophospholipid metabolism and autophagy (putative AMPK/mTOR)	36
Male Kunming mice	Noise-induced depression	Upregulates BDNF/mTOR, 5-HT, NE, and synaptic proteins	37
Male Wistar rats	Chronic constriction injury (neuropathic pain)	Modulates oxidative stress and neurotrophic factors	38
Male Sprague-Dawley rats	Single prolonged stress (PTSD)	Regulates HPA axis; restores 5-HT/NE balance	39
Male Wistar rats	CUMS	Enhances folate transport and tight junction proteins	40
Male Wistar rats	$CoCl_2$ oral administration	Regulates calcium homeostasis and antioxidant enzymes	41
Male ICR mice	Corticosterone (depression + AD model)	Suppresses ER stress	42–43
Male ICR mice	CUMS	Modulates gut microbiota and neurotransmitter levels	44

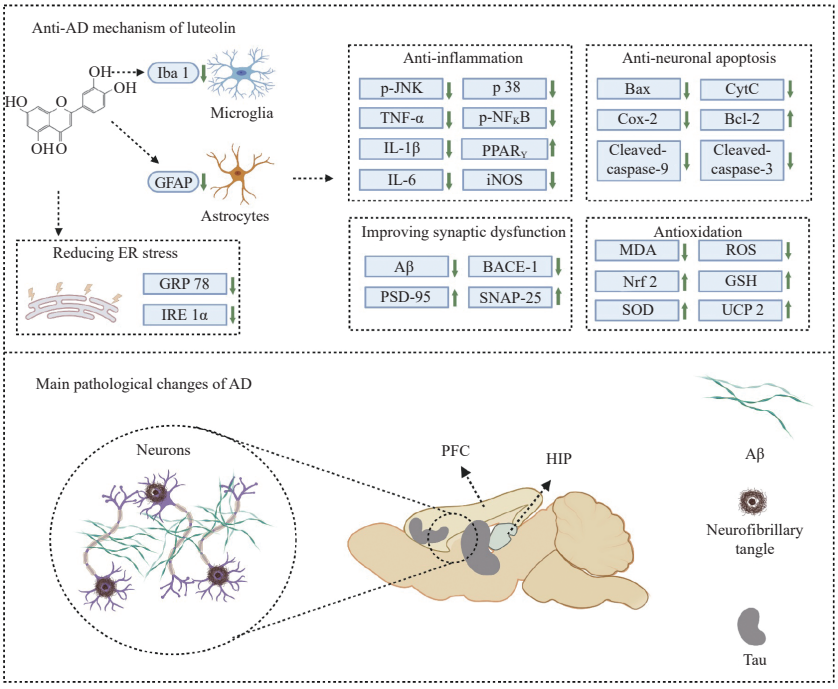


Fig. 3 The mechanism and influence site of luteolin on AD. Luteolin has the potential to alleviate neuroinflammation by mitigating glial cell activation and, through its anti-inflammatory and antioxidative properties, suppress oxidative stress and cellular apoptosis. Moreover, it can modulate autophagy, reducing the excessive accumulation of Aβ and abnormally phosphorylated Tau, thereby ameliorating AD-like phenotypes. Furthermore, its therapeutic impact on AD involves regulating synaptic plasticity to diminish neuronal injury and apoptosis.

Table 2 The main mechanism and influence site of luteolin on AD.

Animal or cell line	Model	Main mechanism	Reference
3×Tg-AD mice + C6 glioma cells	3×Tg-AD; LPS-induced	Inhibits ER stress and glial inflammation	49
Male C57BL/6N mice	ICV $A\beta_{1-42}$	Inhibits JNK; reduces Aβ neuroinflammation	50
Male Sprague-Dawley rats	Hippocampal $A\beta_{1-42}$	Reduces glial activation; increases BDNF/GDNF	51
Swiss albino male mice	Sporadic AD (STZ)	Anti-oxidation; reduces Aβ aggregation and tau phosphorylation	52
3×Tg-AD mice	3×Tg-AD	PPARγ-dependent; reduces oxidative stress and mitochondrial dysfunction	53
Male Sprague-Dawley rats	Hippocampal $A\beta_{25-35}$	Co-administration with L-theanine improves insulin signaling	54
Swiss albino male mice	Hippocampal $A\beta_{1-42}$	Combination with exercise enhances autophagy and reduces Aβ	55
Male Wistar rats	ICV-STZ	Prevents CA1 pyramidal neuron loss	56
Tg2576 mice	Traumatic brain injury	Reduces Aβ, GSK-3β, tau phosphorylation and inflammation	57
Human brain microvascular endothelial cells + human AS	BBB model with $fA\beta_{1-40}$	Inhibits p38 MAPK/NF-κB; protects BBB	58
Male Sprague-Dawley rats	Chronic cerebral hypoperfusion	Clears free radicals; reduces Aβ deposition	59
Male C57BL/6J mice	High-fat diet	Improves glucose metabolism and insulin resistance; increases BDNF	60

phagic clearance in AD patients.

The three core pathologies of AD mirror those of depression. Luteolin tackles neuroinflammation, OS and synaptic dysfunction alike. PD offers a further test of this framework.

6. Luteolin and PD

Dopaminergic neuron loss in the substantia nigra defines PD, a process linked to α-synuclein (α-Syn) overexpression and Lewy body formation [63-64]. α-Syn triggers oxidative stress, disrupts dopamine metabolism and the mitochondrial respiratory chain, and fuels neuroinflammation, all of which luteolin counteracts (Fig. 4, Table 3).

6.1. Luteolin modulates central immune dysfunction

Microglial activation driven by α-Syn promotes neurotoxic ROS and inflammatory mediators [74-77]. Luteolin dose-dependently reduces these responses, reshapes microglial transcriptomes toward an anti-inflammatory, phagocytic phenotype, and lowers nitric oxide release [78]. In PD models, a luteolin-containing formulation (co-ultraPEALut) dampens astrocyte activation, iNOS expression, and tyrosine hydroxylase loss while enhancing autophagy [67, 78]. Despite consistent anti-inflammatory effects across systems, the relative importance of microglia versus astrocytes remains model-dependent: rotenone-challenged BV-2 cells show strong microglial modulation, whereas MPTP-treated mice exhib-

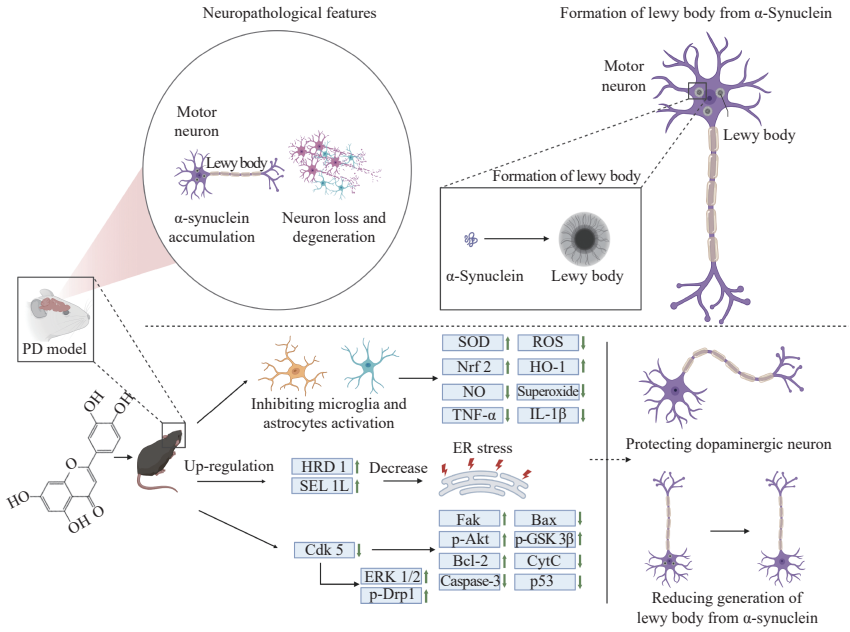


Fig. 4 The mechanism and influence site of luteolin on PD. The excessive expression of α-Syn and the formation of LBs in the substantia nigra can lead to OS, neuronal damage, aberrant dopamine metabolism, and the accumulation of toxic free radicals, accompanied by disturbances in the mitochondrial respiratory chain. Concurrently, OS can trigger neuroinflammation, ultimately culminating in abnormal apoptosis of dopaminergic neurons. The anti-inflammatory and antioxidative properties of luteolin are likely to intervene at these critical junctures.

Table 3 The main mechanism and influence site of luteolin on PD.

Animal or cell line	Model	Main mechanism	Reference
SH-SY5Y cells	MPP^+	Inhibits α-Syn *via* Cdk5/Erk/Drp1 and FAK/Akt/GSK3β	65
SH-SY5Y cells	6-OHDA	Upregulates HRD1/SEL1L; inhibits ER stress and apoptosis	66
Male CD1 mice + SH-SY5Y cells	MPTP	Reduces astrocyte activation, iNOS and pro-inflammatory cytokines	67
BV-2 cells	Rotenone	Regulates oxidative stress and PD-related inflammatory pathways	68
Male C57BL/6 mice + SH-SY5Y cells	MPTP / MPP^+	Activates ER-mediated pathways; protects dopaminergic neurons	69
PC12 cells	6-OHDA	Inhibits p53/Bax; upregulates Bcl-2	70
PC12 cells	6-OHDA	Reduces ROS and p53; activates Nrf2-ARE	71
PC12 cells	Arsenite	Reduces ROS and α-Syn production	72
Primary neuron-glia (Sprague-Dawley rats)	LPS	Inhibits microglial activation and superoxide production	73

it notable astrocyte involvement [67-68]. Most studies employed only male animals, and human data are confined to small combination trials, preventing attribution of effects solely to luteolin.

6.2. Luteolin activates Nrf2-ARE to lower ROS

Luteolin reduces ROS and α-Syn production, at least partly *via* the Keap1-Nrf2-ARE axis [72, 79-80]. It elevates Nrf2 nuclear translocation and downstream HO-1 expression in various PD models [67, 73]. Nevertheless, the required concentrations (10–20 μmol·L^{-1}) exceed the plasma levels achievable with oral dosing, and no study has used Nrf2-selective inhibitors or knockout animals to establish causality. Whether luteolin engages canonical Keap1-Nrf2 signaling or non-canonical routes (e.g., p62-Keap1 interaction) has yet to be delineated.

6.3. Luteolin suppresses apoptosis and preserves synaptic function

Luteolin inhibits α-Syn generation through Cdk5/Erk/Drp1 and FAK/Akt/GSK3β pathways, upregulates synaptic proteins (GAP43, PSD95, synapsin-1), and prevents MPP^+-induced synaptic loss [65]. It also upregulates ER-associated degradation factors HRD1 and SEL1L to block 6-OHDA-triggered apoptosis [66]. A glycosylated derivative, luteolin-7-*O*-glucoside, activates estrogen receptor signaling and improves motor function in MPTP-treated mice [69]. However, the reported signaling cascades differ with the toxin (MPP^+ *vs* 6-OHDA) and cell line (SH-SY5Y versus PC12). Direct binding of luteolin to apoptosis regulators (e.g., Bcl-2, Caspases) has not been demonstrated, and all evidence remains preclinical. Large-animal studies with clinically relevant endpoints are urgently needed before human trials.

PD shares the same three pathological pillars as depression and AD, neuroinflammation, oxidative stress and synaptic dysfunction, all of which luteolin targets, reinforcing the concept of a unified neuroprotective mechanism across these disorders.

7. Luteolin targets and signalling networks

Although luteolin has been widely reported to regulate multiple signaling pathways (NF-κB, Nrf2, MAPK, PI3K/Akt, JAK/STAT) in depression, AD and PD, definitive evidence identifying its direct molecular targets remains limited. Table 4 summarizes the experimentally validated luteolin-binding proteins reported to date, along with validation methods and evidence strength.

As shown in Table 4 and Fig. 5, only PPARγ has been valid-

Table 4 Experimentally validated direct molecular targets of luteolin and evidence strength.

Target protein	Validation context and confidence	Validation method	Key observation	Reference
PPARγ	Yes (depression); High	X-ray (PDB:3SZ1); MST (KD 0.989 μmol·L^{-1}); GW9662	Binds LBD (Lys265, His266); partial agonist; GW9662 blocks antidepressant effects	16, 81
PDXK	No (human protein); High	X-ray (1.94 Å); SPR (KD 6.61 μmol·L^{-1}); IC_{50} 2.2 μmol·L^{-1}	ATP-competitive inhibitor; regulates GABA/glutamate *via* B6 metabolism	82
CK2	No (plant CK2; human AD relevance); High	X-ray (PDB:4DGN); IC_{50} 0.35 μmol·L^{-1}	Binds ATP pocket (Val116, Lys68); inhibits tau-related kinase	83
GPX4	No (colon cancer); High	CETSA + DARTS + SPR (triple validation)	Orthogonal methods confirm binding; awaits neurological validation	84
Sirt1	No (HUVEC); Medium-High	DARTS; docking	Activates Sirt1/Nrf2 axis; candidate for neurological validation	85
GSK-3β	Yes (AD, in silico); Low-Medium	Docking; MD (200 ns); IC_{50} 1.5 μmol·L^{-1}	ATP-competitive; no SPR/CETSA validation	86–87
Keap1	Yes (PD, MS); Medium (inferred)	Pathway inference (Nrf2 activation)	Activates Nrf2/Keap1; direct binding not SPR-confirmed	88-91
HSPB1	No (endothelial); Medium	DARTS; docking	Activates SLC7A11/GPX4 axis to inhibit ferroptosis	92
IKKα/β	Limited; Low	*In vitro* kinase assay	Inhibits LPS-induced IKK in IEC-18 cells; not neurological	93
TLR4/NLRP3	No (kidney); Low	Docking; Western blot	Inhibits TLR4/MyD88/NLRP3 in kidney; not neurological	94

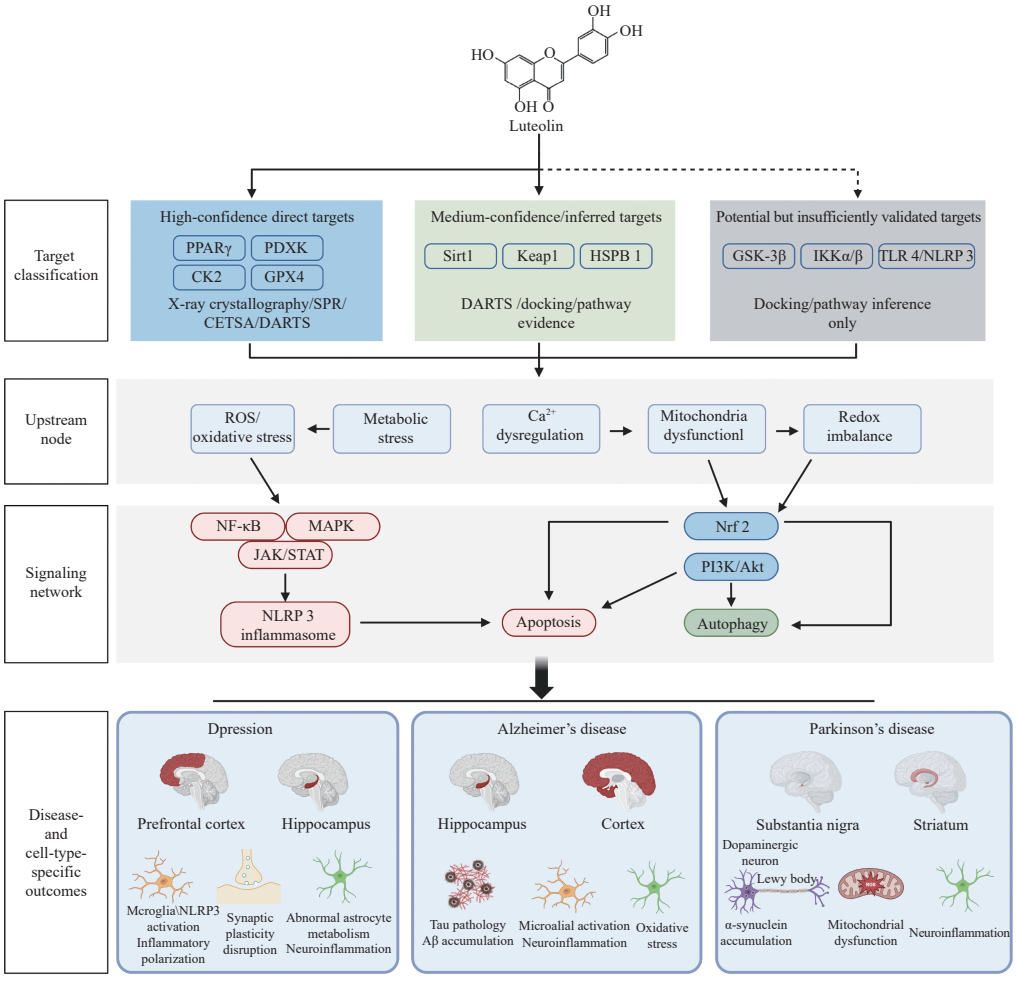


Fig. 5 Proposed mechanism of multi-pathway regulation by luteolin in depression, AD and PD. Luteolin targets are stratified by evidence strength: high-confidence (solid lines: PPARγ, PDXK, CK2, GPX4), partially validated (dashed lines: Sirt1, Keap1, HSPB1), and putative (dotted lines: GSK-3β, IKKα/β, TLR4/NLRP3). These converge on upstream stress nodes (ROS, Ca^{2+}, mitochondrial dysfunction, metabolic imbalance) and downstream signaling (suppression of NF-κB, MAPK, JAK/STAT, NLRP3, apoptosis; activation of Nrf2, PI3K/Akt, autophagy). The final outcomes are shaped by cell type and disease context, leading to microglial anti-inflammatory polarization, neuronal survival, and astrocytic support.

ated with high-confidence structural and biophysical evidence in neurological contexts, supported by X-ray crystallography (PDB:3SZ1) and functional confirmation using the antagonist GW9662 [16, 81]. PDXK and CK2 have crystallographic evidence but await neurological validation [82–83]. Most other proposed targets rely on molecular docking or pathway inference, which constitutes low-strength evidence.

Critically, modern chemical proteomics (TPP, LiP-MS) has not yet been applied to brain tissue. Future studies should prioritize unbiased target identification in disease-relevant models, followed by orthogonal validation (X-ray/SPR/CETSA). This will establish a solid molecular foundation for luteolin's therapeutic

application in neurological disorders.

8. Current applications and challenges of luteolin

8.1. Luteolin in other neuropsychiatric disorders

Luteolin has also shown potential in other neurological conditions, including autism and Huntington's disease [95–96]. Although preclinical studies are promising, clinical translation remains at an early stage. Currently approved drugs for depression, AD, and PD primarily target monoaminergic neurotransmission, Aβ deposition, or dopaminergic degeneration, yet none effectively halts disease progression. Compared with these agents, luteolin still lacks standardized pharmacokinetic characterization, large-scale clinical validation, and precise therapeutic positioning.

8.2. Barriers to clinical translation

Despite considerable neuroprotective potential, the clinical translation and commercialization of luteolin face multidimensional barriers, including poor pharmacokinetics, limited BBB penetration, mechanistic uncertainty, insufficient toxicological evaluation, patent limitations, and competition from emerging biologics.

8.2.1. Mechanistic uncertainty

Luteolin modulates multiple pathways (NF-κB, Nrf2, MAPK, PI3K/Akt, JAK/STAT), but its direct molecular targets remain incompletely defined. Neurodegenerative diseases involve interconnected pathological networks; for example, tau and α-Syn pathologies overlap in AD and PD, and they can cross-seed each other [97-101]. Although luteolin inhibits both tau hyperphosphorylation and α-Syn aggregation, direct evidence linking these effects is lacking. This ambiguity complicates biomarker identification and regulatory evaluation. Moreover, the pleiotropic nature of luteolin, while potentially advantageous, makes target definition more difficult than for single-target therapies [18–19].

8.2.2. Pharmacokinetic defects and delivery challenges

Luteolin suffers from low aqueous solubility, rapid intestinal glucuronidation/sulfation, and low oral bioavailability [102–103]. After absorption, it undergoes extensive phase II metabolism, leading to rapid clearance and low levels of free aglycone [104–105]. BBB penetration is further limited by efflux transporters such as P-glycoprotein [47, 106].

Supplementary Table S1 summarizes the key pharmacokinetic parameters. Three interrelated barriers limit brain exposure: extremely low oral bioavailability (~4%), rapid conversion to inactive plasma conjugates, and poor BBB penetration. Consequently, achieving therapeutic brain concentration would require impractically high oral doses.

To overcome these limitations, several delivery strategies have been explored. For example, biotin-β-cyclodextrin conjugation increased solubility ~1423-fold, and luteolin-loaded graphene oxide nanoparticles improved brain accumulation in zebrafish [107–108]. However, the long-term safety and manufacturing consistency of such nano-formulations require further validation.

8.2.3. Toxicological evaluation and long-term safety concerns

Comprehensive toxicological data for chronic neurological use is lacking. Luteolin is generally considered safe, with no dose-limiting toxicity reported at 100 mg per day in humans, but long-term data are scarce [109]. Due to neurological patients often receive multidrug regimens, potential interactions—e.g., inhibition of OATP transporters by luteolin conjugates—warrant systematic investigation [110]. The absence of GLP-compliant toxicological studies remains a regulatory obstacle.

Although luteolin is generally considered a naturally derived flavonoid with low toxicity, comprehensive toxicological data for long-term neurological use remains lacking. Neurodegenerative diseases typically require chronic administration over several years, raising concerns about cumulative toxicity, metabolic burden and drug-drug interactions.

8.2.4. Insufficient clinical research

Searches of the International Traditional Medicine Clinical Trial Registry (ITMCTR) and the International Standard Randomized Controlled Trial Number (ISRCTN) Registry identified no clinical trials evaluating luteolin as a standalone therapeutic agent. In contrast, searches of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) found 20 registered studies involving luteolin, of which 7 are related to mental illnesses. However, no largescale, multicenter randomized controlled trials have assessed luteolin for depression, AD, or PD. The existing registered studies are either small, exploratory, or involve combination products (e.g., with palmitoylethanolamide). A summary of these trials is provided in Table 5.

9. Conclusion and future perspectives

Luteolin is a promising multifunctional flavonoid for neurological and psychiatric disorders due to its anti-inflammatory, antioxidant and neuroprotective properties. It modulates multiple pathological processes in depression, AD, PD and related conditions, including oxidative stress, microglial activation, mitochondrial dysfunction, synaptic impairment and protein aggregation. This pleiotropy may offer advantages over single-target strategies (Fig. 6).

However, clinical translation remains limited by insufficient mechanistic resolution, poor pharmacokinetics, inadequate BBB penetration, and a lack of largescale clinical validation. Long-term safety, formulation standardization, industrial production and regulatory approval also pose major challenges.

Future research should prioritize several areas: clarifying

Table 5 Clinical trials of luteolin associated with mental illnesses in NIH before 2024.

Main ID	Public title	Date of registration	**Status**
NCT06047899	Influence of Luteolin for Two Weeks on Memory in Healthy Subjects	2023-09-14	Not yet recruiting
NCT05311852	Effects of PEA-LUT on Frontal Lobe Functions and GABAergic Transmission in Long-Covid Patients	2022-03-30	Unfinished: update submitted that met quality control criteria
NCT05204407	Luteolin for the Treatment of People with Schizophrenia	2022-01-11	Recruiting
NCT04489017	Palmitoylethanolamide Combined with Luteoline in Frontotemporal Dementia Patients. A Randomized Controlled Trial	2020-07-28	Undecided to share data
NCT03818451	Co-ultra PEALut Enhances Neuronal Recovery Following Moderate Traumatic Brain Injury	2019-01-28	Recruiting
NCT02909686	Effects of Botanical Microglia Modulators in Gulf War Illness	2016-09-21	No adverse reactions; no significant effect on Gulf War Illness
NCT01847521	Effects of the Anti-inflammatory Flavonoid Luteolin on Behavior in Children with Autism Spectrum Disorders	2013-05-01	Luteolin + quercetin effective in autism; no major adverse effects

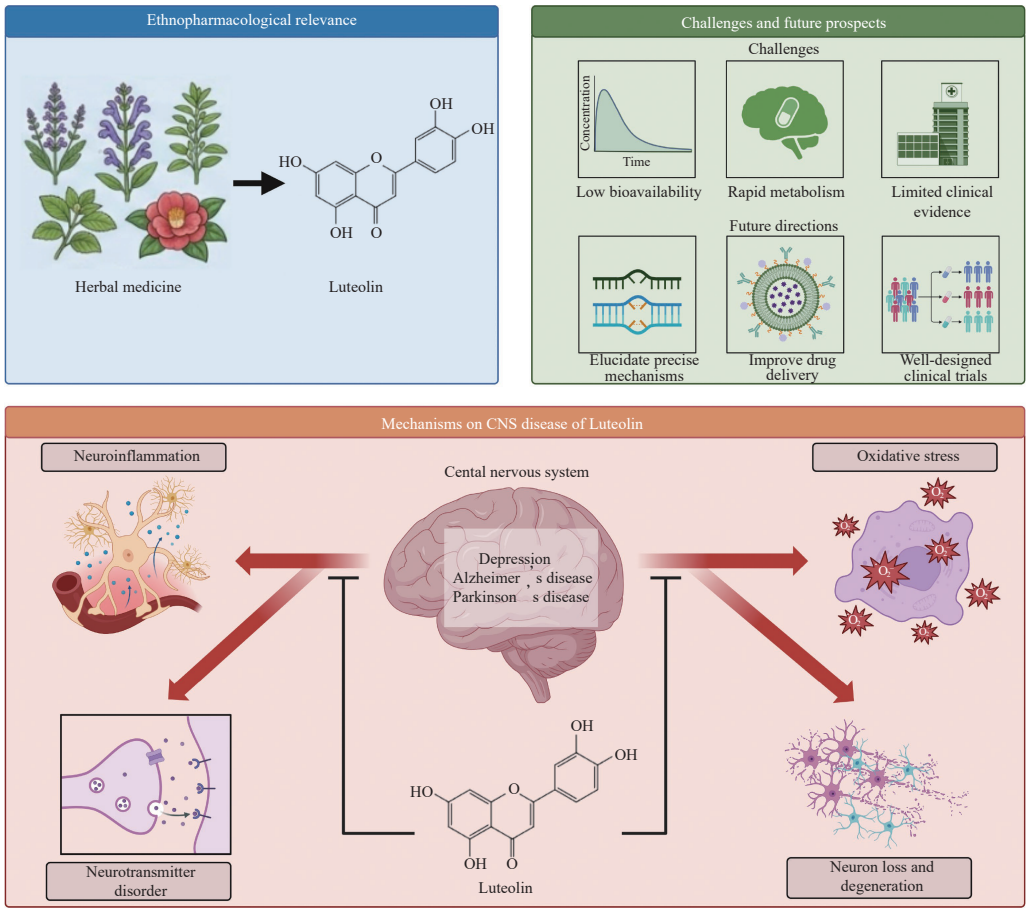


Fig. 6 Neuroprotective effects and translational challenges of luteolin in depression, AD and PD. Luteolin alleviates neuroinflammation, oxidative stress and synaptic dysfunction across depression, AD and PD, but its clinical translation is limited by poor oral bioavailability, rapid metabolism and insufficient clinical evidence.

direct molecular targets and disease-specific networks; developing BBB-targeted nano-formulations or sustained-release carriers; conducting systematic toxicological and pharmacodynamic studies; and performing well-designed multicenter trials. Combination with existing disease-modifying therapies may further improve outcomes.

Overall, luteolin is a compelling candidate for neurotherapeutic development. Advances in mechanistic research, drug delivery and translational investigation will help move it from an experimental compound to a clinically useful agent for neurological diseases.

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Declaration of competing interests

The authors declared no potential conflicts of interest to the research, authorship, and publication of this article.

Data availability

Data will be available on request by sending E-mail to the corresponding authors.

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