Article

Baicalein: Molecular mechanisms, pharmacological properties, clinical applications, and challenges

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Received 24 February 2026; *Accepted 27 March 2026*; *Published online 15 April 2026*; *Published 1 March 2027*

Abstract
Baicalein (5,6,7-trihydroxyflavone), a major bioactive flavonoid aglycone derived primarily from the roots of *Scutellaria baicalensis* Georgi and *Oroxylum indicum* (L.) Kurz, has garnered significant scientific interest over the past decades due to its diverse and potent pharmacological activities. This comprehensive review systematically examines the multifaceted aspects of baicalein, encompassing its discovery, natural sources, chemical properties, extraction and purification methods, and challenging pharmacokinetic profile. The review delves deeply into the extensive spectrum of its pharmacological effects and underlying molecular mechanisms, including its potent anti-cancer, anti-inflammatory, antioxidant, anti-aging, neuroprotective, cardioprotective, hepatoprotective, renoprotective, anti-diabetic, and anti-microbial activities. Furthermore, it provides an up-to-date synthesis of available clinical trial data, safety evaluations, and quality control standards. Despite its remarkable therapeutic potential, the clinical translation of baicalein is significantly hampered by intrinsic challenges, primarily its poor water solubility, low oral bioavailability, and extensive first-pass metabolism. This review critically discusses these obstacles, explores current nanoformulation strategies designed to overcome them, and outlines future research directions necessary to harness the full therapeutic power of this promising natural compound.

Keywords baicalein; *Scutellaria baicalensis*; *Oroxylum indicum*; flavonoids; pharmacokinetics; bioavailability; anti-cancer; neuroprotection; clinical trials.

Network Biology
ISSN 2220-8879
URL: http://www.iaees.org/publications/journals/nb/online-version.asp
RSS: http://www.iaees.org/publications/journals/nb/rss.xml
E-mail: networkbiology@iaees.org
Editor-in-Chief: WenJun Zhang
Publisher: International Academy of Ecology and Environmental Sciences

1 Introduction

Natural products have historically served as a prolific and invaluable source of therapeutic agents, providing the foundation or inspiration for a substantial proportion of modern pharmaceuticals (Zhang, 2017a-d; Newman & Cragg, 2020). In the ongoing search for novel, multi-targeted therapies with favorable safety profiles, particularly for complex diseases like cancer, chronic inflammation, and neurodegeneration, bioactive phytochemicals have emerged as particularly promising candidates (Atanasov et al., 2021). Among the vast

chemical diversity found in medicinal plants, flavonoids, a ubiquitous class of polyphenolic compounds, have attracted immense research attention for their extensive array of health-promoting properties (Panche et al., 2016). Baicalein, a trihydroxyflavone, is one such compound that has risen to prominence within this class. It is the primary bioactive aglycone found in the roots of *Scutellaria baicalensis* Georgi (黄芩; Fig. 1), a perennial herb whose dried roots, known as Huang-Qin（黄芩）, have been a cornerstone of traditional Chinese medicine (TCM) for millennia (Zhao et al., 2019; Baidu Baike, 2026). In TCM, *Scutellariae Radix* is traditionally employed to "clear heat, dry dampness, purge fire, and remove toxins," and is clinically used to treat a variety of conditions, including dysentery, jaundice, hypertension, and respiratory ailments (Zhao et al., 2019; Ma et al., 2024a). The therapeutic efficacy of this botanical drug is largely attributed to its rich flavonoid content, with baicalein, along with its glycoside baicalin and wogonin, being its most characteristic and active constituents (Hu et al., 2022).

Fig. 1 *Scutellaria baicalensis* Georgi (Source: https://baike.baidu.com/item/%E9%BB%84%E8%8A%A9/406188).

The profound pharmacological interest in baicalein stems from its remarkable ability to modulate a wide range of critical signaling pathways involved in the pathogenesis of numerous human diseases (Paul et al., 2024). Over the past two decades, an exponential increase in preclinical studies has demonstrated that baicalein exerts pleiotropic effects, including potent anti-cancer, anti-inflammatory, antioxidant, neuroprotective, cardioprotective, and anti-diabetic activities (Zhao et al., 2019; Lei et al., 2024; Hu et al., 2022). At the molecular level, these effects are mediated through the compound's capacity to scavenge reactive oxygen species (ROS), chelate transition metal ions, and, most importantly, interact with and modulate a host of cellular signaling molecules and transcription factors, such as NF-κB, PI3K/Akt, MAPK, and Nrf2 (Dinda et al., 2017; Hu et al., 2022). This ability to simultaneously hit multiple targets positions baicalein as an ideal candidate for treating complex, multifactorial diseases where single-target therapies often fall short (Capó et al., 2025).

However, the journey from a promising laboratory finding to a clinically viable therapeutic agent has been fraught with challenges. The major obstacle to baicalein's clinical application is its extremely poor pharmacokinetic profile (Zhang et al., 2019b). Baicalein exhibits very low water solubility (approximately 0.1 mg/mL) and, when administered orally, undergoes rapid and extensive phase II metabolism, primarily glucuronidation and sulfation, in both the intestinal wall and the liver (Zhang et al., 2005; Li et al., 2021). This extensive first-pass metabolism results in poor systemic bioavailability of the parent aglycone, with the

circulating species being predominantly its conjugated metabolites, such as baicalein-7-O-glucuronide (Li et al., 2021). Consequently, achieving and maintaining therapeutic concentrations of the bioactive aglycone *in vivo* remains a significant hurdle. To circumvent these limitations, a considerable body of research has focused on developing advanced drug delivery systems, including nanocrystals, liposomes, phospholipid complexes, and cyclodextrin inclusion complexes, all aimed at improving baicalein's solubility, stability, and bioavailability (Liu et al., 2006; Zhang et al., 2011; Li et al., 2017).

This comprehensive review aims to provide a holistic and critical synthesis of the current state of knowledge on baicalein. It will systematically cover its natural sources, chemical properties, extraction methodologies, and the pharmacokinetic barriers to its use. The review will then provide an in-depth analysis of its wide-ranging pharmacological activities, detailing the underlying molecular mechanisms for each therapeutic effect. Subsequently, it will synthesize the available data from clinical trials, safety evaluations, and quality control measures. Finally, the review will discuss the ongoing challenges, such as bioavailability and formulation, and propose future research directions to translate the exceptional preclinical promise of baicalein into tangible clinical benefits for patients.

2 Discovery and History

The history of baicalein is inextricably linked to the traditional use of its primary botanical source, *Scutellaria baicalensis* Georgi. The roots of this plant have been documented as a medicinal agent in the "Shennong Bencao Jing" (神农本草经; The Divine Farmer's Materia Medica), one of the foundational texts of TCM dating back to approximately 200-300 CE (Zhao et al., 2019). For centuries, *Scutellariae Radix* (Huang-Qin) has been utilized in TCM formulas, often in combination with other herbs, to treat a wide spectrum of ailments characterized by "heat" and "dampness," including gastrointestinal infections, inflammatory conditions, jaundice, and hypertension (Huang and Zhang, 2012; Li and Zhang, 2013; Zhang, 2016a, 2017c, 2018; Ma et al., 2024a; Hu et al., 2022). It remains a key component in numerous modern TCM patent medicines.

The modern scientific discovery and isolation of baicalein as a discrete chemical entity began in the early 20th century with the advancement of phytochemical analytical techniques. The compound was first isolated from the roots of *Scutellaria baicalensis* in the 1930s and 1940s, during a period of intense investigation into the active constituents of medicinal plants (Takido et al., 1975; Shibata et al., 1946). Its chemical structure, 5,6,7-trihydroxyflavone, was elucidated in subsequent years, confirming its identity as a flavonoid aglycone (Fig. 2). The corresponding glycoside, baicalin (baicalein-7-O-glucuronide), was also identified and characterized during this era. For much of the latter half of the 20th century, baicalein was primarily studied as an anti-inflammatory and antioxidant agent, aligning with its traditional uses. However, the last two decades have witnessed an explosion of research uncovering its remarkably diverse pharmacological activities, particularly its potent anti-cancer properties (Li-Weber, 2009; Lei et al., 2024). This transition from a traditional herbal remedy to a subject of intense modern drug discovery research exemplifies the potential of ethnopharmacology to guide the development of new therapeutic leads.

3 Source, Chemistry, and Physicochemical Properties

3.1 Natural Sources

Baicalein is found in a limited number of plant species, with the most commercially and scientifically important being *Scutellaria baicalensis* Georgi (Lamiaceae) (Zhao et al., 2019). The roots of *S. baicalensis* (*Scutellariae Radix*) are the primary source, containing a complex mixture of flavonoids, with baicalin being the most abundant, followed by its aglycone baicalein, wogonin, and other related compounds (Hu et al., 2022). The content of baicalein in the dried roots can vary considerably depending on the geographical origin,

cultivation practices, harvesting time, and post-harvest processing (Ma et al., 2024a). Typically, the concentration of baicalin is much higher than that of its free aglycone. Besides *S. baicalensis*, baicalein is also found in other Scutellaria species, such as *S. lateriflora* L. (American skullcap) and *S. galericulata* L. (Marsh skullcap), although often in lower quantities (Zhang et al., 2019b). Another notable source is the stem bark of *Oroxylum indicum* (L.) Kurz (Bignoniaceae), a tree widely distributed in South and Southeast Asia (Dinda et al., 2015). In traditional medicine systems of India (Ayurveda) and other Asian countries, *O. indicum* is used for similar indications as *S. baicalensis*, and its bark is particularly rich in baicalein (Dinda et al., 2015).

3.2 Chemical Structure and Physicochemical Properties

The chemical structure of baicalein (5,6,7-trihydroxyflavone) is that of a flavone, a subclass of flavonoids characterized by a 2-phenylchromen-4-one backbone ($C_{15}H_{10}O_5$; Fig. 2). The molecule consists of two benzene rings (A and B) linked by a heterocyclic pyrone ring (C). Baicalein is distinguished by the presence of three hydroxyl (-OH) groups at positions 5, 6, and 7 on the A-ring. The structural feature that critically influences its properties is the 5-hydroxy group, which forms a strong intramolecular hydrogen bond with the adjacent 4-carbonyl group. This intramolecular hydrogen bond renders the 5-hydroxyl group relatively inert and significantly contributes to the compound's low water solubility and high lipophilicity (Zhang et al., 2019b). Baicalein is a lipophilic molecule, with a calculated logP value of approximately 2.5-3.0, classifying it as a Biopharmaceutics Classification System (BCS) class II compound: low solubility and high permeability (Amidon et al., 1995; Zhang et al., 2011). Its water solubility is extremely poor, reported to be around 0.1 mg/mL in neutral aqueous solutions (Liu et al., 2006). The molecule is also susceptible to oxidative degradation, particularly in alkaline conditions. The three adjacent hydroxyl groups on the A-ring are the key pharmacophores responsible for its potent antioxidant activity, as they can readily donate hydrogen atoms or electrons to neutralize free radicals and chelate pro-oxidant metal ions (Paul et al., 2024). The conjugated double-bond system across the A, C, and B rings allows for extensive electron delocalization, which stabilizes the resulting radical after hydrogen donation, a key feature of effective antioxidants (Dinda et al., 2017).

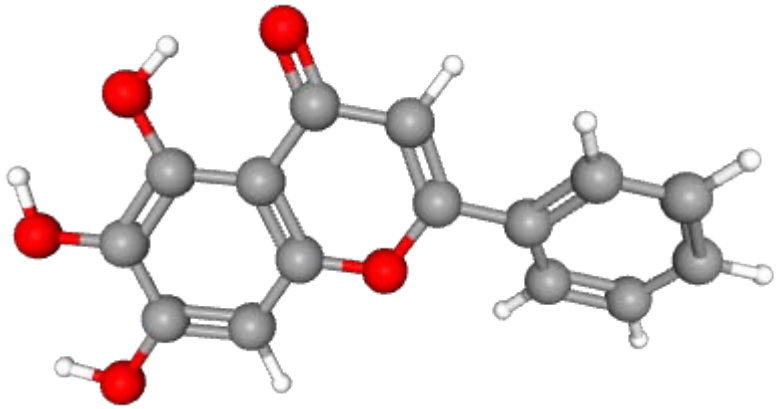

Fig. 2 Chemical structure of baicalein (5,6,7-trihydroxyflavone) (National Center for Biotechnology Information, 2026).

4 Extraction and Purification

The extraction and purification of baicalein from plant material is a crucial step for both research and potential industrial-scale production. The primary goal is to obtain the compound in high yield and purity. Given that baicalin is the predominant flavonoid in *S. baicalensis* roots, industrial production often involves a two-step process: the extraction of baicalin followed by its enzymatic or acidic hydrolysis to the aglycone baicalein

(Zhao et al., 2019). Traditional extraction methods utilize polar solvents such as methanol, ethanol, or water, often under reflux or with the aid of ultrasonication to enhance efficiency. For baicalein, a typical process involves defatting the powdered root material with a non-polar solvent like petroleum ether, followed by extraction with a hydroalcoholic solution (e.g., 60-80% ethanol) (Zhao et al., 2019). The crude extract is then concentrated and subjected to various purification steps. Column chromatography over macroporous resins (e.g., D101, AB-8) is a common and scalable method for initial enrichment of total flavonoids (Hu et al., 2022). Subsequent purification to obtain baicalein involves recrystallization or more advanced chromatographic techniques such as preparative high-performance liquid chromatography (HPLC) (Ma et al., 2024a).

For laboratory-scale isolation of baicalein from its glycoside, a common approach is to hydrolyze baicalin. Baicalin can be extracted and isolated in high purity, then treated with hydrolytic enzymes (e.g., β-glucuronidase) or mild acids to cleave the glucuronic acid moiety, yielding baicalein (Dinda et al., 2015). Modern green chemistry approaches are also being explored, including the use of deep eutectic solvents (DES) and supercritical fluid extraction (SFE) as more environmentally friendly alternatives to conventional organic solvents (Ma et al., 2024a).

5 Pharmacokinetics

The pharmacokinetic (PK) profile of baicalein is perhaps the most significant factor limiting its clinical development (Zhang et al. 2019a). While its *in vitro* potency across a range of pharmacological assays is impressive, this does not readily translate *in vivo* due to several interconnected barriers. These challenges are collectively responsible for its extremely low oral bioavailability. The key PK parameters and barriers are detailed in Table 1.

Table 1 Key pharmacokinetic barriers and parameters for baicalein.

Parameter/Barrier	Description	Key Findings	References
Solubility	Low water solubility (BCS Class II)	~0.1 mg/mL in neutral water; limits dissolution	Liu et al., 2006; Zhang et al., 2011
Permeability	High (BCS Class II)	High intestinal permeability (Papp ~1.7 × 10^{-5} cm/s)	Zhang et al., 2007b
First-pass Metabolism	Extensive in gut and liver	Rapid and extensive phase II conjugation (glucuronidation, sulfation)	Zhang et al., 2005; Li et al., 2021
Systemic Exposure	Very low after oral administration	Parent compound rapidly cleared; conjugated metabolites dominate plasma	Li et al., 2021
Cmax (200 mg, human)	Peak plasma concentration	~20 ng/mL after oral dose	Li et al., 2021
Tmax (human)	Time to reach Cmax	~1-2 hours after oral administration	Li et al., 2021
Relative Bioavailability	Compared to oral suspension	Nanocrystals: 166%; HP-β-CD complex: 165%	Zhang et al., 2011; Liu et al., 2006
Protein Binding	Extensive plasma protein binding	>90% bound, primarily to albumin	Zhang et al., 2019b
Half-life (t½)	In rats	Short, ~1-2 hours	Zhang et al., 2005

5.1 Absorption and First-Pass Metabolism

Following oral administration, baicalein is absorbed rapidly from the gastrointestinal tract due to its high lipophilicity (Zhang et al., 2007b). However, its absorption is dissolution-rate limited because of its extremely low aqueous solubility (Liu et al., 2006). Once absorbed by enterocytes, the compound becomes a prime substrate for phase II conjugating enzymes, particularly UDP-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs) (Zhang et al., 2005; Xiao & Högger, 2013). This leads to the formation of baicalein-7-O-glucuronide and baicalein-7-O-sulfate, among other conjugates. A portion of these conjugates may be effluxed back into the intestinal lumen by ATP-binding cassette (ABC) transporters such as multidrug resistance-associated protein 2 (MRP2) (Akao et al., 2004). Baicalein that survives intestinal metabolism then enters the portal circulation and is transported to the liver, where it undergoes a second round of extensive phase II metabolism, further reducing the amount of parent aglycone that reaches the systemic circulation (Zhang et al., 2005).

5.2 Bioavailability Enhancement Strategies

To overcome these PK limitations, a wide array of advanced drug delivery systems have been developed. These approaches are designed to increase solubility, protect the compound from premature metabolism, enhance intestinal permeability, or bypass the first-pass effect altogether (Zhao et al., 2019). Table 2 summarizes some of the most successful strategies.

Table 2 Nanocarrier and formulation strategies to enhance baicalein bioavailability.

Formulation Strategy	Key Principle	*In vivo* Outcome (vs. free baicalein)	References
Nanocrystals	Increased surface area for dissolution	Oral bioavailability ↑ by 166%; pulmonary delivery gave PK similar to IV	Zhang et al., 2011
HP-β-CD Complex	Inclusion complex improves aqueous solubility	Relative bioavailability ↑ to 165% after oral administration	Liu et al., 2006
Phospholipid Complex	Amorphous state with improved lipophilicity and permeability	BaPC-MD showed AUC 5.01-fold higher; Cmax significantly increased	Li et al., 2017
Liposomes	Encapsulation protects from degradation	Significantly altered PK parameters; enhanced stability	Yu et al., 2015
Solid Dispersion	Amorphous form with hydrophilic carriers	Improved dissolution rate and oral absorption	Yan et al., 2008

The development of baicalein nanocrystals using an anti-solvent precipitation method followed by high-pressure homogenization resulted in a formulation with significantly enhanced dissolution and a 1.67-fold increase in oral bioavailability (Zhang et al., 2011). In a groundbreaking study, pulmonary administration of baicalein nanocrystals resulted in rapid and extensive absorption, producing a PK profile almost identical to intravenous injection, thus completely bypassing first-pass metabolism (Zhang et al., 2011). The formation of an inclusion complex with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) significantly improved the solubility of

baicalein in neutral aqueous solutions. Pharmacokinetic studies in rats showed that the relative bioavailability of the co-lyophilized Ba/HP-β-CD product was 165.0% compared to free baicalein, attributed to a significantly earlier tmax and higher Cmax of the conjugated metabolite (Liu et al., 2006). A novel matrix dispersion based on a baicalein-phospholipid complex (BaPC-MD) was developed using PVP-K30 as a dispersant. This formulation transformed baicalein into an amorphous state, enhancing its water-solubility and n-octanol solubility, and significantly increased its permeability in Caco-2 cell assays. The oral bioavailability was dramatically improved, with the BaPC-MD exhibiting an AUC 5.01-fold higher than that of pure baicalein (Li et al., 2017). These and other formulation efforts represent critical advancements for translating baicalein into a clinically viable product.

6 Pharmacological Activities and Mechanisms of Action

The broad-spectrum therapeutic potential of baicalein is rooted in its ability to interact with and modulate a diverse array of cellular signaling pathways. Its pharmacological effects are often the result of a complex interplay between its direct antioxidant activity, its ability to modulate key inflammatory mediators, and its capacity to interfere with cell survival and proliferation pathways. In the view of network biology, baicalein is a regulatory and controlling factor in the human biological network (Zhang, 2016b, 2018, 2026, 2027a-c). Fig. 3 provides a schematic overview of baicalein metabolic regulation pathway.

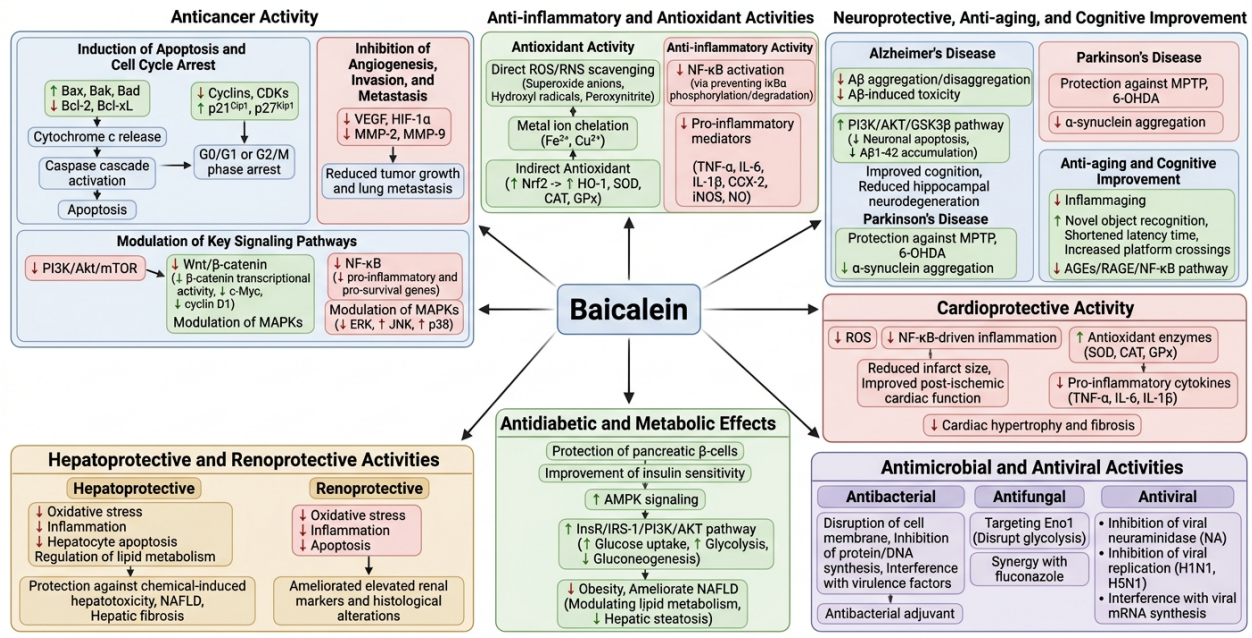

Fig. 3 Schematic overview of the baicalein metabolic regulation pathway.

6.1 Anticancer Activity

The anticancer activity of baicalein is one of the most extensively studied areas of its pharmacology. An overwhelming body of *in vitro* and *in vivo* preclinical evidence demonstrates that baicalein can effectively inhibit the growth and progression of a wide spectrum of human cancers, including cancers of the breast, lung, colon, liver, prostate, and many others (Lei et al., 2024; Gao et al., 2016; Rahmani et al., 2022). Unlike conventional chemotherapeutics that typically target a single pathway, baicalein acts as a multi-targeted agent,

simultaneously interfering with several of the "hallmarks of cancer" (Hanahan & Weinberg, 2011). The major mechanisms are summarized below and in Table 3.

6.1.1 Induction of Apoptosis and Cell Cycle Arrest

A primary mechanism by which baicalein suppresses tumor growth is by inducing programmed cell death (apoptosis) and causing cell cycle arrest. In various cancer cell lines, baicalein triggers both the intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways (Li-Weber, 2009). This is achieved by modulating the expression of Bcl-2 family proteins, leading to a decrease in the anti-apoptotic protein Bcl-2 and an increase in the pro-apoptotic proteins Bax and Bak (Lei et al., 2024; Aryal et al., 2014). This shift in the Bcl-2/Bax ratio causes the release of cytochrome c from the mitochondria, activating the caspase cascade and ultimately leading to cell death (Aryal et al., 2014). Baicalein also arrests the cell cycle at various checkpoints. It has been shown to induce G0/G1 or G2/M phase arrest in different cancer cell types by downregulating cyclins and cyclin-dependent kinases (CDKs) and upregulating CDK inhibitors such as p21Cip1 and p27Kip1 (Rahmani et al., 2022; Lei et al., 2024).

6.1.2 Inhibition of Angiogenesis, Invasion, and Metastasis

For a tumor to grow beyond a minimal size and to metastasize, it must induce the formation of new blood vessels (angiogenesis) and acquire the ability to invade surrounding tissues. Baicalein has demonstrated potent anti-angiogenic, anti-invasive, and anti-metastatic properties. It suppresses angiogenesis by downregulating the expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which are crucial for degrading the extracellular matrix during invasion and metastasis (Lei et al., 2024; Yang et al., 2019). In a mouse model of breast cancer, baicalein significantly reduced tumor growth and lung metastasis (Yang et al., 2019). Similarly, in colorectal cancer models, baicalein was found to suppress growth and metastasis by modulating key pathways like PI3K/Akt, MAPK, and TLR4/NF-κB (Manna et al., 2025).

6.1.3 Modulation of Key Signaling Pathways

The anticancer effects of baicalein are mediated through its interference with multiple, often cross-talking, signaling pathways that are commonly dysregulated in cancer. The most well-characterized of these include:

- PI3K/Akt/mTOR Pathway (Huang and Zhang, 2012; Li and Zhang, 2013; Zhang, 2016a, 2017c, 2018): This pathway is a central regulator of cell survival, growth, and metabolism, and is frequently hyperactivated in cancer. Baicalein is a potent inhibitor of this pathway, leading to reduced cell survival and proliferation and increased apoptosis (Lei et al., 2024; Aryal et al., 2014).
- MAPK Pathway (Huang and Zhang, 2012; Li and Zhang, 2013; Zhang, 2016a, 2017c): Baicalein modulates the MAPK signaling cascade, which includes ERK, JNK, and p38. It often inhibits the pro-survival ERK pathway while activating the stress-activated JNK and p38 pathways, which can promote apoptosis (Li-Weber, 2009; Lei et al., 2024).
- Wnt/β-catenin Pathway: Aberrant activation of Wnt signaling is a hallmark of many cancers, including colorectal cancer. Baicalein has been shown to inhibit this pathway, leading to reduced β-catenin transcriptional activity and decreased expression of its target genes, such as c-Myc and cyclin D1 (Lei et al., 2024; Yang et al., 2019).
- NF-κB Pathway (Huang and Zhang, 2012; Li and Zhang, 2013; Zhang, 2016a): Nuclear factor-kappa B (NF-κB) is a master regulator of inflammation and cell survival, and its constitutive activation is common in cancer. Baicalein inhibits the activation of the NF-κB pathway, suppressing the transcription of pro-inflammatory and pro-survival genes (Dinda et al., 2017; Manna et al., 2025).

Table 3 Key molecular targets and anticancer mechanisms of baicalein.

Hallmark of Cancer	Mechanism of Action	Key Pathways/Targets Affected	References
Proliferation	Induction of cell cycle arrest (G0/G1, G2/M)	↓ Cyclins, CDKs; ↑ p21Cip1, p27Kip1; ↓ PI3K/Akt/mTOR, Wnt/β-catenin	Rahmani et al., 2022; Lei et al., 2024
Survival / Apoptosis	Induction of intrinsic & extrinsic apoptosis	↑ Bax, Bak, Bad; ↓ Bcl-2, Bcl-xL; activation of caspases; ↓ PI3K/Akt/mTOR; modulation of MAPKs	Aryal et al., 2014; Li-Weber, 2009; Lei et al., 2024
Angiogenesis	Inhibition of new blood vessel formation	↓ VEGF, HIF-1α; ↓ MMP-2, MMP-9	Lei et al., 2024
Invasion & Metastasis	Inhibition of migration and tissue invasion	↓ MMP-2, MMP-9; ↓ PI3K/Akt, MAPK, TLR4/NF-κB	Manna et al., 2025; Lei et al., 2024; Yang et al., 2019
Inflammation	Suppression of pro-inflammatory tumor microenvironment	↓ NF-κB; ↓ COX-2; ↓ TNF-α, IL-6, IL-1β	Dinda et al., 2017; Manna et al., 2025
Immune Evasion	Modulation of tumor immune microenvironment	Activation of $CD4^+$ and $CD8^+$ T cells; modulation of cytokines	Manna et al., 2025
Cancer Stem Cells	Targeting of cancer stem cell populations	↓ CSC markers (e.g., CD44, CD133); modulation of self-renewal pathways	Lei et al., 2024

6.2 Anti-inflammatory and Antioxidant Activities

The anti-inflammatory and antioxidant properties of baicalein are fundamental to many of its other therapeutic effects, including its cardioprotective, neuroprotective, and hepatoprotective actions. These two activities are closely linked, as oxidative stress is both a cause and a consequence of inflammation (Dinda et al., 2017).

6.2.1 Antioxidant Activity

Baicalein is a potent direct and indirect antioxidant. Its direct antioxidant activity stems from the presence of the three hydroxyl groups on its A-ring, which can readily donate hydrogen atoms to neutralize a wide range of reactive oxygen species (ROS) and reactive nitrogen species (RNS), including superoxide anions, hydroxyl radicals, and peroxynitrite (Dinda et al., 2017; Hu et al., 2022). Furthermore, baicalein is a strong chelator of redox-active metal ions such as iron (Fe^{2+}) and copper (Cu^{2+}), which catalyze the production of highly damaging hydroxyl radicals via the Fenton reaction. By sequestering these ions, baicalein prevents the formation of these harmful species (Zhao et al., 2019). Beyond its direct scavenging and chelating activities, baicalein also acts as an indirect antioxidant by activating the Nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway (Hu et al., 2022). Nrf2 is a transcription factor that controls the expression of a battery of endogenous antioxidant and cytoprotective enzymes, such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Paul et al., 2024). By activating Nrf2, baicalein enhances the cell's intrinsic defense mechanisms against oxidative damage.

6.2.2 Anti-inflammatory Activity

The anti-inflammatory effects of baicalein are primarily mediated through its potent inhibition of the NF-κB signaling pathway (Dinda et al., 2017). NF-κB is a transcription factor that sits at the heart of the inflammatory response, driving the expression of a multitude of pro-inflammatory genes, including those encoding cytokines (TNF-α, IL-6, IL-1β), chemokines, adhesion molecules, and inducible enzymes like cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (Huang and Zhang, 2012; Li and Zhang, 2013; Zhang, 2016a,

2017c, 2018; Liu et al., 2017). Baicalein inhibits the activation of NF-κB by preventing the phosphorylation and subsequent degradation of its inhibitory protein, IκBα, thereby retaining NF-κB in the cytoplasm in an inactive state (Dinda et al., 2017). By blocking NF-κB, baicalein effectively suppresses the production of a wide range of pro-inflammatory mediators, leading to a robust anti-inflammatory effect. This has been demonstrated in numerous *in vitro* and *in vivo* models of inflammation, including those involving microglial cells, where baicalein suppressed the release of NO, TNF-α, and IL-6, and inhibited the expression of COX-2 and NF-κB (Zhao et al., 2019).

6.3 Neuroprotective, Anti-aging, and Cognitive Improvement

The ability of baicalein to mitigate oxidative stress and neuroinflammation, combined with its other activities, positions it as a promising therapeutic agent for a range of acute and chronic neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), cerebral ischemia, and age-related cognitive decline (Zhao et al., 2019; Bie et al., 2017). A comprehensive review by Sarup et al. (2025) highlights the multifaceted neuroprotective perspectives of baicalein and baicalin in AD.

6.3.1 Alzheimer's Disease

The pathology of AD is complex, involving the accumulation of amyloid-beta (Aβ) plaques, hyperphosphorylation of tau protein leading to neurofibrillary tangles, chronic neuroinflammation, and extensive oxidative stress, all culminating in neuronal death and cognitive impairment (Nussbaum & Ellis, 2003; Mattson, 2004). Baicalein has been shown to target multiple aspects of AD pathology. It directly inhibits the aggregation of Aβ peptides and can disaggregate pre-formed fibrils (Bie et al., 2017). It also protects neuronal cells from Aβ-induced toxicity by reducing oxidative stress and suppressing the inflammatory response triggered by Aβ aggregates (Sarup et al., 2025). A recent study by Lee et al. (2026) demonstrated that baicalein significantly improved cognition and reduced hippocampal neurodegeneration in APP/PS1 transgenic AD mice. Mechanistically, baicalein activated the PI3K/AKT/GSK3β pathway, leading to a decrease in neuronal apoptosis and a reduction in Aβ1-42 accumulation (Lee et al., 2026). By activating this pro-survival pathway, baicalein helped maintain neuronal health and function.

6.3.2 Parkinson's Disease and Other Neurodegenerative Conditions

In PD models, baicalein has shown protective effects against neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA). Its neuroprotective effects are attributed to its ability to reduce oxidative stress, inhibit neuroinflammation, and prevent the aggregation of α-synuclein, a key protein in PD pathology (Bie et al., 2017). Furthermore, baicalein has demonstrated neuroprotective effects in models of cerebral ischemia/reperfusion injury, where it helps to reduce infarct size and improve neurological outcomes by suppressing oxidative stress, inflammation, and apoptosis (Chao et al., 2013).

6.3.3 Anti-aging and Cognitive Improvement

The anti-aging effects of baicalein are closely tied to its ability to combat age-related increases in oxidative stress and chronic low-grade inflammation ("inflammaging") (Paul et al., 2024). In a D-galactose-induced aging rat model, a standard model for studying aging and cognitive decline, baicalein treatment significantly attenuated memory decline. This was demonstrated by an increased recognition index in the novel object recognition test, shortened latency time, and increased platform crossings in the Morris water maze test (Duan et al., 2017). These improvements were associated with the attenuation of inflammation and metabolic dysfunction. Another study found that apigenin and baicalein ameliorated cognitive deficits and thoracic aortic structural deterioration in aging rats by inhibiting the AGEs/RAGE/NF-κB pathway (Ma et al., 2024b). These findings provide strong evidence for baicalein's potential as an agent to delay age-related cognitive decline.

6.4 Cardioprotective Activity

The cardioprotective potential of baicalein has been demonstrated in numerous preclinical models of cardiovascular disease (CVD), including myocardial infarction (MI), ischemia/reperfusion (I/R) injury, cardiac hypertrophy, and hypercholesterolemia-induced cardiac damage (Huang et al., 2005; AlSaad et al., 2020). The mechanisms underlying these effects are primarily its potent antioxidant and anti-inflammatory actions. During an MI or I/R event, a massive burst of ROS is generated, leading to oxidative damage of cardiomyocytes and triggering a strong inflammatory response that exacerbates tissue injury (Huang et al., 2005). By scavenging ROS and suppressing the NF-κB-driven inflammatory cascade, baicalein can significantly reduce infarct size and improve post-ischemic cardiac function. In a rat model of hypercholesterolemia, a major risk factor for CVD, treatment with baicalein was shown to improve cardiac dysfunctions by activating cellular antioxidant enzymes (SOD, CAT, GPx) and suppressing the levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) (AlSaad et al., 2020). Furthermore, baicalein has been shown to attenuate cardiac hypertrophy and fibrosis by inhibiting pro-fibrotic signaling pathways (Huang et al., 2005).

6.5 Hepatoprotective and Renoprotective Activities

The liver and kidneys are primary sites of xenobiotic metabolism and are therefore highly susceptible to damage from drugs, toxins, and metabolic disorders. Baicalein has demonstrated potent protective effects against various forms of liver and kidney injury (AlSaad et al., 2020; Hu et al., 2022). Its hepatoprotective effects have been shown in models of chemical-induced hepatotoxicity (e.g., carbon tetrachloride, acetaminophen), alcoholic and non-alcoholic fatty liver disease (NAFLD), and hepatic fibrosis (Hu et al., 2022). The protective mechanisms include the reduction of oxidative stress, suppression of inflammation, inhibition of hepatocyte apoptosis, and regulation of lipid metabolism (Hang et al., 2018; Paul et al., 2024). Similarly, baicalein has been shown to protect against renal injury induced by various insults, including ischemia/reperfusion, nephrotoxic drugs (e.g., cisplatin, gentamicin), and hypercholesterolemia (AlSaad et al., 2020). Its renoprotective effects are again attributed to its ability to reduce oxidative stress, inflammation, and apoptosis within the renal tissues. In hypercholesterolemic rats, baicalein treatment ameliorated the elevated renal markers and histological alterations induced by cholesterol overload, demonstrating its multi-organ protective potential (AlSaad et al., 2020).

6.6 Antidiabetic and Metabolic Effects

Baicalein has emerged as a promising natural agent for the management of type 2 diabetes mellitus (T2DM) and its associated metabolic complications. Its antidiabetic effects are multifaceted, involving the protection of pancreatic β-cells, the improvement of insulin sensitivity in peripheral tissues, and the regulation of glucose and lipid metabolism (Fu et al., 2014; Hang et al., 2018; Fang et al., 2020). In obese diabetic mouse models, baicalein treatment was shown to protect pancreatic β-cell function, thereby preserving insulin secretion capacity (Fu et al., 2014). In insulin-resistant cells and animal models, baicalein improves insulin sensitivity, an effect that may be mediated through the activation of the AMPK signaling pathway and the enhancement of insulin signaling via the PI3K/Akt pathway (Fang et al., 2020). A study by Wang et al. (2024) confirmed that baicalein promotes glucose uptake and glycolysis while inhibiting gluconeogenesis in insulin-resistant HepG2 cells, an effect attributed to the regulation of the InsR/IRS-1/PI3K/AKT pathway. Furthermore, baicalein has been shown to reduce obesity and ameliorate NAFLD, a condition commonly associated with T2DM, by modulating lipid metabolism and reducing hepatic steatosis (Fang et al., 2020).

6.7 Antimicrobial and Antiviral Activities

Baicalein exhibits a broad spectrum of antimicrobial activity against a variety of pathogens, including bacteria, fungi, and viruses (Paul et al., 2024; Sithisarn et al., 2013; Mu et al., 2025). Its antibacterial activity extends to both Gram-positive and Gram-negative bacteria. The mechanisms of action are multifaceted, including disruption of bacterial cell membrane integrity, inhibition of protein and DNA synthesis, and interference with

bacterial virulence factors (Yun et al., 2012). A recent study by Li et al. (2025) highlights baicalein as a potential antibacterial adjuvant that can suppress antimicrobial resistance and enhance the efficacy of conventional antibiotics. Against fungi, baicalein has demonstrated potent activity against *Candida albicans* and other pathogenic fungi, with studies showing it can act by targeting key enzymes like Eno1 to disrupt glycolysis and can act synergistically with fluconazole (Hu et al., 2022; Yang et al., 2019). In terms of antiviral activity, baicalein has shown particular promise against influenza viruses. It has been found to inhibit the viral neuraminidase (NA) enzyme, a key target of the anti-influenza drugs oseltamivir and zanamivir (Sithisarn et al., 2013; Ding et al., 2014). Baicalein inhibits the replication of various influenza A virus strains, including H1N1 and H5N1, in cell culture and animal models. It has also been reported to interfere with viral mRNA synthesis, providing an additional antiviral mechanism (Su et al., 2012). A Phase IIa clinical trial (NCT03830684) is currently underway to evaluate the effectiveness and safety of baicalein tablets for the treatment of influenza fever, highlighting its translational potential (DrugBank, 2024).

7 Clinical Trials and Human Studies

While the preclinical evidence for baicalein is extensive and compelling, the number of completed clinical trials is still limited, though a growing body of evidence is emerging. These studies have primarily focused on establishing the safety, tolerability, and pharmacokinetic profile of baicalein in healthy volunteers, with a few early-phase trials exploring its efficacy in specific diseases.

7.1 Safety, Tolerability, and Pharmacokinetics in Humans

Multiple Phase I clinical trials have consistently demonstrated that baicalein is safe and well-tolerated in healthy human subjects across a range of doses. A single-center, randomized, double-blind, placebo-controlled multiple-ascending-dose study by Li et al. (2021) involved 36 healthy subjects who received 200, 400, and 600 mg of baicalein tablets or placebo. The study concluded that baicalein was generally safe and well-tolerated. All adverse events were mild and resolved without intervention, with only one moderate case of fever in the 600 mg group that was deemed unrelated to the study drug (Li et al., 2021). Pharmacokinetically, oral baicalein tablets were rapidly absorbed, with peak plasma levels reached within 2 hours after multiple administrations (Li et al., 2021). Another Phase I study evaluating single ascending doses of baicalein chewable tablets (100-2800 mg) in 72 healthy adults confirmed the favorable safety profile, with no serious adverse events reported (Li et al., 2014). These studies are crucial as they establish a safe dose range for further efficacy trials.

7.2 Clinical Efficacy Studies

A landmark randomized, double-blind, placebo-controlled trial by Li et al. (2018) investigated the effects of baicalin (the glycoside) in 374 patients with both coronary artery disease (CAD) and rheumatoid arthritis (RA). Although this trial used baicalin rather than baicalein, it is highly relevant as baicalin is metabolized to baicalein *in vivo*. Patients received 500 mg of baicalin or placebo daily for 12 weeks. The results showed that baicalin significantly reduced blood lipids (total cholesterol and LDL-cholesterol) and inflammatory markers (high-sensitivity C-reactive protein, hs-CRP) in these high-risk patients, supporting its further clinical application (Hang et al., 2018). As of 2024, an ongoing Phase IIa clinical trial (NCT03830684) is actively recruiting patients to evaluate the effectiveness and safety of baicalein tablets in improving symptoms in healthy adults with influenza fever (DrugBank, 2024). The outcome of this trial will provide much-needed clinical efficacy data for baicalein as an antiviral agent.

8 Quality Control and Standardization

For baicalein to be developed as a reliable pharmaceutical or nutraceutical product, rigorous quality control

(QC) and standardization are paramount. The primary analytical technique for the identification and quantification of baicalein in bulk substances, plant extracts, and finished products is high-performance liquid chromatography (HPLC), often coupled with ultraviolet (UV) or diode-array detection (DAD) (Ma et al., 2024a). The typical HPLC method utilizes a reversed-phase C18 column with a mobile phase consisting of methanol, acetonitrile, or a combination of these with an aqueous phase containing a small percentage of acid (e.g., acetic acid, formic acid, or phosphoric acid) to improve peak symmetry (Zhao et al., 2019). Detection is commonly performed at wavelengths around 280 nm or 320 nm, where baicalein exhibits strong absorbance. Reference standards of known purity are used for calibration and quantification. Pharmacopoeias, such as the Chinese Pharmacopoeia, provide official standards for the quality control of *Scutellariae Radix*, including limits for the content of baicalin and, to a lesser extent, baicalein (Chinese Pharmacopoeia Commission, 2020). For new formulations, validated stability-indicating assays must be developed to monitor the degradation of baicalein over time and under various storage conditions. The recent development of certified reference materials for baicalein in *Scutellaria baicalensis* and its extracts is a crucial step toward ensuring inter-laboratory comparability and long-term quality assurance (Ma et al., 2024b).

9 Safety and Toxicology

A critical advantage of baicalein over many conventional synthetic drugs is its apparent low toxicity and favorable safety profile. Both preclinical toxicology studies and clinical trials have consistently reported that baicalein is safe and well-tolerated, even at relatively high doses (Li et al., 2014; Li et al., 2021). Acute toxicity studies in rodents have reported a high median lethal dose (LD50), indicating a wide margin of safety. For example, studies on baicalin (the glycoside) have shown an LD50 of over 4,000 mg/kg in mice, with a subacute no-observed-adverse-effect level (NOAEL) of 2,000 mg/kg, suggesting that baicalein likely has a similarly favorable profile (Yang et al., 2025). No significant target organ toxicities have been identified in repeat-dose toxicity studies. The most common adverse events reported in human clinical trials were mild and transient, including minor gastrointestinal discomfort (Li et al., 2021). No severe or serious adverse events have been attributed to baicalein administration. However, as with any bioactive compound, there is a potential for drug-drug interactions (DDIs). Because baicalein is known to inhibit certain cytochrome P450 (CYP) enzymes, particularly CYP2C9, it could theoretically alter the metabolism of co-administered drugs that are substrates of these enzymes (Si et al., 2009). Furthermore, its high affinity for drug transporters like MRP2 could also lead to DDIs (Akao et al., 2004). While these interactions have been demonstrated *in vitro*, their clinical significance has not been fully established. A comprehensive evaluation of potential DDIs is needed before baicalein can be widely co-administered with other medications.

10 Challenges, Limitations, and Future Perspectives

Despite the immense potential of baicalein, several significant challenges and limitations must be addressed to successfully translate its preclinical promise into clinical reality.

10.1 Major Challenges

- Poor Pharmacokinetics (The "Achilles' Heel"): As detailed throughout this review, the low aqueous solubility and extremely low oral bioavailability due to extensive first-pass metabolism remain the single biggest hurdle. Without an effective delivery system, achieving therapeutic concentrations of the parent aglycone *in vivo* is impossible.
- Lack of Definitive Clinical Proof of Efficacy: While preclinical studies are abundant and positive, there is a paucity of large, robust, randomized, double-blind, placebo-controlled clinical trials demonstrating the efficacy of baicalein for any specific indication. The ongoing Phase IIa trial for influenza is a critical step forward.

- Potential for Drug-Drug Interactions: The potential for baicalein to inhibit CYP enzymes and interact with drug transporters raises a concern for adverse DDIs, especially if it is to be used as an adjunctive therapy with other medications. This needs thorough clinical investigation.
- Translating Multi-targeted Effects: The very pleiotropic nature of baicalein, while an advantage for complex diseases, makes it difficult to deconvolute its primary mechanism of action. This complexity can be a challenge for regulatory approval, which typically favors agents with a well-defined, single mechanism.

10.2 Future Perspectives

- Advanced Nanomedicine Formulations: The most pressing future direction is the continued development and clinical translation of advanced baicalein formulations. Nanocrystals, liposomes, polymer conjugates, and targeted nanoparticles are not just academic exercises; they are the most viable path to a clinically useful product. Future research should focus on scalable manufacturing processes, long-term stability, and, crucially, clinical evaluation of these optimized formulations.
- Structure-Activity Relationship (SAR) Studies: A deeper understanding of the SAR of baicalein could lead to the design of synthetic analogs with improved pharmacological properties. Modifications could be made to the scaffold to block the site of glucuronidation (the 7-OH group) or to enhance solubility while maintaining or improving potency.
- Combination Therapies: Baicalein has shown synergistic effects with conventional chemotherapeutic agents and antibiotics in preclinical studies (Lei et al., 2024; Yun et al., 2012). Well-designed clinical trials to test these combinations for specific cancers or infections are a promising avenue. Such combinations could allow for lower doses of the conventional drug, reducing its toxicity while maintaining or enhancing efficacy.
- Expanding Clinical Research: The results of the Phase IIa influenza trial are eagerly awaited. Positive results would be a major catalyst for further clinical development. Beyond influenza, given the robust preclinical data, clinical trials for baicalein in other indications, such as mild cognitive impairment or early-stage AD, inflammatory bowel disease, and NAFLD, are warranted.
- Biomarker Development: To facilitate clinical development, there is a need to identify and validate pharmacodynamic biomarkers for baicalein's activity. For instance, in a clinical trial for an inflammatory disease, measuring a panel of cytokines or NF-κB activity in accessible cells could serve as a proof-of-mechanism.

11 Conclusion

Baicalein is a remarkable natural flavonoid with a broad spectrum of potent pharmacological activities, including robust anti-cancer, anti-inflammatory, antioxidant, neuroprotective, cardioprotective, and antimicrobial effects. Its ability to modulate multiple key signaling pathways, combined with its excellent safety profile, makes it a highly attractive lead compound for the treatment of complex, multifactorial diseases. However, its intrinsic poor pharmacokinetic properties—specifically its low water solubility and extremely low oral bioavailability—represent a formidable translational barrier. This "Achilles' heel" has prevented its widespread clinical use. The successful future of baicalein as a therapeutic agent is contingent upon the continued development and clinical validation of advanced drug delivery systems capable of overcoming these bioavailability challenges. The preliminary clinical data on safety are encouraging, and ongoing efficacy trials are eagerly awaited. With strategic formulation efforts, continued exploration of its molecular mechanisms, and rigorous clinical testing, baicalein holds the potential to transition from a promising phytochemical in the laboratory to a valuable new medicine in the clinic, fulfilling the promise that its long history in traditional medicine has always suggested.

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