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REVIEW

Recent Advances in the Pharmacological Properties of Scutellarin: Mechanistic Insights and Therapeutic Potential

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ABSTRACT

Scutellarin, a flavonoid glycoside primarily derived from *Scutellaria baicalensis*, has garnered increasing scientific interest for its multifaceted pharmacological properties. This review summarizes recent advances in our understanding of scutellarin's therapeutic effects, including its antioxidant, anti-inflammatory, neuroprotective, cardioprotective and anticancer activities. Emphasis is placed on elucidating its molecular mechanisms of action, such as modulation of the NF-κB, Nrf2, and PI3K/Akt pathways, and its role in regulating oxidative stress, inflammation, and apoptosis. Additionally, we discuss formulation innovations, including nanoparticle and liposomal delivery systems, aimed at overcoming scutellarin's poor oral bioavailability and enhancing therapeutic performance. Key limitations in current research such as variability in raw material quality, few clinical trial data, and challenges with regulatory approval in Western markets are critically examined. By outlining these gaps and highlighting future directions, this review provides a comprehensive synthesis to support the translational development of scutellarin as a promising therapeutic candidate.

Keywords: Scutellarin, Pharmacological Properties, Molecular Mechanisms, Mechanistic Pathways, Drug Delivery Systems, Clinical Translation, Therapeutic Applications, Drug Development

1. Introduction

Scutellarin is a flavonoid glycoside (flavone glucuronide) primarily derived from the medicinal plant *Scutellaria baicalensis*. Scutellarin has gained significant attention for its multifaceted pharmacological effects [146]. Traditionally utilized in Chinese herbal medicine, it has recently emerged as a promising candidate in modern therapeutic development [130]. Its chemical structure, defined by a flavone backbone conjugated with glucuronic acid, contributes to its unique bioactivity and pharmacokinetic behavior, including favorable absorption, distribution, and metabolic stability [3].

This review presents a focused synthesis of current findings related to scutellarin's therapeutic actions and underlying molecular mechanisms. Increasing evidence supports its role in the management of various diseases, including inflammation, neurodegeneration, cardiovascular disorders, and cancer. By summarizing the recent advancements, identifying knowledge gaps, and outlining potential research directions, this work aims to contribute to the scientific understanding and clinical translation of this bioactive natural compound.

1.1. Review methodology

For this narrative review on the pharmacological properties of scutellarin, a comprehensive literature search was conducted across major scientific databases, including PubMed, Scopus, and Web of

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Science. Keywords such as “scutellarin,” “Scutellaria baicalensis,” “antioxidant,” “anti-inflammatory,” “neuroprotective,” “cardioprotective,” “anticancer,” “mechanism of action,” and “formulation” were used to identify relevant studies. The search focused on publications from 2016–2026 to highlight recent advances. Both experimental studies (in vitro and in vivo) and relevant clinical reports were considered, while commentaries, editorials, and non-English articles were excluded. The included 147 studies were evaluated for their contributions to understanding scutellarin’s mechanisms, therapeutic potential, and translational implications. This approach allowed for a structured yet flexible synthesis of the current knowledge in the field.

2. Pharmacological properties of Scutellarin

Scutellarin is a naturally occurring flavonoid glucuronide with well-documented anti-inflammatory and antioxidant activities, exerting protective effects across multiple chronic disease models. Its pharmacological actions are primarily mediated through inhibition of key pro-inflammatory signaling pathways, including NF-κB, PI3K/Akt, and MAPK, alongside activation of cytoprotective antioxidant pathways such as Nrf2–ARE. Through this coordinated regulation of inflammatory and oxidative stress responses, scutellarin preserves mitochondrial function, vascular integrity, and cellular survival, contributing to its demonstrated efficacy in osteoarthritis, pulmonary fibrosis, renal injury, cardiovascular, and neurodegenerative disorders. Although its therapeutic potential is supported by extensive in vitro and in vivo evidence, clinical translation remains constrained by poor bioavailability and rapid clearance, prompting ongoing efforts to improve extraction efficiency and develop advanced delivery systems. Collectively, these properties position scutellarin as a multi-target anti-inflammatory bioactive compound with significant promise for the management of inflammation-driven chronic diseases [90, 146].

Scutellarin, a flavonoid compound found in the plant Scutellaria baicalensis, exhibits a range of pharmacological properties, including potent antioxidant and anti-inflammatory effects [122]. These properties make it a promising therapeutic agent for various conditions, particularly those associated with oxidative stress and chronic inflammation [87]. Beyond redox and inflammatory regulation, scutellarin exhibits robust neuroprotective activity in ischemic brain injury by activating the PI3K/Akt–Nrf2 signaling axis and suppressing NF-κB–driven neuroinflammation. In cellular and animal models of cerebral ischemia/reperfusion, scutellarin promotes Nrf2 nuclear translocation, upregulates antioxidant defenses (HO-1, SOD), limits ROS accumulation, and preserves blood–brain barrier integrity, collectively reducing infarct volume and improving neurological function. Concurrently, PI3K/Akt pathway activation enhances neuronal survival through upregulation of anti-apoptotic Bcl-2 and inhibition of Bax and caspase-3–mediated apoptosis, effects that are abolished by pharmacological PI3K inhibition. These findings establish PI3K/Akt-dependent coordination of antioxidant, anti-inflammatory, and anti-apoptotic mechanisms as a central basis for scutellarin’s neuroprotective efficacy. The following subsections extend this mechanistic framework to its cardioprotective and anticancer actions, highlighting scutellarin’s multi-system therapeutic relevance and translational potential [125,27].

2.1. Antioxidant activity of Scutellarin

Scutellarin is a flavonoid compound which exhibits potent antioxidant properties by targeting specific oxidative stress pathways rather than relying on the broader effects associated with whole-plant extracts [90]. Its antioxidant potential has been demonstrated through multiple mechanisms, including direct scavenging of reactive oxygen species (ROS), electron donation, and metal ion chelation. These actions collectively prevent oxidative damage to cellular macromolecules such as DNA, lipids, and proteins, which are key contributors to chronic diseases like cancer, cardiovascular disorders, and neurodegeneration [52].

Mechanistically, scutellarin exerts its antioxidant effects by neutralizing free radicals such as superoxide anions (O_2^-), hydroxyl radicals (•OH), and hydrogen peroxide (H_2O_2), thereby halting chain reactions that propagate oxidative stress. The phenolic hydroxyl groups on its molecular structure allow it to donate electrons, effectively stabilizing reactive intermediates [13]. Furthermore, scutellarin chelates transition metal ions like Fe^{2+} and Cu^{2+}, which catalyze ROS formation through Fenton-type reactions. By binding these pro-oxidant metals, scutellarin prevents further ROS generation [111].

Beyond its chemical antioxidant effects, scutellarin modulates cellular defense systems by activating the Nrf2/ARE signaling pathway. This activation leads to the upregulation of antioxidant enzymes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and glutathione peroxidase (GPx) [62]. It also suppresses the MAPK and NF-κB signaling cascades, which are often activated during oxidative stress and inflammation, thereby reducing the transcription of

Table 1. Antioxidant activity of Scutellarin across experimental models.

Model Type	Disease or Stress Model	Dose/ Concentration	Mechanism Observed	Strength of Evidence	Key Finding/Clinical Relevance
In vitro assay	DPPH radical scavenging	$IC_{50} = 9.2$ μM	Direct free radical scavenging	$IC_{50} = 9.2$ μM	Demonstrates potent intrinsic antioxidant capacity of scutellarin [8]
In vitro assay	Ferric ion reduction (FRAP)	Not reported	Electron-donating reducing power	High reducing capacity (qualitative)	Supports redox-modulating potential relevant to oxidative stress mitigation [92]
In vitro assay	Lipid peroxidation (ORAC)	$IC_{50} = 7.8$ μM	Inhibition of oxidative membrane damage	$IC_{50} = 7.8$ μM	Indicates protection against lipid oxidative injury [6]
In vitro assay	Phenolic redox activity	Not applicable	Phenolic hydrogen donation	Moderate phenolic equivalence	Phenolic structure contributes to antioxidant function [5]
Cell model	Oxidative stress–induced ROS accumulation	Not reported	Intracellular ROS suppression	Significant ROS reduction (quantitative not reported)	Suggests cytoprotective antioxidant effects in biological systems [57]

pro-inflammatory genes and further cellular damage [125].

Experimental studies provide robust evidence for these mechanisms. In vitro, scutellarin significantly reduced ROS levels and lipid peroxidation in H_2O_2-treated human umbilical vein endothelial cells (HUVECs), with an IC_{50} of 21.4 μM in the DPPH radical scavenging assay [82]. In an in vivo model of carbon tetrachloride (CCl_4)-induced oxidative liver damage in rats, oral administration of scutellarin at 50 mg/kg over 14 days led to significant restoration of antioxidant enzyme levels and reduction in malondialdehyde (MDA), a marker of lipid peroxidation [83].

Scutellarin acts as a targeted antioxidant compound capable of both direct chemical radical neutralization and modulation of endogenous defense mechanisms. Through its interaction with the Nrf2, MAPK, and NF-κB pathways, it offers considerable therapeutic potential for managing diseases driven by oxidative stress. Table 1 summarizes the antioxidant activity of scutellarin across various experimental models, detailing model types, stressors, doses, mechanisms, and the strength of evidence.

This multifaceted antioxidant activity makes scutellarin a valuable tool for combating oxidative stress and its associated pathologies.

2.2. Anti-inflammatory effects of Scutellarin

Scutellarin, a bioactive flavonoid compound, demonstrates significant anti-inflammatory effects by modulating key molecular pathways involved in the inflammatory response. One of its primary mechanisms is the inhibition of the nuclear factor kappa B (NF-κB) signaling cascade [74]. NF-κB plays a central role in regulating the expression of various pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) [37]. Scutellarin suppresses the activation and nuclear translocation of the NF-κB p65 subunit by stabilizing IκBα and blocking its phosphorylation and degradation, thereby preventing the transcription of downstream inflammatory genes [66].

In addition to its effects on NF-κB, scutellarin modulates the mitogen-activated protein kinase (MAPK) pathway, particularly the c-Jun N-terminal kinase (JNK) and p38 MAPK branches. These kinases are critical mediators of cellular responses to stress and inflammatory stimuli, and their inhibition by scutellarin contributes to a reduction in inflammatory signal propagation [58]. This dual modulation of NF-κB and MAPK pathways allows scutellarin to attenuate the amplification of inflammatory responses at multiple regulatory levels [61].

Furthermore, scutellarin interferes with the arachidonic acid cascade by inhibiting key enzymes such as cyclooxygenase (COX) and 5-lipoxygenase (5-LOX), both of which are responsible for the biosynthesis of pro-inflammatory lipid mediators like prostaglandins and leukotrienes. This action helps suppress the generation of these mediators, thereby limiting vascular permeability, leukocyte recruitment, and pain associated with inflammation [85].

Emerging evidence also suggests that scutellarin interacts with the phosphoinositide 3-kinase (PI3K)/Akt pathway, enhancing Akt phosphorylation and exerting a regulatory effect over both NF-κB and MAPK signaling. This crosstalk contributes to a broader anti-inflammatory profile by influencing cell survival, cytokine production, and immune modulation [145].

Taken together, scutellarin's anti-inflammatory effects are mediated through its multitargeted

Table 2. Anti-inflammatory effects of Scutellarin in preclinical models.

Model Type	Disease or Inflammatory Stimulus	Dose/ Concentration	Mechanism Observed	Strength of Evidence	Outcome/Clinical Implication
Cell	LPS-stimulated RAW 264.7 macrophages	25 μM	Inhibition of TNF-α, IL-6, NO production	~55% inhibition	Demonstrates macrophage-targeted anti-inflammatory activity [91,76]
Animal	Carrageenan-induced paw edema	20 mg/kg (oral)	Suppression of inflammatory mediators	50–60% edema inhibition	Confirms in vivo efficacy against acute inflammation [99]
Cell	NF-κB luciferase reporter system	Not reported	NF-κB signaling inhibition	Significant pathway suppression	Identifies molecular anti-inflammatory mechanism [53]
Animal	DSS-induced colitis (mouse)	Not reported	Reduced immune cell infiltration	~45% DAI reduction	Indicates therapeutic promise in inflammatory bowel disease [68]
Cell	Inflamed HT-29 intestinal epithelial cells	30 μM	Reduced IL-8 secretion, NF-κB nuclear translocation	~60% inhibition	Supports gut-protective anti-inflammatory role [11]
Cell + Animal	Cytokine storm models (nano-scutellarin)	Not specified	Enhanced cytokine suppression	~70% inhibition (in vitro); improved survival	Nanodelivery significantly enhances bioavailability and efficacy [104]

inhibition of key signaling networks such as NF-κB, MAPK, PI3K/Akt, and arachidonic acid metabolism. These mechanisms underscore its therapeutic potential in treating chronic inflammatory conditions, providing a strong pharmacological basis for its continued investigation and application. Table 2 presents the anti-inflammatory effects of scutellarin in preclinical models, including cell and animal systems, inflammatory stimuli, dose ranges, observed mechanisms, and translational relevance.

Scutellarin's antioxidant and anti-inflammatory properties make it a promising therapeutic agent for a wide range of conditions. Its ability to combat oxidative stress and modulate inflammatory pathways suggests its potential for preventing and treating chronic diseases [12].

2.3. Neuroprotective effects of Scutellarin

Scutellarin, a flavonoid glycoside recognized for its multi-targeted pharmacological properties, has shown substantial neuroprotective potential through its regulation of oxidative stress, neuroinflammation, and protein misfolding [126], key features in the pathology of neurodegenerative diseases such as Alzheimer's and Parkinson's disease [29]. Unlike crude plant extracts, scutellarin exerts effects through well-characterized mechanisms at the molecular level.

In the context of Alzheimer's disease, one of the critical mechanisms attributed to scutellarin is its ability to counteract the neurotoxicity associated with amyloid-beta (Aβ) peptides. Aβ plaques disrupt synaptic function and induce neuronal apoptosis [140]. Scutellarin interferes with this process by inhibiting Aβ aggregation and promoting its clearance, thereby mitigating plaque-induced neuronal injury [67]. Furthermore, scutellarin modulates modulate cholinergic neurotransmission by regulating the activity of acetylcholinesterase (AChE), an enzyme responsible for the degradation of acetylcholine [17]. By limiting AChE activity, scutellarin helps maintain cholinergic signaling, which is essential for cognitive function and memory retention in Alzheimer's pathology.

Beyond amyloid toxicity, scutellarin plays a role in reducing neuronal oxidative stress by activating the Nrf2/ARE pathway. Activation of this transcription factor leads to upregulation of antioxidant enzymes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and glutathione peroxidase (GPx), which collectively protect neurons from reactive oxygen species (ROS)-induced damage. This antioxidative mechanism is particularly important in slowing down neuronal degeneration and preserving synaptic integrity [143].

In Parkinson's disease, the neuroprotective effect of scutellarin is partly mediated by its inhibition of α-synuclein aggregation. The accumulation of misfolded α-synuclein proteins into Lewy bodies is a hallmark of Parkinsonian pathology [139]. Scutellarin inhibits interfere with the nucleation and elongation phases of α-synuclein fibril formation, potentially reducing the formation of neurotoxic aggregates. This property supports its role in mitigating the loss of dopaminergic neurons in the substantia nigra [4].

Additionally, scutellarin influences other inflammatory and apoptotic pathways involved in

Table 3. Neuroprotective effects of Scutellarin in cellular and Animal models.

Model Type	Disease/ Stress Model	Dose/ Concentration	Mechanism Observed	Strength of Evidence	Outcome/Translational Significance
Cell	H_2O_2-induced oxidative stress (PC12 cells)	25 μM	ROS inhibition, cytoprotection	82% cell viability	Protects neurons from oxidative injury [38]
Animal	Alzheimer's disease mouse model	Not reported	Cognitive enhancement, antioxidant defense	~70% improvement in memory tests	Suggests therapeutic potential in AD [110]
Cell	Primary cortical neurons	10 μM	Anti-apoptotic signaling, ROS suppression	76% cell viability	Prevents neuronal apoptosis [54]
Animal	Ischemic stroke (rat)	Not reported	Reduced infarction, neuronal recovery	68% motor function improvement	Indicates post-stroke neuroprotection [63]
Cell	SH-SY5Y neuroblastoma cells	20 μM	NF-κB inhibition, reduced cytokines	79% cell viability	Links anti-inflammatory action to neuroprotection [73]
Animal	LPS-induced neuroinflammation (rat)	Not reported	Microglial suppression	83% behavioral improvement	Supports use in neuroinflammatory disorders [28]

neurodegeneration. It downregulates the expression of pro-inflammatory cytokines such as TNF-α and IL-1β by inhibiting NF-κB signaling and suppresses apoptosis through modulation of the PI3K/Akt and Bcl-2/Bax signaling balance. These actions help stabilize mitochondrial function and prevent neuronal cell death in response to stress and protein toxicity [27].

Scutellarin's neuroprotective capacity is attributed to its multifaceted regulatory effects on oxidative stress, neuroinflammation, cholinergic dysfunction, and protein aggregation. These mechanisms highlight its strong therapeutic promise as a neuroprotective agent in the treatment of Alzheimer's, Parkinson's, and related neurodegenerative disorders. Table 3 reports the neuroprotective effects of scutellarin in cellular and animal models, capturing disease or stress models, dosing, mechanistic observations, and the potential translational significance of the findings.

Protecting dopaminergic neurons: Scutellarin may also protect dopaminergic neurons, which are particularly vulnerable in Parkinson's disease, from damage caused by oxidative stress and inflammation [123].

2.4. Cardiovascular benefits of Scutellarin

Scutellarin has emerged as a promising flavonoid compound with multiple cardioprotective actions, supported by its ability to modulate oxidative stress, vascular inflammation, endothelial function, and thrombogenesis [69]. Its pharmacological profile suggests significant therapeutic potential in the prevention and management of cardiovascular diseases such as atherosclerosis, hypertension, and ischemic stroke [141].

A central mechanism through which scutellarin confers cardiovascular protection is its antioxidant capacity. It activates the Nrf2/ARE pathway, which leads to the upregulation of endogenous antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). This response helps neutralize reactive oxygen species (ROS), thereby preventing oxidative damage to vascular endothelial cells [141]. By stabilizing cellular redox balance, scutellarin mitigates oxidative stress–induced endothelial dysfunction, a key event in the early development of atherosclerosis [136].

In addition to its antioxidant properties, scutellarin exhibits potent anti-inflammatory effects in vascular tissues. It inhibits the NF-κB signaling pathway, which in turn suppresses the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and adhesion molecules like ICAM-1 and VCAM-1. This modulation reduces leukocyte adhesion and vascular inflammation, contributing to improved arterial integrity and reduced plaque formation [1].

Scutellarin also improves vascular tone through its vasorelaxant effects. It enhances nitric oxide (NO) bioavailability by upregulating endothelial nitric oxide synthase (eNOS) expression and inhibiting oxidative degradation of NO. The resulting vasodilation leads to improved blood flow and reduced systemic vascular resistance, which may contribute to its antihypertensive effects [86]. Additionally, by interfering with calcium influx pathways in vascular smooth muscle cells, scutellarin helps induce smooth muscle relaxation, further supporting its role in blood pressure regulation [112].

Moreover, scutellarin exhibits anti-thrombotic activities by inhibiting platelet aggregation and suppressing coagulation factor activation. It downregulates thromboxane A2 synthesis and inhibits fibrin formation, which reduces the risk of thrombus development. These anti-platelet and anticoagulant effects make scutellarin a potential candidate for the prevention of cardiovascular events such as myocardial infarction and ischemic stroke [20].

Scutellarin promotes cardiovascular health through its integrated actions on oxidative stress, inflammation, vascular function, and thrombosis. These properties position it as a multifunctional cardiovascular agent with applications in both primary prevention and adjunctive therapy for a wide range of vascular-related diseases.

2.5. Anticancer potential of Scutellarin

Scutellarin, a naturally occurring flavonoid glycoside and target multiple molecular and cellular pathways implicated in tumor development and progression. Its bioactivity has been primarily attributed to its ability to disrupt fundamental processes essential for cancer cell survival, including apoptosis, proliferation, angiogenesis, and oncogenic signaling [32]. A major mechanism through which scutellarin exerts its antitumor effect is the induction of apoptosis. It facilitates programmed cell death in malignant cells by modulating apoptotic regulators such as caspases and members of the Bcl-2 family. This contributes to the selective elimination of cancer cells while minimizing damage to normal tissue [50]. In parallel, scutellarin has demonstrated antiproliferative effects by interfering with cell cycle regulation. It downregulates cyclins and cyclin-dependent kinases, arresting the cycle at critical checkpoints and preventing uncontrolled cellular replication [9].

Scutellarin also impairs angiogenesis, the formation of new blood vessels that tumors rely on for oxygen and nutrient supply. By downregulating angiogenic factors and interfering with pro-angiogenic signaling pathways such as VEGF/PI3K/Akt, it starves tumors of their vascular support. This inhibition of neovascularization contributes to reduced tumor growth and metastatic potential [71]. Moreover, scutellarin affects several signaling cascades that are often dysregulated in cancer, including NF-κB, STAT3, and Wnt/β-catenin pathways. Its interference with these networks helps suppress cancer cell survival, inflammation, invasion, and resistance to apoptosis. These multi-targeted actions suggest that scutellarin not only hampers tumor development but may also enhance responsiveness to conventional therapies [98]. Overall, the anticancer potential of scutellarin is attributed to its integrated effects on cell death, growth suppression, angiogenic blockade, and signal modulation. These mechanisms form a compelling foundation for its continued investigation as a natural anticancer agent, particularly in combination with existing chemotherapeutic strategies. Further translational studies are warranted to elucidate its clinical relevance, bioavailability, and safety in humans. Scutellarin has demonstrated notable anticancer activity across a range of experimental cancer models, including breast, lung, and colorectal cancers, primarily through mechanisms involving apoptosis induction and inhibition of tumor progression. Table 4 compiles the anticancer potential of scutellarin across experimental models, providing information on cancer types, doses, mechanistic effects, strength of evidence, and clinical implications.

Scutellarin's diverse pharmacological properties, including its neuroprotective, cardiovascular, and anticancer effects, make it a promising therapeutic agent for a wide range of conditions [146]. Further research is needed to fully understand its mechanisms of action and optimize its therapeutic potential.

2.6. ADME and metabolite profile of Scutellarin

Scutellarin's pharmacokinetic profile comprising its absorption, distribution, metabolism, and excretion (ADME), plays a critical role in determining its therapeutic efficacy. Upon oral administration, scutellarin exhibits relatively poor absorption in the gastrointestinal tract due to its high polarity and limited permeability. Once absorbed, it is rapidly distributed, though its bioavailability remains low, primarily due to extensive first-pass metabolism and limited membrane permeability [105].

Metabolically, scutellarin undergoes hydrolysis by intestinal and hepatic enzymes to yield scutellarein, its aglycone form. Scutellarein is considered an active metabolite and retain or even enhance some of the pharmacological activities attributed to the parent compound, particularly its antioxidant and anti-inflammatory effects. The conversion of scutellarin to scutellarein is thus a key step influencing its biological action in vivo [79]. Excretion of scutellarin and its metabolites occurs predominantly via the biliary route, with a smaller portion eliminated in urine. However, due to the rapid metabolism and clearance, the systemic bioavailability of scutellarin remains a challenge for clinical applications. This limitation has prompted the development of various delivery strategies, including nanoparticle-based formulations, liposomes, and solid lipid carriers, all aimed at enhancing its solubility, stability, and absorption [51]. These advanced delivery systems have

Table 4. Anticancer potential of Scutellarin across experimental Models.

Model Type	Cancer Type	Dose/ Concentration	Mechanism Observed	Strength Evidence	Outcome/Clinical Relevance
Cell	Breast cancer (MCF-7)	25 μM	Caspase-mediated apoptosis	72% growth inhibition	Demonstrates strong cytotoxic activity [137]
Xenograft	Lung cancer	Not reported	Angiogenesis suppression	68% tumor volume reduction	Confirms in vivo antitumor efficacy [55]
Cell	Hepatocellular carcinoma (HepG2)	30 μM	Mitochondrial apoptosis pathway	74% inhibition	Indicates potency against liver cancer [109]
Cell	Cervical cancer (HeLa)	20 μM	G_2/M cell-cycle arrest, apoptosis	82% inhibition	Highlights strong antiproliferative effect [59]

shown promise in preclinical models, improving the pharmacokinetic parameters and therapeutic outcomes of scutellarin. While scutellarin demonstrates potent bioactivity in experimental systems, its clinical potential is currently hampered by poor bioavailability. Continued research into its metabolic pathways and the optimization of delivery systems is essential to fully harness its therapeutic benefits.

3. Recent advances in research

Recent research has shed light on novel mechanisms through which scutellarin exerts its therapeutic effects. These discoveries have expanded our understanding of this promising natural compound and its potential applications [120].

Regulation of MicroRNAs: Emerging research suggests that scutellarin can modulate the expression of microRNAs (miRNAs), small non-coding RNA molecules that play a crucial role in regulating gene expression [94]. Scutellarin regulates specific miRNAs involved in various cellular processes, including inflammation, apoptosis, and cell proliferation. This novel mechanism of action adds to the complexity of scutellarin's therapeutic effects and opens new avenues for exploring its potential in treating various diseases [26].

Mitochondrial Protection: Scutellarin protect mitochondria, the powerhouses of cells, from damage caused by oxidative stress. This protective effect is attributed to scutellarin's ability to enhance mitochondrial function, reduce oxidative stress, and prevent mitochondrial dysfunction [101]. This mechanism is particularly relevant in neurodegenerative diseases, where mitochondrial dysfunction plays a significant role in disease progression [56].

Immune Modulation: Recent studies have revealed that scutellarin can modulate the immune system, potentially contributing to its therapeutic effects in various conditions [33]. Scutellarin suppresses the activation of immune cells, such as T cells and macrophages, and reduce the production of pro-inflammatory cytokines. This immune-modulatory effect suggests that scutellarin may have therapeutic potential in autoimmune diseases and inflammatory conditions [91].

These novel mechanisms of action highlight the growing understanding of scutellarin's therapeutic potential. Further research is needed to fully elucidate these mechanisms and explore their implications for developing new therapeutic strategies [74].

3.1. Formulation innovations

Recent advancements in drug delivery systems have significantly improved the therapeutic potential of scutellarin. These formulation innovations are primarily aimed at enhancing its bioavailability, protecting it from metabolic degradation, enabling targeted delivery, and prolonging its therapeutic activity [45]. From a translational standpoint, these formulation and combination strategies are designed to overcome the principal pharmacokinetic and development barriers that have constrained scutellarin's clinical advancement, particularly its poor oral bioavailability, lack of standardized quality control, and limited clinical validation. By leveraging nanoformulations and rational co-therapies, recent research aims to enhance systemic exposure, therapeutic consistency, and efficacy, while aligning scutellarin development with emerging regulatory and personalized medicine frameworks required for successful clinical translation [30]. Conventional delivery of scutellarin is limited by poor solubility and rapid metabolism; therefore, novel carriers such as nanoparticles, liposomes, and microspheres have been investigated to address these limitations [39].

Nanoparticles have shown particular promise in scutellarin delivery. Among them, poly(lactic-co-glycolic acid) (PLGA)-based nanoparticles have been widely studied for their biocompatibility and controlled release properties [133]. Encapsulation of scutellarin in PLGA nanoparticles has been reported to protect the compound from premature degradation and significantly improve its accumulation in

target tissues [95]. Mechanistically, nanoscale encapsulation improves oral bioavailability by protecting scutellarin from enzymatic degradation and first-pass metabolism, enhancing transepithelial transport across the intestinal barrier, and reducing efflux transporter–mediated drug loss. By facilitating mucus penetration and modulating tight-junction or carrier-mediated uptake, nanocarriers increase systemic exposure and prolong circulation time, enabling more efficient accumulation at disease-relevant tissues and an overall improvement in therapeutic index [7]. For instance, intravenous administration of scutellarin-loaded nanoparticles has demonstrated enhanced neuroprotective effects in animal models of cerebral ischemia-reperfusion injury by promoting targeted delivery to the brain (Chang [134]). These findings underscore the promise of nanoparticle-enabled delivery systems, particularly membrane-engineered nanocarriers, in facilitating clinical translation for neurological disorders by enhancing blood–brain barrier penetration and improving CNS targeting. By leveraging biomimetic cell membrane coatings to modulate nanoparticle–BBB interactions, such platforms can overcome a key delivery bottleneck in neurotherapeutics, while ongoing advances in biosafety evaluation, scalable manufacturing, and regulatory alignment remain essential for their successful clinical deployment [138].

Liposomes, which are spherical vesicles composed of phospholipid bilayers, also offer a viable approach to improving the pharmacokinetic profile of scutellarin. Scutellarin-loaded liposomes have been found to increase bioavailability and promote targeted release at the site of action [22]. By recapitulating key features of biological membranes, liposomes enhance cellular uptake and prolong systemic circulation by shielding encapsulated drugs from rapid clearance, while simultaneously altering biodistribution to favor target tissues. These properties have translated into improved therapeutic indices and reduced off-target toxicity in several clinically approved liposomal formulations, underscoring their value as a mature and regulatory-validated platform for sustaining effective drug concentrations [16]. Notably, liposomal scutellarin has shown enhanced osteogenic potential in vitro and in vivo, suggesting possible applications in bone tissue engineering and regeneration [80]. This formulation-driven enhancement underscores the relevance of delivery systems in expanding scutellarin's therapeutic indications beyond conventional anti-inflammatory and neuroprotective roles.

Additionally, microspheres, particularly those prepared using biodegradable polymers [31], have been developed to enable sustained release of scutellarin over extended periods. This approach can reduce dosing frequency and maintain therapeutic plasma concentrations, which is beneficial in managing chronic conditions [113]. Sustained-release delivery systems are particularly advantageous in chronic cardiovascular and inflammatory diseases, where maintaining stable therapeutic plasma levels is critical to efficacy and adherence. By reducing peak–trough fluctuations associated with conventional dosing, advanced SR platforms such as polymeric matrices, lipid-based carriers, and mucoadhesive or pH-responsive systems, can prolong drug release, lower dosing frequency, and improve tolerability, thereby supporting more consistent disease control and patient compliance [25]. Preliminary studies indicate that microsphere-based delivery systems can improve the stability and bioactivity of scutellarin, although more in vivo evaluations are needed to confirm these effects [135].

These formulation innovations ranging from nanoparticles and liposomes to microspheres are pivotal in overcoming the inherent pharmacokinetic challenges of scutellarin. By improving solubility, stability, and tissue-targeting capabilities, such delivery systems are essential for translating scutellarin into viable clinical applications across neurological, cardiovascular, and bone-related therapeutic areas. Collectively, they reposition scutellarin from a bioactive flavonoid to a formulation-optimized therapeutic candidate with realistic translational potential.

3.2. Combination therapies and drug synergy

Combining scutellarin with other therapeutic agents has demonstrated synergistic pharmacological effects in several preclinical models, particularly in cancer and neurodegenerative disorders. Such combination strategies may enhance therapeutic efficacy, mitigate drug resistance, and allow dose reduction of cytotoxic drugs, thereby improving safety profiles [106].

Scutellarin and Cisplatin: Co-administration of scutellarin with cisplatin has been reported to synergistically enhance antitumor activity against ovarian cancer cells. This combination increases platinum-DNA adduct formation, intensifies caspase-mediated apoptosis, and reduces cisplatin-induced nephrotoxicity in some models, possibly due to scutellarin's antioxidant properties [127].

Scutellarin and 5-Fluorouracil (5-FU): Scutellarin potentiates the anticancer effects of 5-FU in colorectal and gastric cancer models. The dual treatment suppresses tumor proliferation by modulating apoptotic gene expression (e.g., upregulating Bax, downregulating Bcl-2), inhibits angiogenesis, and improves survival outcomes in xenograft models [128].

Scutellarin and Doxorubicin: Emerging evidence indicates that scutellarin may reduce doxorubicin-induced cardiotoxicity while maintaining or enhancing its anticancer efficacy. This protective effect may be mediated via Nrf2/HO-1 pathway activation and oxidative stress suppression, making scutellarin a potential adjuvant in anthracycline-based regimens [107].

Scutellarin and Temozolomide: In glioblastoma models, scutellarin has been explored as a sensitizing agent when combined with temozolomide, the standard chemotherapeutic for brain tumors. Preclinical results suggest improved drug penetration across the blood-brain barrier, increased tumor apoptosis, and reduced MGMT expression which is a key marker of resistance [93].

Scutellarin in Neurodegenerative Disease Models: In neuroprotection studies, scutellarin combined with memantine (an NMDA receptor antagonist used in Alzheimer's therapy) has shown additive effects in reducing neuronal oxidative damage and improving cognitive performance in animal models. Such findings highlight its potential for adjunctive use in neurodegenerative conditions [43].

These studies emphasize the growing relevance of scutellarin in combination therapies. By targeting multiple molecular pathways such as oxidative stress, apoptosis, angiogenesis and inflammation. scutellarin enhances the pharmacological profiles of conventional drugs. Nonetheless, translational studies and clinical trials are urgently needed to optimize dosing strategies, evaluate pharmacokinetic interactions, and confirm safety and efficacy in human subjects.

3.3. Mechanistic pathways of Scutellarin

Scutellarin exerts its pharmacological effects through multiple interrelated molecular pathways that underlie its anti-inflammatory, antioxidant, neuroprotective, cardioprotective, and anticancer activities. A central anti-inflammatory mechanism of scutellarin involves inhibition of the NF-κB signaling cascade through upstream suppression of IKKβ and IκBα phosphorylation, thereby preventing p65 nuclear translocation. In models of pressure- and hypoxia-induced retinal ganglion cell injury, this effect is tightly coupled to activation of the Keap1/Nrf2 antioxidant axis, resulting in reduced oxidative stress and coordinated downregulation of NF-κB–dependent pro-inflammatory mediators, including TNF-α, IL-6, and IL-1β. Concurrent attenuation of NF-κB signaling limits apoptosis by decreasing Bax and cleaved caspase-3 while restoring Bcl-2 expression, underscoring the integrated redox–inflammatory control underlying scutellarin's neuroprotective efficacy [21]. This anti-inflammatory action helps in reducing immune-mediated tissue damage across various disease models [41].

In addition to its anti-inflammatory effects, scutellarin activates the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, promoting the expression of antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and heme oxygenase-1 (HO-1). Mechanistically, scutellarin promotes disruption of the Keap1–Nrf2 complex, relieving Keap1-mediated repression and allowing cytoplasmic stabilization and nuclear accumulation of Nrf2, where it binds antioxidant response elements (AREs) to drive transcription of cytoprotective genes involved in redox homeostasis and stress resistance [15]. These antioxidants play a crucial role in mitigating oxidative stress, a common contributor to neurodegenerative and cardiovascular conditions [118].

Scutellarin also modulates apoptosis by influencing the expression of Bcl-2 family proteins and regulating the activation of caspase-3 and caspase-9, thereby inhibiting cell death and preserving tissue integrity. Specifically, scutellarin disrupts mitochondrial apoptotic homeostasis by shifting the Bcl-2 family balance toward a pro-apoptotic state, characterized by Bax upregulation and Bcl-2 downregulation, leading to loss of mitochondrial membrane potential, cytochrome c release, and activation of the caspase-9/caspase-3 cascade with subsequent PARP cleavage [115].

In cancer models, it suppresses cell proliferation and invasion by downregulating the mitogen-activated protein kinase (MAPK) pathway. Inhibition of MAPK subfamilies particularly JNK and p38, alongside ERK, interferes with oncogenic signaling that governs tumor cell proliferation, migration, and survival, while also modulating apoptosis, autophagy, DNA damage responses, and drug efflux mechanisms. By disrupting MAPK crosstalk with PI3K/Akt and NF-κB pathways and reshaping the tumor microenvironment, suppression of JNK/p38 signaling has emerged as a promising strategy to attenuate tumor aggressiveness and overcome chemotherapy resistance in cancer models [75]. Moreover, its engagement with the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway supports cell survival, enhances angiogenesis, and promotes tissue regeneration, particularly in ischemic or injured tissues [102]. Activation of the PI3K/Akt pathway by scutellarin underlies its cardioprotective actions by preserving endothelial function, enhancing nitric oxide bioavailability, and promoting survival signaling that limits ischemia-induced endothelial and cardiomyocyte apoptosis. Through these mechanisms, scutellarin supports vascular homeostasis and myocardial

resilience, providing a rational molecular basis for its therapeutic potential in cardiovascular disease management [141].

A comparative evaluation of scutellarin's mechanistic pathways across different disease contexts reveals distinct patterns of pathway dominance. In models of oxidative stress and inflammation, NF-κB and Nrf2 signaling act as central regulators, where NF-κB inhibition via suppression of IκB-α phosphorylation, reduces pro-inflammatory mediators such as IL-1β, IL-6, TNF-α, iNOS, and COX-2, while Nrf2 activation enhances antioxidant defenses by upregulating SOD, CAT, and HO-1. The coordinated modulation of these pathways not only attenuates reactive oxygen species (ROS) accumulation but also reinforces the anti-inflammatory response, highlighting their functional crosstalk as a critical mechanism for cellular protection [142]. In contrast, The PI3K/Akt pathway functions as a central mediator of cardioprotective and tissue-regenerative processes by promoting cell survival, angiogenesis, and repair of ischemic or damaged tissues. In hypoxia-stimulated models, activation of PI3K/Akt such as via miRNA-enriched exosomes, enhances endothelial proliferation, migration, and neovascularization, thereby accelerating tissue regeneration and restoring vascular integrity in compromised or diabetic environments [65]. For anticancer activity, scutellarin exerts effects by modulating MAPK signaling and regulating both intrinsic and extrinsic apoptotic pathways, leading to cell-cycle arrest, induction of programmed cell death, and suppression of tumor cell proliferation, invasion, and survival. By restoring apoptosis in otherwise resistant cancer cells, these mechanisms represent critical molecular targets for natural-product–based anticancer therapy and highlight scutellarin's potential as a selective and multi-targeted chemotherapeutic agent [14]. To enhance clarity, a summarized comparison of these signaling pathways, their molecular targets, and disease-specific outcomes is presented in Table 5, highlighting pathway dominance across inflammatory, neurodegenerative, cardiovascular, and cancer models.

Despite these general trends, some inconsistencies remain in the literature. For instance, PI3K/Akt signaling exerts context-dependent effects, promoting neuronal survival, angiogenesis, and tissue repair in neuroprotective settings, while in cancer, hyperactivation of the same pathway can drive cell proliferation, survival, and tumor progression. This duality underscores the pathway's pivotal role in both physiological homeostasis and pathological conditions, highlighting the need for carefully targeted modulation in therapeutic interventions [42]. Similarly, The extent of NF-κB or MAPK pathway inhibition by bioactive compounds can vary markedly across studies, with some flavonoids and other natural products producing inconsistent or even contradictory outcomes in similar inflammatory models, reflecting differences in experimental conditions, cell types, dosing regimens, and disease contexts such as ulcerative colitis [60]. These gaps underscore the need for more context-specific investigations to delineate the precise conditions under which scutellarin modulates these pathways, as well as to clarify potential interactions or crosstalk between signaling cascades in complex disease models. Overall, this comparative perspective emphasizes that while scutellarin exerts multi-target effects, its efficacy is highly context-dependent, and understanding these nuances is critical for translating preclinical findings into therapeutic applications. Through these interconnected signaling pathways, scutellarin demonstrates multi-target therapeutic potential in the management of inflammation, oxidative damage, cancer, and neurovascular disorders.

4. Current challenges in Scutellarin research

Scutellarin, a promising natural compound with a wide range of therapeutic potential, faces several challenges in its development and clinical application [84]. These challenges primarily revolve around its bioavailability, standardization, and clinical trial limitations [116] Chief among these limitations are scutellarin's poor aqueous solubility and rapid metabolic clearance, which markedly reduce oral bioavailability and systemic exposure. These pharmacokinetic constraints compromise the consistency and reproducibility of its therapeutic effects across preclinical and clinical studies, despite its demonstrated multi-targeted efficacy in oxidative stress, inflammation, apoptosis, and vascular protection [90]. Another major challenge lies in standardization and quality control. As a plant-derived flavonoid, scutellarin's content and pharmacological potency are influenced by factors such as plant genotype, geographical origin, harvesting season, and specific plant parts used. For instance, flavonoid accumulation differs between the aerial parts, which peak in spring and the roots, which accumulate more in autumn and thereby result in variations in antioxidant activity and anticancer efficacy. Such heterogeneity complicates dose optimization, cross-study comparisons, and reproducibility, posing a significant barrier to consistent clinical development [18].

The limited number of rigorously designed human clinical trials further restricts scutellarin's translational potential. While preclinical studies consistently

Table 5. Summary of major signaling pathways modulated by Scutellarin across disease models.

Signaling pathway	Key molecular targets	Primary disease context(s)	Dominant biological effects	Representative outcomes
NF-κB	IκBα, p65, TNF-α, IL-6, IL-1β	Inflammation, neurodegeneration, cardiovascular disorders	Anti-inflammatory	Reduced cytokine production, suppression of immune-mediated tissue damage, attenuation of chronic inflammation [91]
Nrf2/ARE	Nrf2, Keap1, HO-1, SOD, CAT	Oxidative stress–related disorders, neurodegeneration, cardiovascular diseases	Antioxidant, cytoprotective	Enhanced antioxidant enzyme expression, reduced ROS accumulation, protection against oxidative injury [125]
PI3K/Akt	PI3K, Akt, mTOR, eNOS	Cardiovascular diseases, ischemic injury, tissue regeneration	Pro-survival, pro-angiogenic	Improved cell survival, enhanced angiogenesis, resistance to ischemia-induced apoptosis [23]
MAPK (ERK, JNK, p38)	ERK1/2, JNK, p38 MAPK	Cancer, inflammation	Anti-proliferative, anti-invasive	Inhibition of tumor cell growth, reduced migration and invasion, modulation of stress responses [129]
Apoptosis pathways (intrinsic)	Bcl-2, Bax, cytochrome c, caspase-3, caspase-9	Cancer, neurodegeneration	Pro- or anti-apoptotic (context-dependent)	Induction of apoptosis in cancer cells; protection against excessive cell death in non-malignant tissues [47]

demonstrate its neuroprotective, cardiovascular, and anti-inflammatory effects, human evidence is largely indirect, often derived from combination formulations such as breviscapine rather than purified scutellarin. This reliance on mixed preparations hampers precise mechanistic attribution, dose–response determination, and regulatory confidence, underscoring the need for well-controlled clinical studies to validate scutellarin's therapeutic efficacy in cardiovascular and other chronic diseases [144]. Safety profiling remains a critical gap for scutellarin. Although traditionally regarded as safe, its long-term toxicological profile, potential herb–drug interactions, population-specific tolerability, and pharmacokinetic characteristics have not been comprehensively evaluated. Like many plant-derived natural products, scutellarin's chemical complexity, potential for contamination or variability, and lack of standardized dosing underscore the need for rigorous preclinical and clinical safety studies, robust pharmacovigilance, and harmonized quality control to ensure safe and reliable therapeutic use [2]. Collectively, these challenges underscore the need for integrated formulation optimization, standardized production pipelines, rigorous clinical validation, and safety-focused translational strategies to advance scutellarin beyond experimental promise toward clinical applicability.

4.1. Bioavailability and ADME challenges

Scutellarin, despite its broad pharmacological potential, suffers from poor oral bioavailability, which significantly limits its clinical utility. After oral administration, only a small fraction of the compound reaches systemic circulation. This is primarily due to its poor water solubility and extensive first-pass metabolism in the gastrointestinal tract [121]. Upon ingestion, scutellarin undergoes rapid hydrolysis to form scutellarein, a major metabolite, which is then subject to further phase II metabolism, including glucuronidation and sulfation, in the intestinal mucosa and liver. These metabolic transformations reduce the concentration of active parent compound in circulation, limiting its therapeutic efficacy.

The compound also exhibits limited permeability across intestinal epithelial membranes, which further contributes to its low absorption. Distribution studies have shown that scutellarin tends to accumulate in organs such as the liver and kidneys, but its ability to reach target sites like the brain or inflamed tissues is often inadequate without specialized delivery systems. Moreover, its elimination occurs rapidly through biliary and renal excretion, leading to a short half-life in plasma [7].

To overcome these ADME-related limitations, several formulation strategies have been explored. Nanoformulations, including polymeric nanoparticles, have been employed to enhance scutellarin's solubility and protect it from enzymatic degradation during gastrointestinal transit. These systems also improve its ability to cross biological barriers and deliver the drug to specific target tissues [40]. Liposomal delivery systems, which involve encapsulating scutellarin in phospholipid bilayers, offer an

additional advantage by improving absorption and prolonging systemic circulation time [103]. Another promising approach is cocrystallization, where scutellarin is combined with suitable coformers to form more soluble crystalline structures. This method significantly enhance its dissolution rate and intestinal absorption [96].

Together, these advanced formulation strategies aim to address the inherent ADME challenges of scutellarin, making it a more viable candidate for therapeutic applications in both acute and chronic conditions.

4.2. Standardization and quality control

Standardization and quality control are essential for ensuring the safety, consistency, and therapeutic efficacy of scutellarin-containing formulations. One of the major challenges lies in the variability of raw materials used in the production of scutellarin [100]. Since scutellarin is typically derived from botanical sources, such as Erigeron breviscapus, differences in plant genetics, cultivation conditions, harvesting time, and post-harvest processing can lead to significant fluctuations in the concentration and purity of the compound. These inconsistencies can compromise both the reproducibility of research outcomes and the reliability of clinical applications [19].

Purity is another critical concern. Crude extracts often contain a mixture of flavonoids, phenolic compounds, and other phytochemicals, which may interfere with the intended pharmacological effects of scutellarin or introduce unwanted side effects. Without proper purification and identification, it becomes difficult to attribute therapeutic outcomes specifically to scutellarin, making quality assurance even more challenging. Additionally, the lack of standardized protocols for processing and purifying the compound increases the risk of contamination and variation in potency.

Batch-to-batch reproducibility is equally important for clinical translation. Variations in extraction efficiency and analytical inconsistencies between production runs can lead to significant differences in final product quality. To address these challenges, researchers have been developing standardized extraction procedures that ensure consistent yield and composition of scutellarin across different batches. These methods are designed to minimize variability and optimize the recovery of the active compound from plant materials [88].

Reliable analytical techniques, such as high-performance liquid chromatography (HPLC), are also being employed to accurately quantify scutellarin content and assess its purity. These analytical tools are vital for enforcing stringent quality control measures and verifying that each batch meets predefined specifications [34]. By combining standardized extraction protocols with robust analytical testing, the pharmaceutical development of scutellarin can achieve higher consistency, better safety profiles, and improved therapeutic outcomes.

4.3. Clinical trials

Although scutellarin has demonstrated considerable therapeutic promise in preclinical models, direct evaluation of scutellarin as a single-molecule intervention in large, randomized clinical trials remains limited. Most human evidence is derived from studies using breviscapine, a standardized Erigeron breviscapus flavonoid extract containing over 85% scutellarin. Widely used in China for decades, breviscapine has demonstrated cardiovascular benefits including vasodilation, endothelial and myocardial protection, antithrombosis, anti-inflammatory effects, and mitigation of ischemia/reperfusion injury, and is commonly administered alongside conventional therapies for ischemic stroke, cerebrovascular insufficiency, and a range of cardiovascular conditions [35]. Clinical studies using breviscapine—administered via injection or oral formulations—have demonstrated dose-dependent neuroprotective effects in models of cerebral ischemia/reperfusion injury and post-stroke conditions. These benefits include improved neurological function and cognitive performance, enhanced cerebral blood flow, attenuation of pro-inflammatory cytokines, reduction of oxidative stress and apoptotic markers, and inhibition of NF-κB signaling and microglial activation. Collectively, these findings provide indirect but compelling evidence supporting scutellarin's translational potential in neurovascular and microcirculatory disorders [64]. Existing clinical investigations specifically isolating scutellarin are generally limited in scale and scope, with many studies characterized by small sample sizes, short treatment durations, and heterogeneous outcome measures. These methodological limitations restrict definitive conclusions regarding efficacy and safety and contribute to the slow progression of scutellarin from experimental research to broader clinical adoption. Importantly, the reliance on combination herbal formulations or injectable preparations further complicates attribution of clinical outcomes solely to scutellarin.

A major barrier to successful clinical development is the compound's low oral bioavailability, which complicates dosing strategies and may prevent therapeutic plasma concentrations from being consistently achieved. This pharmacokinetic limitation can

undermine the interpretation of efficacy results in human studies and contribute to interindividual variability in therapeutic response [70]. Compared with established antioxidants and anti-inflammatory drugs such as edaravone or conventional NSAIDs, scutellarin demonstrates a favorable safety and tolerability profile across preclinical and clinical settings. Its pharmacodynamic activity including inhibition of NF-κB, MAPK, and PI3K/Akt pathways, as well as activation of Nrf2/ARE antioxidant signaling, effectively mitigates inflammation and oxidative stress in diverse tissues. However, oral administration results in low systemic exposure and a short half-life, underscoring that its limited clinical efficacy stems from pharmacokinetic constraints rather than intrinsic pharmacological weakness, thereby highlighting the critical need for formulation optimization and innovative delivery strategies [146].

To advance scutellarin toward wider clinical use, there is a clear need for well-designed, adequately powered randomized controlled trials that directly evaluate purified scutellarin in defined patient populations. These studies should incorporate standardized sourcing and extraction procedures, validated dosing regimens, pharmacokinetic–pharmacodynamic correlations, and clinically meaningful endpoints. In parallel, the development of improved delivery systems, including nanoformulations, lipid-based carriers, or injectable preparations, is essential to enhance bioavailability and therapeutic consistency [24]. Addressing these issues through rigorous clinical research and pharmaceutical innovation will be critical for validating scutellarin's therapeutic value and supporting its broader clinical translation.

4.4. Toxicity, drug interactions, and safety profile

Scutellarin is generally considered to have a favorable safety profile based on available preclinical data; however, some toxicological concerns have been reported. Animal studies have shown that high doses of scutellarin may induce hepatotoxicity, particularly with prolonged exposure, suggesting a need for caution in liver-compromised individuals. In vitro studies using human liver microsomes have also indicated that scutellarin can interact with cytochrome P450 enzymes, especially CYP3A4 and CYP2C9, potentially altering the metabolism of co-administered drugs [32].

Cell-based toxicity assays have reported mild cytotoxicity at elevated concentrations, though these effects were typically dose-dependent and reversible. Despite these findings, comprehensive toxicokinetic and long-term safety studies are lacking, and clinical data on adverse effects remain sparse [97].

Given these observations, further investigations are necessary to define the safe dosage range, evaluate chronic toxicity, and assess possible herb-drug interactions. Establishing a clear safety profile through both preclinical and clinical toxicological studies will be essential before scutellarin can be considered for routine therapeutic use.

5. Future directions for Scutellarin research

Scutellarin has emerged as a mechanistically rich, multi-target bioactive compound whose therapeutic relevance extends beyond conventional antioxidant or flavonoid classifications. Rather than acting through a single dominant pathway, accumulating evidence indicates that scutellarin engages a network-level mode of action, simultaneously modulating redox homeostasis, inflammatory signaling, mitochondrial function, and cell survival pathways. Analogous to natural products targeting regulated cell death (RCD) networks in diabetic retinopathy, scutellarin appears to orchestrate "network rewiring" by balancing pro- and anti-apoptotic factors, normalizing autophagic flux, suppressing inflammasome activation, and activating cytoprotective nodes such as Nrf2 and PI3K/Akt. Supported by convergent data from cellular, animal, and limited human studies, this systems-level activity distinguishes scutellarin from structurally related flavonoids and positions it as a promising candidate for network pharmacology–driven drug development [46].

5.1. Exploration of new therapeutic areas

Scutellarin has been most extensively studied in cerebrovascular and cardiovascular disorders, including ischemic stroke, myocardial infarction, and diabetes-related vascular complications. In these contexts, scutellarin consistently improves endothelial function, enhances cerebral and myocardial perfusion, reduces oxidative damage, and suppresses pro-inflammatory cytokine production. Across more than 20 preclinical studies, scutellarin's protective effects consistently converge on critical molecular nodes, including NF-κB, MAPK, Nrf2, and mitochondrial apoptotic regulators. By modulating these pathways, it not only suppresses inflammatory cascades and oxidative stress but also stabilizes mitochondrial integrity and cell survival. This convergence mirrors the mechanistic focus of NF-κB-targeted interventions in oncology, where precise modulation of inflammatory signaling is essential for improving therapeutic outcomes. The reproducibility of scutellarin's effects across diverse cellular and animal models provides quantitative and mechanistic support for its vascular

protective and cytoprotective profile, reinforcing its candidacy for translational development [10].

Beyond vascular disease, recent mechanistic synthesis highlights scutellarin's expanding relevance in neurodegenerative disorders. In models of Alzheimer's and Parkinson's diseases, scutellarin exerts neuroprotective effects by reducing ROS accumulation, inhibiting neuronal apoptosis, suppressing microglial activation, and preserving synaptic integrity. At least ten independent cellular and animal studies demonstrate that scutellarin and its primary in vivo metabolite, scutellarein, improve neuronal viability, cognitive performance, and behavioral outcomes in models of ischemia/reperfusion and neurodegeneration. Observed effects include attenuation of neuronal cell damage, reduction of cerebral edema, normalization of excitatory and inhibitory neurotransmitters (Glu, Asp, Gly, GABA, Tau), and enhancement of Ca^{2+}-ATPase and Na^{+}/K^{+}-ATPase activity. The reproducibility and dose-dependent nature of these findings underscore a robust neuroprotective signal, positioning scutellarin as a potential disease-modifying adjunct rather than a purely symptomatic neuroprotective agent [108].

Scutellarin's anti-inflammatory activity, particularly its ability to modulate NF-κB and MAPK signaling, also supports its potential application in chronic inflammatory diseases such as inflammatory bowel disease. In preclinical colitis and epithelial inflammation models, scutellarin reduces pro-inflammatory cytokine release, limits immune cell infiltration, and restores intestinal barrier integrity. These effects place scutellarin within a growing class of multi-target anti-inflammatory agents capable of addressing both immune dysregulation and epithelial dysfunction, a dual requirement for effective IBD management [131].

Its immunomodulatory capacity further extends its therapeutic scope to autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus. By regulating immune cell activation, attenuating oxidative stress, and suppressing aberrant cytokine cascades, scutellarin demonstrates the potential to slow disease progression while minimizing broad immunosuppression. This balanced immunoregulatory profile, supported by emerging in vivo data, aligns with contemporary strategies seeking safer alternatives to long-term steroid or biologic therapies [72].

Taken together, scutellarin represents a multi-pathway therapeutic candidate with relevance across neurodegeneration, cardiovascular disease, metabolic disorders, chronic inflammation, and autoimmunity. Future research should prioritize disease-specific systems biology analyses to map target–pathway–outcome relationships and identify patient populations most likely to benefit from scutellarin-based interventions. Carefully designed clinical trials integrating pharmacokinetics, biomarker-driven endpoints, and mechanistic validation will be essential for clinical positioning.

5.2. Advances in drug delivery and formulation strategies

Despite its strong pharmacodynamic profile, scutellarin's clinical translation remains constrained by poor aqueous solubility and limited oral bioavailability. Addressing these limitations is not merely a formulation challenge but a prerequisite for realizing the compound's multi-target therapeutic effects in humans. Without delivery optimization, the mechanistic advantages observed in preclinical models are unlikely to be reproduced consistently in clinical settings.

Nanoparticle-based delivery systems, including polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions, have demonstrated substantial improvements in scutellarin's stability, cellular uptake, and tissue distribution. Quantitative preclinical studies indicate that nanotechnology-enabled delivery can enhance the bioavailability of poorly soluble flavonoids and polyphenols including scutellarin, by two- to three-fold, resulting in improved cellular uptake, stability, and controlled release. These enhancements translate into significantly greater neuroprotective and anticancer efficacy in cellular and animal models, mirroring the successes observed with nanocarrier-based curcumin formulations, and reinforcing the translational potential of nanomaterial-assisted strategies for overcoming pharmacokinetic limitations [132]. These improvements directly translate into lower effective doses, reduced off-target toxicity, and improved therapeutic windows are major considerations for regulatory approval and clinical adoption.

Liposomal formulations have similarly improved solubility and systemic exposure, leading to prolonged circulation time and enhanced biodistribution in animal models. These properties are particularly relevant for scutellarin's application in vascular and neurological disorders, where sustained therapeutic levels are critical for efficacy [48]. From a translational perspective, liposomal delivery systems provide a clinically validated and scalable platform with established manufacturing protocols and regulatory precedents. Leveraging such systems for scutellarin, one of the key bioactive flavonoids from *Scutellaria baicalensis*, can enhance solubility, stability, and bioavailability while facilitating predictable pharmacokinetics. Coupled with mechanistic insights from in vitro and in vivo studies, this approach strengthens the feasibility

of advancing scutellarin-based therapeutics toward rigorous preclinical and clinical evaluation [81].

Pharmaceutical strategies such as co-crystal formation and cyclodextrin complexation are also being explored to enhance dissolution rate and oral absorption. These approaches offer scalable, regulatory-friendly solutions that may bridge the gap between experimental formulations and commercial pharmaceutical products [89]. Unlike complex nanocarriers, these strategies are particularly attractive for oral dosage forms and may accelerate clinical translation through simplified formulation design.

Emerging hydrogel-based and transdermal delivery systems provide alternative routes of administration that bypass first-pass metabolism and enable controlled drug release. Such systems are especially attractive for chronic conditions requiring long-term dosing, where maintaining stable plasma concentrations and minimizing systemic toxicity are essential Jacob *et al.*, [49], Edo, Mafe, Akpoghelie, & Gaaz *et al.*, [29]. These platforms align well with patient-centric therapeutic strategies, improving compliance and long-term treatment outcomes.

Overall, future progress in scutellarin research will depend on the integration of mechanistic insight, quantitative pharmacology, and advanced formulation science. Positioning scutellarin as a network-acting therapeutic supported by optimized delivery platforms and mechanistically informed clinical trials offers a clear pathway toward meaningful clinical translation rather than incremental flavonoid-based development. Such an approach elevates scutellarin from a promising natural compound to a clinically actionable therapeutic candidate.

5.3. Regulatory challenges and pathways toward clinical translation

As scutellarin continues to show therapeutic promise across conditions such as stroke, cardiovascular disease, neurodegeneration, and inflammatory disorders, its progression toward clinical application faces several regulatory challenges. One key issue lies in its classification as a plant-derived flavonoid, positioning it at the interface between conventional pharmaceuticals and herbal medicinal products [117]. This ambiguous classification of scutellarin complicates its regulatory positioning, particularly in Western jurisdictions where botanical drugs are evaluated under distinct frameworks compared with synthetic small molecules. Unlike conventional pharmaceuticals, natural products such as scutellarin present unique challenges due to their chemical complexity, variability in source material, and multi-target bioactivities, necessitating rigorous authentication, standardization, and mechanistic validation to satisfy evidentiary standards for safety, efficacy, and quality [114]. This dual identity creates divergent regulatory expectations across regions: in China, scutellarin-containing products such as breviscapine are approved as prescription drugs under structured frameworks that integrate innovative medications into the national healthcare system, whereas in Western jurisdictions, comparable compounds are more often classified and regulated as dietary supplements or botanical products. These differences reflect contrasting policy priorities, evidentiary requirements, and healthcare delivery mechanisms, highlighting the complexity of global development and market access for natural product–derived therapeutics [147].

In regulatory frameworks governed by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), botanical-derived compounds face heightened scrutiny related to purity, batch-to-batch consistency, and reproducibility of pharmacological effects [36]. These challenges are compounded by natural variability in plant sources and differences in extraction protocols, necessitating robust quality control strategies. Without rigorous standardization and validated analytical benchmarks, regulatory approval in Western markets remains difficult to achieve. For scutellarin to progress as a pharmaceutical-grade compound, validated analytical methods, clear impurity profiles, and Good Manufacturing Practice (GMP)-compliant production processes will be essential.

Another significant barrier is the absence of universally accepted regulatory guidelines defining scutellarin's therapeutic dosage ranges, routes of administration, and drug–drug interaction profiles. This uncertainty is further compounded by scutellarin's low intrinsic bioavailability, which limits systemic exposure and complicates the extrapolation of effective doses from preclinical ischemia and myocardial injury models to humans, where the timing, context, and multifactorial pathophysiology of stroke or cardiac ischemia demand precise pharmacokinetic and pharmacodynamic alignment [119]. Establishing these parameters is particularly important given evidence suggesting interactions with cytochrome P450 enzymes and the potential for hepatotoxicity at high doses [78]. Compared with established synthetic drugs used in similar indications, scutellarin currently lacks the comprehensive toxicological and long-term safety datasets required for full regulatory approval in Western markets.

The development of advanced pharmaceutical formulations, including nanoencapsulated, liposomal, or injectable scutellarin, presents both an opportunity and a regulatory challenge. While such systems may overcome bioavailability limitations and enhance therapeutic efficacy, however, nanotechnology-based

formulations introduce additional regulatory complexity, including requirements for thorough characterization of nanoparticle physicochemical properties, detailed evaluation of biodistribution and tissue accumulation, and rigorous long-term safety assessments to address potential systemic or organ-specific toxicity [134]. These considerations require regulatory pathways capable of accommodating novel delivery technologies without compromising safety standards [44]. Achieving regulatory harmonization between botanical drug frameworks and emerging nanomedicine guidelines will be essential, as predictable, coherent, and internationally aligned regulatory pathways are increasingly recognized as critical for the safe, efficient, and commercially viable development of nanotechnology-based therapeutics [77].

Ultimately, large-scale, randomized, and well-controlled clinical trials conducted in accordance with Good Clinical Practice (GCP) remain indispensable for regulatory acceptance. The limited number of Western-led, scutellarin-specific clinical trials constitutes a significant bottleneck for regulatory approval by agencies such as the FDA and EMA, despite extensive preclinical evidence demonstrating its broad pharmacological activities including neuroprotection, cardiovascular support, anti-inflammatory, antioxidant, anticancer, antiviral, and metabolic regulatory effects [126]. While the established clinical use of breviscapine offers a valuable precedent, regulatory agencies will require direct evidence that purified scutellarin, its principal active flavonoid, consistently reproduces key pharmacological effects such as improved microcirculation, vasodilation, antithrombotic activity, and platelet inhibition, while also demonstrating predictable pharmacokinetics, dose–response relationships, and acceptable safety margins in humans [124]. Strategic collaboration among academic researchers, regulatory authorities, and pharmaceutical developers will be essential to define clear approval pathways and facilitate the transition of scutellarin from bench to bedside.

6. Limitations

This review is limited by the scarcity of clinical trial data on scutellarin, as most available findings are derived from preclinical studies. Additionally, variability in experimental models, doses, and outcome measures across studies hinders direct comparison and standardization of results. These limitations highlight the need for more robust, well-designed clinical investigations to validate scutellarin's therapeutic potential.

7. Conclusion

Scutellarin demonstrates considerable promise across several pharmacological domains, including neuroprotection, anti-inflammatory activity, cardioprotection, and anticancer potential. Despite strong preclinical evidence, its clinical translation remains limited due to challenges such as poor bioavailability, inconsistent formulation standards, and a lack of large-scale clinical trials. Advancing drug delivery systems, refining its pharmacokinetic profile, and deepening our understanding of its molecular mechanisms will be essential to fully realize its therapeutic potential. Continued research efforts focused on combination therapies, standardized formulations, and well-designed human studies will be critical for integrating scutellarin into mainstream clinical practice. Mechanistically, scutellarin functions as a multi-pathway modulator, integrating NF-κB–driven anti-inflammatory effects, Nrf2-mediated antioxidant defense, PI3K/Akt and MAPK survival signaling, and apoptosis regulation, thereby supporting its efficacy across neurologic, cardiovascular, inflammatory, and oncologic models. Recent advances in formulation science have substantially strengthened its translational outlook by overcoming intrinsic bioavailability limitations and improving tissue targeting, positioning scutellarin as a formulation-enabled therapeutic candidate rather than a conventional flavonoid. Future progress will depend on rigorously standardized production, pharmacokinetic–pharmacodynamic alignment, and adequately powered clinical trials designed to meet Western regulatory expectations.

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Conflict of interest

The authors declare no conflict of interest.

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Authors' contributions

Hind A. Satar collected the data from the literature and prepared the first draft of the manuscript. **Ahmed Ahmed** and **Muna Bufaroosha** reviewed the draft and contributed to its revision and improvement. **Emad Yousif** supervised the work, approved the final version of the manuscript, and served as the team leader.

Code availability

Not applicable

Consent to participate

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Papers of particular interest, published recently, have been highlighted as: •Of importance ••Of major importance

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