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Scutellaria baicalensis in cancer therapy: multidimensional mechanisms and therapeutic potential

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Abstract

Scutellaria baicalensis is a traditional Chinese medicinal material that has attracted much attention for its anticancer potential due to its rich content of bioactive flavonoids such as baicalein, baicalin, and wogonin. This review synthesizes the available evidence and elucidates the multiple mechanisms by which these compounds exert their antitumor effects, including induction of apoptosis, cell cycle arrest, epigenetic regulation, metabolic reprogramming, and tumor microenvironment remodeling. Flavonoids in Scutellaria baicalensis target key oncogenic pathways, thereby inhibiting cancer cell proliferation, metastasis, and angiogenesis while enhancing immune surveillance. Notably, they are able to reverse drug resistance by inhibiting efflux transporters, restoring chemosensitivity, and impairing DNA repair mechanisms, highlighting their therapeutic versatility. Preclinical studies have highlighted the synergistic effects of Scutellaria baicalensis derivatives in combination with conventional chemotherapy or radiotherapy. Scutellaria baicalensis provides a holistic approach to address tumor heterogeneity and therapeutic resistance by combining traditional phytomedicine with modern pharmacological strategies, making it a valuable adjunct in next-generation cancer therapy.

KEYWORDS

Scutellaria baicalensis, Flavonoids, Signaling regulation, Molecular mechanism, Cancer therapy

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Introduction

Cancer remains a formidable global health challenge, with its incidence and mortality rates escalating across diverse populations.Despite advancements in conventional therapies—including surgery, chemotherapy, radiotherapy, and targeted molecular agents—significant limitations persist. Chemoresistance, systemic toxicity, and tumor heterogeneity frequently compromise treatment efficacy(1), necessitating the exploration of alternative strategies to complement or refine existing modalities. In this context, natural products derived from traditional medicinal systems have garnered renewed scientific interest for their potential to modulate oncogenic pathways with reduced adverse effects.

Traditional Chinese medicine (TCM) is a treasure trove of empirical knowledge accumulated over thousands of years, providing a rich collection of bioactive compounds with proven therapeutic efficacy. In recent decades, a paradigm shift has occurred in the study of drug mechanisms of TCM-derived drugs, especially in the field of oncology. Notably, bioactive components isolated from medicinal plants, such as paclitaxel from Taxus brevifolia and artemisinin from Artemisia annua, have been widely used in cancer treatment research, validating the systematic study of phytotherapy(2). These success stories have promoted the efforts to discover more phytomedicines with anti-tumor properties, focusing on their mechanisms of action at the molecular, cellular, and systemic levels. Among the many TCMs, Scutellaria baicalensis has emerged as a promising candidate for cancer intervention.

Scutellaria baicalensis is a perennial herbaceous plant of the Lamiaceae family. Its dried root is a common medicinal material in traditional Chinese medicine. It has been used to clear away heat, detoxify and stop bleeding. It can treat a variety of inflammations, respiratory infections, various gastrointestinal diseases and liver diseases, and appears in many classic herbal formulas(3). Phytochemical analysis studies have discovered a variety of active ingredients in Scutellaria baicalensis, and these compounds have laid the foundation for subsequent studies aimed at elucidating the mechanisms by which this herb regulates physiological and pathological processes. In recent years, increasing evidence has shown that Scutellaria baicalensis has potential anti-cancer effects. This provides a scientific framework for its long-term therapeutic application.

Flavonoids are the most abundant and pharmacologically active secondary metabolites in Scutellaria baicalensis, among which baicalin and its aglycone baicalein are the main compounds(4). Baicalin is a flavonoid glycoside that occupies an important position due to its significant anti-proliferative and anti-inflammatory properties(5). Baicalin hydrolysis can produce baicalein, an aglycone that can enhance cell permeability and effectively inhibit key kinases associated with oncogenic signaling(6). Wogonin is another aglycone derivative that exhibits significant pro-apoptotic activity by regulating the mitochondrial pathway. Notably, compounds such as baicalin, baicalin, wogonin, and wogonin have been identified as key bioactive molecules that exhibit broad-spectrum antitumor activity in preclinical models. These compounds are able to modulate key oncogenic pathways, including cell cycle regulation, induction of apoptosis, inhibition of angiogenesis, and suppression of tumor metastasis. In addition, emerging evidence suggests that they have synergistic effects with traditional chemotherapeutic drugs, highlighting their potential application in combination therapy to circumvent drug resistance. This review aims to summarize the current research results on Scutellaria baicalensis in the field of cancer treatment, especially focusing on its mechanism of action and therapeutic potential, and provide a reasonable reference direction for further research on the anti-tumor effects of traditional Chinese medicine.

1.The main active ingredients in Scutellaria baicalensis

Scutellaria baicalensis root extracts have remarkable chemical diversity, with flavonoids being the most abundant and biologically active. These compounds share a common core structure of C6-C3-C6 flavonoids, but differ in

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substitution patterns and glycosylation states. These structural differences determine their solubility, membrane permeability, and interactions with molecular targets(7). Early phytochemical analyses have identified more than three dozen different flavonoids in Scutellariae, a few of which have been observed to have antitumor activity. The major glycoside component in Scutellariae is baicalin. This 7-O-β-D-glucuronide has a polyphenolic hydroxyl structure, which gives it antioxidant and free radical scavenging abilities(8). Its small molecular weight and high lipid solubility facilitate rapid absorption and cell penetration, which may be related to its strong antitumor activity. The hydroxyl and keto structures of baicalin enable it to interact with a variety of biomolecules (e.g., enzymes, receptors, DNA) and regulate cell signaling pathways(9). In addition, its lipid solubility allows it to easily pass through cell membranes and target intracellular molecular mechanisms.

As the aglycone counterpart of baicalin, baicalein is a 6-hydroxy derivative of flavonoids with a typical flavonoid skeleton structure. The phenolic hydroxyl group and conjugated double bonds in its structure give it antioxidant and electrophilic properties(10). In addition, the high lipid solubility and small molecular weight of baicalein make it easy to penetrate the cell membrane and enhance bioavailability. Several studies have shown that baicalein induces G1 arrest by downregulating cyclin D1 and triggers the intrinsic apoptotic pathway through mitochondrial membrane depolarization(11). This dual effect highlights its ability to both slow cancer cell proliferation and promote cancer cell clearance. Wogonin and wogonoside are another pair of important flavonoids in the genus Scutellaria. The structure of wogonin is similar to baicalein, with a methoxy substitution at the C-8 position, which affects its lipophilicity and target selectivity(12). Wogonoside retains a glucuronic acid moiety at the C-7 position, which is similar to the glycosylation site in baicalin. Preclinical studies have shown that wogonin inhibits angiogenesis by interfering with vascular endothelial growth factor (VEGF) signaling and suppresses NF-κB activation in multiple tumor types(13). The delicate balance between free and bound states emphasizes the importance of metabolic transformation in regulating biological activity. A clear understanding of these major components of Scutellaria baicalensis provides a foundation for elucidating their mechanistic roles in cancer treatment.

2.Molecular mechanisms of action in cancer

The molecular mechanisms by which Scutellariae baicalensis exerts its anticancer effects encompass a range of intracellular processes, including tumor suppression, induction of apoptosis, epigenetic regulation and intervention of metabolic reprogramming, and modulation of the tumor microenvironment (TME). Elucidation of these pathways holds promise for improving therapeutic options utilizing bioactive flavonoids derived from this traditional herb. The aforementioned active compounds in Scutellaria baicalensis interact with cancer cells through complex molecular mechanisms. Early studies highlighted the ability of Scutellaria baicalensis to induce apoptosis in cancer cells. The loss of mitochondrial membrane potential is induced by the upregulation of pro-apoptotic proteins such as Bax, followed by the release of cytochrome c into the cytosol, ultimately leading to the activation of caspase-9. Simultaneous downregulation of Bcl-2 proteins further shifts the balance toward cell death(14). In addition to apoptosis, cell cycle regulation is also a key anticancer mechanism. Baicalein and wogonin have been shown to inhibit the expression of cyclin D1 and CDK4, inducing G1 arrest. This blockade inhibits Rb phosphorylation, effectively suppressing E2F-dependent transcription and DNA synthesis(15). In certain tumor models, wogonin induces G2/M arrest by inhibiting Cdc25C phosphatase, thereby blocking the activation of the cyclin B1-CDK1 complex that regulates mitotic entry(16). Invasion and metastasis involve epithelial-mesenchymal transition (EMT), matrix degradation mediated by matrix metalloproteinases (MMPs), and cytoskeletal remodeling. Treatment with flavonoids from Scutellaria baicalensis inhibits EMT markers such as N-cadherin and vimentin, while restoring the expression of E-cadherin. Downregulation of both MMP-2 and MMP-9 reduces extracellular matrix degradation, thereby inhibiting invasive potential. Angiogenesis is another key process that it targets. For example, wogonin effectively inhibits VEGF

DOI 10.58832/ctr.2025.6.6.4

secretion by interfering with the stability of HIF-1α under hypoxic conditions(17). This results in reduced endothelial cell proliferation and atrophy of neovascularization, starving solid tumors of oxygen and nutrient supply. Elucidating the molecular basis of flavonoid active substances in regulating cancer cell fate will help to rationally integrate Scutellaria components into combination therapies with traditional chemotherapeutic drugs or targeted drugs.

2.1 Induction of cancer cell apoptosis

The molecular mechanism of baicalin and baicalein as the main active substances in Scutellaria baicalensis induced apoptosis through multiple pathways. In terms of regulating the Wnt/AKT pathway, baicalin and baicalein inhibited the activity of GSK-3β and downregulated PI3K/AKT signal transduction, thereby reducing the expression of the pro-survival protein C-Myc and blocking the proliferation of tumor cells. In terms of activating the mitochondrial apoptosis pathway, by upregulating the expression of the pro-apoptotic protein Bax and downregulating the expression of the anti-apoptotic protein Bcl-2, the mitochondrial membrane potential was destroyed, cytochrome C (Cyt-C) was released into the cytoplasm, and the cascade reaction of Caspase-9 and Caspase-3 was activated, and finally PARP-1 was cleaved, triggering an irreversible apoptotic program. In terms of strengthening p53-dependent cell apoptosis, by activating p53 protein, it enhances its regulation of downstream target genes, while inhibiting XIAP and TNF-related survival signals, further enhancing the apoptotic effect. In terms of epigenetic and microenvironmental regulation, the expression of microRNA-21 is inhibited, its stabilizing effect on β-catenin and C-Myc is reduced, and the survival signal of tumor cells is blocked. In addition, baicalin and baicalein may also synergistically inhibit the pro-survival microenvironment by regulating GHT (or Hedgehog) pathway-related molecules and inflammatory mediators. Baicalin and baicalein synergistically induce cell cycle arrest, mitochondrial dysfunction and DNA damage repair failure through the above-mentioned multi-target effects, ultimately achieving efficient pro-apoptotic effects(17) (Figure 1).

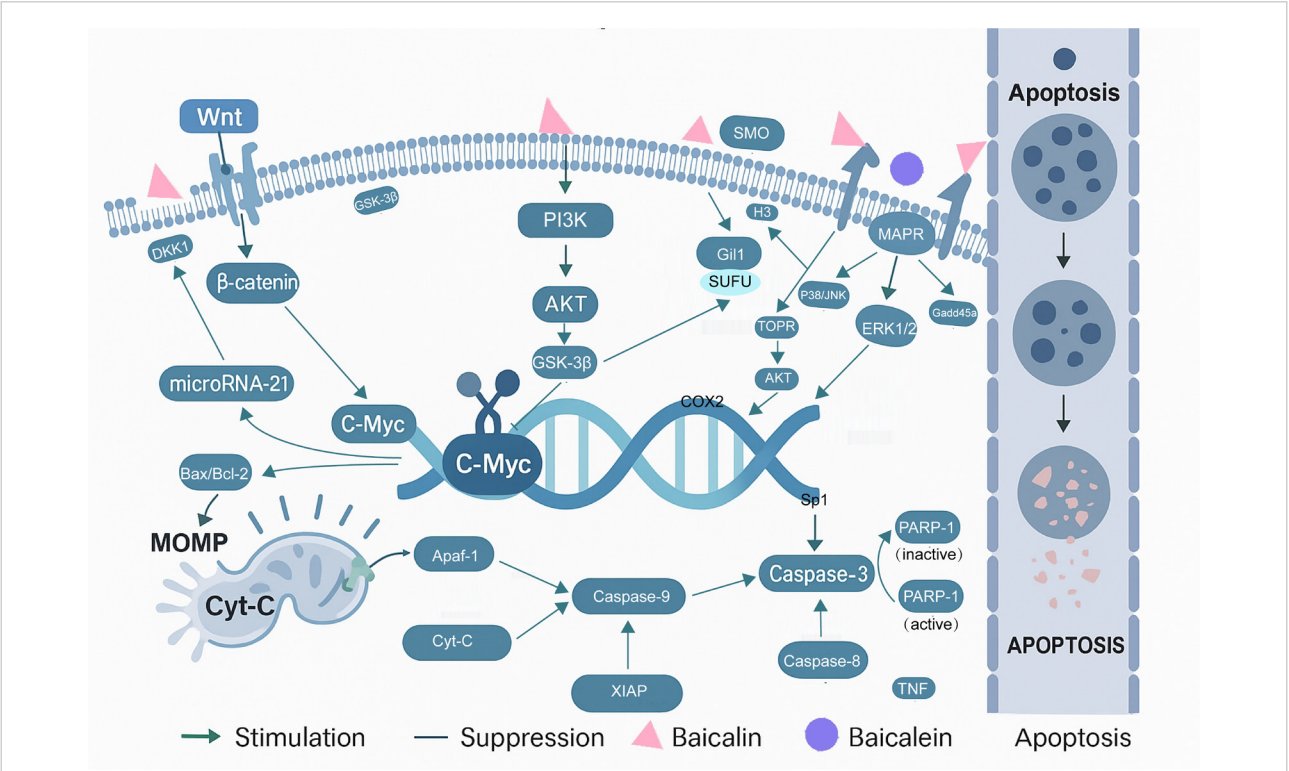

FIGURE 1

Mechanisms of baicalin and baicalein-induced apoptosis.

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Mechanisms of baicalin and baicalein inducing apoptosis. In terms of Wnt/AKT signaling regulation, baicalin and baicalein significantly reduce the expression of the pro-survival protein C-Myc by inhibiting GSK-3β activity and blocking PI3K/AKT signaling transduction, effectively inhibiting tumor cell proliferation. At the level of mitochondrial apoptosis pathway activation, by regulating Bax upregulation and Bcl-2 downregulation, mitochondrial membrane potential collapse is triggered, cytochrome C is released into the cytoplasm, and then the Caspase-9/3 cascade reaction is activated, and finally the irreversible apoptosis program is initiated through PARP-1 cleavage. In terms of enhancing the p53-dependent apoptotic effect, by activating p53 protein, its regulation of target genes such as Bax is enhanced, while XIAP apoptosis inhibitor and TNF-related survival signals are inhibited, forming a cascade amplification effect. From the perspective of epigenetic and microenvironmental regulation, by inhibiting microRNA-21 expression, its stabilizing effect on β-catenin and C-Myc is reduced, and the key molecule of the Hedgehog pathway SUFU and the inflammatory mediator TNF are synergistically regulated, doubly inhibiting the pro-survival microenvironment. These multi-target mechanisms of action synergistically lead to cell cycle arrest, mitochondrial dysfunction, and failure of the DNA repair system, ultimately producing a potent pro-apoptotic effect.

Baicalin induces cancer cell apoptosis through multiple pathways. In breast cancer cells, baicalin induces apoptosis by activating caspase-3, reducing the expression of anti-apoptotic protein Bcl-2, and increasing the expression of pro-apoptotic protein Bax. It also inhibits the PI3K/AKT signaling pathway and activates endoplasmic reticulum stress (ERS). The Wnt/β-catenin pathway is another pathway for baicalin to induce apoptosis in breast cancer cells. It inhibits the Wnt3α/β-catenin signaling pathway and upregulates Nischarin protein expression, thereby inhibiting breast cancer cell proliferation and promoting apoptosis. In addition, in gastric cancer cells, baicalin induces G2/M phase arrest by inhibiting the PI3K/AKT pathway and promotes apoptosis by activating the BTG3 protein(18). Baicalein, as a precursor compound of baicalin, exerts apoptosis regulation through metabolic activation. In some gynecological cancers, baicalein induces apoptosis by inhibiting the PI3K/AKT/mTOR pathway, while suppressing angiogenesis and metastasis(19).

2.2 Regulation of tumor autophagy

Tumor autophagy constitutes a highly regulated catabolic process that sustains cellular homeostasis under stress. In cancer cells, autophagy serves a dual role, functioning either as a survival mechanism upon nutrient deprivation or as an execution pathway when excessively activated. Scutellaria baicalensis–derived flavonoids have emerged as potent modulators of autophagic flux, with each compound targeting distinct signaling nodes to tip the balance toward tumor suppression. Baicalein promotes the nuclear translocation of the transcription factor TFEB by binding to and degrading MAP4K3 protein, thereby inducing autophagy and inhibiting the development of non-small cell lung cancer. Knockdown of MAP4K3 can mimic the autophagy-inducing effect of baicalin, while overexpression of MAP4K3 significantly resists the effect of baicalin(20). In a nude mouse xenograft tumor model, baicalein significantly inhibited the growth of H1299 lung cancer cells, and its mechanism was closely related to MAP4K3 degradation and autophagy activation(20). In colorectal cancer, baicalin inhibited the survival of colorectal cancer cells in a dose-dependent manner(21). Combination with the autophagy inhibitor chloroquine (CQ) enhanced baicalin-induced apoptosis, as manifested by increased Caspase-3 activation and LC3-II (autophagy marker) expression, suggesting that inhibiting protective autophagy can enhance the anti-cancer effect of baicalin(22). Baicalein also activates Parkin/TBK1-dependent mitophagy in hepatocellular carcinoma and promotes the clearance of damaged mitochondria. This process involves the participation of autophagy receptor proteins such as NDP52 and OPTN(23). The autophagy regulation of wogonin has a "double-edged sword" characteristic. In lung cancer and renal cancer, wogonin inhibits tumor growth and metastasis by activating autophagy(24), while in non-small cell lung cancer, wogonin enhances chemotherapy sensitivity by inhibiting autophagy-related proteins (such as ATG4D)(25). In addition, wogonin can induce autophagy and ferroptosis at the same time. In cervical cancer, it inhibits the Nrf2/GPX4 axis, significantly increases lipid peroxidation and ferroptosis markers (such as ACSL4), and inhibits autophagy-related proteins, thereby synergistically inhibiting tumor growth(26).

2.3 Remodeling of the TME

TME exerts profound influence over cancer progression through dynamic interactions among tumor cells, immune

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infiltrates, stromal constituents, and extracellular matrix (ECM) components. Natural compounds derived from Scutellaria baicalensis, including baicalein, baicalin, wogonin, and wogonoside, demonstrate substantial potential for TME remodeling. These flavonoids modulate immune surveillance, suppress stromal activation, and restrain angiogenic signals, thereby shifting the TME toward an antitumor state. In terms of immune cell regulation, baicalin and wogonin can exert anti-tumor effects by regulating immune cells in the TME. Studies have shown that baicalin can promote the polarization of tumor-associated macrophages to the pro-inflammatory M1 type, thereby enhancing tumor cell apoptosis and inhibiting the immunosuppressive microenvironment(27). Wogonin and other components may alleviate the immunosuppressive state by regulating the differentiation of regulatory T cells (Treg). Baicalin and wogonin, the main ingredients in Dahuangzhechong Pills (DHZCP), improve the suppressive immune state of hepatocellular carcinoma mice by regulating the balance of Treg/Th1(28). In terms of signal pathway inhibition, baicalin inhibits the PI3K/AKT pathway, downregulates p53 expression, and induces apoptosis of nasopharyngeal carcinoma cells(29). By inhibiting the Wnt/β-catenin signaling pathway, baicalein blocks the migration and invasion of breast cancer cells, and upregulates Nischarin protein expression to enhance the anti-tumor effect(30). In terms of angiogenesis and matrix remodeling, baicalein and baicalin inhibit angiogenesis and matrix remodeling by regulating tumor endothelial cells, fibroblasts and ECM. Baicalein reduces the expression of ECM components such as collagen (COL1A1) and fibronectin (FN), thereby inhibiting tumor angiogenesis and metastasis(31). Baicalin improves the immunosuppressive TME and reduces the infiltration of myeloid-derived suppressor cells (MDSCs) by downregulating PD-L1 expression(32). In colorectal cancer, baicalin treatment has been found to improve the tumor immunosuppressive environment by downregulating PD-L1 expression and the proportion of MDSCs in CT26 tumors and upregulating the percentage of CD4 and CD8 T cells(33), thereby improving anti-tumor immunity. In addition, baicalin can also reverse the immune escape phenomenon by reducing lactic acid accumulation in the TME, such as inhibiting lactic acid-mediated PD-L1 expression in oral squamous cell carcinoma and enhancing anti-tumor immune response(34).

2.4 Epigenetic regulation in cancer

Epigenetic alterations constitute a fundamental mechanism by which Scutellaria baicalensis–derived flavonoids exert antitumor activity. Aberrant DNA methylation, histone modifications and noncoding RNA expression patterns frequently silence tumor suppressors or activate oncogenes. Baicalein can increase histone acetylation levels by inhibiting the activity of histone deacetylases (such as HDAC-8 and HDAC10), thereby activating the expression of tumor suppressor genes. For example, in acute myeloid leukemia, baicalein induces apoptosis of leukemia cells by inhibiting HDAC-8(35). In hepatocellular carcinoma, baicalein inhibits the expression of HDAC10 by upregulating miR-3178, thereby inhibiting tumor cell proliferation and inducing apoptosis(36). In addition, Scutellaria baicalensis can also degrade HDAC-1 through the ubiquitin proteasome pathway and increase the acetylation levels of histone H3 and HSP90, thereby enhancing the anti-cancer effect of epigenetic regulation. Baicalein can target histone H3K9 demethylase KDM4E, increase H3K9me3 levels in triple-negative breast cancer, inhibit tumor cell proliferation and induce apoptosis(37). Also in triple-negative breast cancer, wogonin can inhibit the transcription of TXNRD2 by reducing H3K27 acetylation modification, leading to reactive oxygen species (ROS) accumulation and inducing cell senescence(38). At the same time, NF-κB activation and STAT3 inhibition were observed in wogonin-induced senescent cells, and the regulation of these two transcription factors may involve epigenetic remodeling of chromatin structure. In terms of methylation modification, in the type 2 diabetes (T2D)-induced liver cancer model, baicalin significantly inhibited the epigenetic modification (DNA 5mC and RNA mA) of the HKDC1 gene, especially targeting RNA mA sites, and achieved this regulation by inhibiting the activity of METTL3(39). In pancreatic ductal adenocarcinoma, baicalin regulates the RNA stability of target genes (such as FGFBP1) by inhibiting the expression of m6A methyltransferase METTL3 and demethylase FTO. This regulation may inhibit liver metastasis of cancer by reducing the infiltration of cancer-associated fibroblasts (CAFs) in the TME. Wogonin inhibits the proliferation and metastasis of ovarian cancer cells by stabilizing TET2 protein and promoting increased DNA hydroxymethylation levels(40). This epigenetic regulatory effect is also associated with activation of the AMPK signaling pathway, indicating that it affects epigenetic modifications through metabolic reprogramming. Combining these epigenetic effects with standard therapies may enhance clinical efficacy, and it is worth further studying to

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optimize the combined regimen.

2.5 Interventions for metabolic reprogramming

Metabolic reprogramming is a hallmark of cancer, enabling malignant cells to maintain uncontrolled proliferation, evade apoptosis, and resist therapeutic damage. Targeting these dysregulated metabolic pathways represents a promising cancer intervention strategy. Scutellaria baicalensis and its bioactive flavonoids exhibit multi-target regulatory effects on cancer metabolism by regulating glucose utilization, lipid synthesis, and amino acid metabolism. Baicalin has been shown to inhibit glucose uptake and metabolism in tumor cells by regulating key signaling pathways. In melanoma, baicalin significantly reduced glucose uptake and metabolism in tumor cells by inhibiting the mTOR-HIF-1α signaling pathway, thereby inhibiting tumor growth(41). In non-small cell lung cancer, baicalein induces cancer cell apoptosis by regulating glutamine metabolism and the mTOR pathway(42). In lung cancer studies, baicalin has been found to induce cancer cell apoptosis by inhibiting the glutamine metabolic pathway(43). Experiments have shown that lung cancer cells treated with baicalin have reduced glutamine consumption and decreased mTOR activity, leading to cell cycle arrest and increased apoptosis. Glutamine is an important substrate for tumor cells to synthesize nucleotides and maintain redox balance. The intervention of baicalin in this pathway may inhibit tumor proliferation by limiting the supply of metabolic intermediates. Baicalin can downregulate sterol regulatory element binding protein (SREBP1) and inhibit lipid biosynthesis in tumor cells. Lipid metabolic reprogramming is a key link in tumor cell membrane synthesis and energy storage. The intervention of baicalin may limit tumor progression by disrupting lipid homeostasis.

Wogonin significantly inhibits the expression of fatty acid synthase, reduces lipid accumulation and induces cell apoptosis in prostate cancer by activating the AKT-SREBP1-FASN signaling pathway(44). Animal experiments have shown that intravenous injection of 100 mg/kg of wogonin can significantly inhibit tumor growth without obvious toxicity. This mechanism suggests that it blocks the energy supply of tumor cells by intervening in lipid metabolic reprogramming. In melanoma (HT144 cells), wogonin inhibits the Hedgehog (Hh) signaling pathway (downregulating the expression of Patched and Smo proteins), reduces the activity of key glycolytic enzymes, and reduces the production of lactate, ATP and the expression of GLUT1, thereby inhibiting the glucose metabolism reprogramming and proliferation of tumor cells(45). Wogonin reduces the metabolic reprogramming of tumor cells by inhibiting the PI3K/AKT and Wnt/β-catenin signaling pathways(12). Experiments have shown that after wogonoside treatment of cutaneous squamous cell carcinoma, the activation of the above pathways was significantly downregulated, resulting in a decrease in the expression of CSC markers and a decrease in the proportion of CD133+ cells, thereby weakening the self-renewal ability of CSCs(46).

2.6 Treatment resistance

Treatment resistance remains a major obstacle in effective cancer therapy, often arising from genetic instability, tumor heterogeneity, and dynamic adaptation to therapeutic stress. Increasing evidence highlights the ability of Scutellaria baicalensis–derived flavonoids to overcome treatment resistance through modulation of multiple cellular processes, including apoptosis re-sensitization, inhibition of drug efflux transporters, suppression of survival signaling pathways, and restoration of chemosensitivity. Baicalin has shown significant potential in reversing chemoresistance. In breast cancer, baicalin can reverse tamoxifen resistance by inhibiting glycolysis and mitochondrial biogenesis and downregulating the expression of hypoxia-inducible factor HIF-1α(47). In addition, baicalin reduces the efflux of chemotherapeutic drugs from cells by inhibiting the activity of drug transporters such as ABCG2 (breast cancer resistance protein), thereby enhancing chemotherapy sensitivity(48). For example, the combination of baicalein and cisplatin can reduce the expression of resistance-related proteins such as p-Akt and p-mTOR in ovarian cancer cells and restore cisplatin sensitivity(49). Baicalin also plays a significant role in cancer resistance. In ovarian cancer, baicalin can enhance the sensitivity of cisplatin to resistant ovarian cancer cells. Studies have found that baicalein inhibits tumor growth and metastasis by inhibiting the expression of SLC7A6, reducing the phosphorylation levels of Akt, mTOR and Erk signaling pathways, and reducing the expression of Bcl-2 and MMP2(11). The research on baicalin in tumor treatment resistance mainly focuses on reversing chemotherapy

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resistance, overcoming radiotherapy resistance, and enhancing sensitivity by regulating multiple signaling pathways.

Wogonin can reverse multidrug resistance by inhibiting the function of breast cancer resistance protein (BCRP/ABCG2) and reducing the efflux of chemotherapy drugs. For example, in colorectal cancer, baicalin combined with autophagy inhibitors (such as chloroquine) can synergistically enhance the anti-tumor effect. In esophageal cancer, baicalin regulates glucose metabolism by targeting HIF-1α protein and downregulates the Cyclin D1/CDK4 axis to induce cell cycle arrest (G1), thereby reversing the radiotherapy resistance of esophageal cancer(50). In chronic myeloid leukemia (CML), wogonin overcomes imatinib resistance by reversing the methylation of the SHP-1 gene and inhibiting the JAK2/STAT5 signaling pathway(51). Wogonin affects tumor resistance through pathway regulation. Wogonin can enhance the killing effect of gemcitabine on resistant pancreatic cancer cells by inhibiting the AKT signaling pathway. Experiments have shown that wogonin combined with gemcitabine significantly inhibits the proliferation of resistant cells and reduces tumor growth in mouse models(52). By inhibiting the CDK4-RB pathway, wogonin induces apoptosis in resistant renal cell carcinoma cells and reverses sunitinib resistance, providing a new strategy for the treatment of advanced renal cancer(15). These flavonoids can restore the susceptibility of cancer cells to conventional therapies by targeting drug efflux, reactivating cellular pathways, and disrupting survival adaptability. Integrating scutellaria baicalensis-derived compounds into combination therapies is of great significance for overcoming drug resistance and improving clinical efficacy.

3.Synergistic and combined therapy

Despite considerable advances in understanding the antitumor mechanisms of Scutellaria baicalensis and its active flavonoids, clinical translation remains a critical frontier. Natural compounds such as baicalein, baicalin, wogonin, and wogonoside have demonstrated potent anticancer activities across preclinical models, including inhibition of proliferation, induction of apoptosis, modulation of autophagy, and reversal of treatment resistance. Nevertheless, the complexity of their pharmacokinetics, bioavailability, and interaction with existing therapies poses challenges that require systematic investigation before routine clinical application. Baicalin, characterized by its broad-spectrum anticancer effects, exhibits relatively low oral bioavailability due to poor water solubility and extensive first-pass metabolism(53). Efforts to enhance its clinical applicability have included the development of novel drug delivery systems such as nanoparticles, liposomes, and polymer-based carriers. These approaches not only improve systemic exposure but also facilitate targeted delivery to tumor tissues, thereby minimizing off-target effects. Early-phase clinical studies evaluating baicalein-enriched formulations have reported favorable safety profiles, supporting its further exploration as an adjuvant to standard chemotherapeutics.

Baicalin, a glucuronide conjugate of baicalein, demonstrates enhanced aqueous solubility, yet its rapid metabolism in vivo limits its therapeutic window. Strategies such as co-administration with bioavailability enhancers or structural modification through glycosylation have shown promise in extending its half-life and improving pharmacodynamic stability. Moreover, baicalin's capacity to modulate immune responses and attenuate chemotherapy-induced toxicity positions it as a compelling candidate for combination regimens aimed at both tumor suppression and supportive care. Wogonin, with its notable capacity to inhibit oncogenic signaling pathways and eradicate cancer stem cells, faces similar pharmacological hurdles(54). Encapsulation within biodegradable carriers and chemical derivatization have been employed to overcome these limitations, with preclinical results demonstrating improved biodistribution and sustained antitumor efficacy. Wogonoside, while sharing mechanistic similarities with wogonin, benefits from enhanced metabolic stability conferred by its glycoside structure. Its ability to modulate oxidative stress and sensitize resistant tumor cells further highlights its translational potential, particularly in refractory malignancies. Collectively, the transition of Scutellaria baicalensis–derived flavonoids

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from bench to bedside necessitates a multidimensional strategy. Optimization of formulation technologies, identification of predictive biomarkers for response, integration into rational combinatorial protocols, and execution of rigorously designed clinical trials will be essential steps. Understanding the pharmacological behavior of these compounds in the human body, alongside their mechanistic synergy with conventional therapies, will ultimately determine their success in reshaping modern cancer treatment paradigms.

3.1 Synergistic effect with chemotherapy drugs

Combination therapy has become a cornerstone strategy for improving efficacy and overcoming drug resistance in cancer treatment. Scutellaria baicalensis-derived flavonoids, including baicalein, baicalin, wogonin, and baicalin, have shown promising potential in combination with conventional chemotherapeutic drugs. They can modulate multiple oncogenic pathways, enhance the sensitivity of tumor cells to chemotherapeutic drugs, and reduce side effects, making them valuable adjuncts in multimodal treatment approaches.

Baicalein has shown significant synergistic effects in combination with standard chemotherapeutic drugs. In gastric cancer, baicalein combined with cisplatin significantly inhibited cell proliferation (SGC-7901 and resistant strain SGC-7901/DDP) and enhanced the efficacy of cisplatin by regulating Akt/mTOR and Nrf2/Keap1 signaling pathways without significantly increasing liver and kidney toxicity(55). Baicalein combined with 5-FU produced a synergistic killing effect on colorectal cancer resistant cells (RKO-R10), and in vivo experiments showed that the combined treatment was superior to single-drug in inhibiting tumor growth(56). In pancreatic neuroendocrine tumors, the combination of baicalein and everolimus significantly reduced cell survival and enhanced the efficacy by activating the AMPK pathway(57). In addition, the combination of Cmb8, a compound composed of baicalin and wogonin, and CPT-11 not only enhanced the anti-tumor effect in the colorectal cancer model, but also reduced chemotherapy-induced gastrointestinal damage(58). The combination of baicalein and baicalin can enhance the cytotoxicity, apoptosis-promoting and genotoxic effects of doxorubicin and docetaxel on breast cancer MCF-7 cells(59).

The stronger effect of baicalin may be related to the increased biological activity after deglycosylation. As a natural flavonoid compound, baicalin also has a strong effect in combination with other chemotherapeutic drugs in tumor treatment. Combining baicalin with chemotherapeutic drugs can also reduce liver and kidney toxicity. For example, in the treatment of liver cancer, baicalin combined with astragalus polysaccharide (APS) enhances chemotherapy sensitivity while protecting normal tissues(60). On the other hand, wogonin significantly enhances the anti-cancer effect when combined with irinotecan in the treatment of colorectal cancer. Studies have shown that in drug-resistant colon cancer stem cells (LOVO/DX cells), 20 μM irinotecan combined with 25 μM wogonin can significantly inhibit cell proliferation and induce apoptosis, and the apoptosis-inducing effect on drug-resistant cells is stronger than that on sensitive cells (LOVO cells). In addition, the combination of irinotecan and high concentrations of wogonin (50 μM) can also induce cancer cell necrosis. Wogonin has also been shown to reverse pancreatic cancer resistance to gemcitabine. In gemcitabine-resistant pancreatic cancer cells, wogonin significantly enhanced gemcitabine cytotoxicity by inhibiting the Akt signaling pathway and suppressed tumor growth in an orthotopic mouse model. Integrating these active compounds into combination therapies offers a promising strategy for cancer treatment that could greatly improve anticancer efficacy while mitigating drug resistance and toxicity.

3.2 Sensitization effect of radiotherapy

Radiotherapy remains a primary modality in the treatment of various malignancies, yet intrinsic and acquired radioresistance often compromise therapeutic outcomes. Emerging evidence suggests that Scutellaria baicalensis–derived flavonoids, including baicalein, baicalin, wogonin, and wogonoside, possess potent radiosensitizing properties. These compounds target multiple cellular processes such as DNA damage repair, oxidative stress regulation, and survival signaling, ultimately enhancing the efficacy of radiotherapy. Baicalein has been shown to sensitize tumor cells to ionizing radiation through multiple mechanisms. The combination of baicalein and bismuth oxide nanoparticles (BiONPs) can significantly increase the generation of ROS during radiotherapy (photons, electrons,

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etc.), enhancing the killing effect of radiotherapy on ovarian cancer cells. In hormone-resistant prostate cancer, baicalein inhibits Ezrin protein expression, blocks the cell cycle and promotes apoptosis, thereby enhancing radiosensitivity(61). Baicalein can also achieve radiosensitization by inhibiting DNA damage repair after radiotherapy. By inhibiting the Hippo signaling pathway and activating the AMPK signaling, baicalein can reduce the DNA damage repair ability of tumor cells after radiotherapy, thereby enhancing the sensitivity of colorectal cancer cells to radiation.

In terms of signal pathway regulation, baicalin inhibits the JAK2/STAT3 signaling pathway, reduces tumor cell survival and promotes apoptosis, while reversing radiotherapy-induced EMT, thereby enhancing the radiosensitivity of Hela cells. Baicalin exhibits antioxidant effects in normal cells, but may enhance the killing effect of radiotherapy in tumor cells by inducing oxidative stress. For example, when combined with low-dose radiotherapy (4 Gy), baicalin improves the tumor hypoxia microenvironment and enhances radiosensitivity through nanodelivery systems (such as Cuhemin-Au)(62). Biomimetic nanozymes deliver baicalin to the tumor site in a targeted manner, improving drug utilization and enhancing the radiosensitization effect. For example, the copper-based nanoplatform significantly inhibits tumor progression under low-dose radiotherapy with fewer side effects. In hepatocellular carcinoma, wogonin enhances the killing effect of radiotherapy on tumor cells by upregulating p21 protein expression, inducing cell cycle arrest, and inhibiting the expression of key proteins for DNA damage repair. p21 interference experiments further confirmed its core role in radiosensitization(63). Studies on colorectal cancer have shown that wogonin combined with radiotherapy significantly increased the apoptosis rate of HCT116R cells, and its strong binding ability with SULT2B1 protein was verified by molecular docking, suggesting that this target may be the key to reversing radioresistance. Some studies have explored the combined application of wogonin and nanotechnology. For example, bionic nanozyme delivery systems can improve the hypoxic microenvironment of tumors and enhance radiosensitivity. Nanoplatforms based on metal complexes (Ru-Se) enhance ROS generation by simulating the activity of cytochrome P450 enzymes, achieving physical-chemical dual sensitization.

Conclusion

The multifaceted anticancer properties of Scutellaria baicalensis and its bioactive flavonoids highlight their potential as therapeutic candidates for cancer. Accumulating preclinical evidence suggests that they are able to modulate multiple oncogenic pathways, from induction of apoptosis and cell cycle arrest to epigenetic remodeling and metabolic reprogramming. Notably, these compounds exhibit pleiotropic tumor suppressive effects by targeting key nodes for cancer cell survival, such as PI3K/AKT, Wnt/β-catenin, and NF-κB signaling, while remodeling the tumor microenvironment through immunomodulation and inhibition of angiogenesis. Their ability to circumvent drug resistance by inhibiting efflux transporters, restoring chemosensitivity, and interfering with DNA repair mechanisms further enhances their therapeutic relevance. Synergistic effects with conventional chemotherapy and radiotherapy highlight the translational value of integrating Scutellaria baicalensis derivatives into combination regimens. Despite these advances, challenges remain in optimizing pharmacokinetic profiles and bioavailability, necessitating innovative delivery systems, such as nanoparticle encapsulation and structural derivatization. By understanding the drug action mechanisms of Scutellaria baicalensis derivatives and integrating traditional therapies with modern pharmacological paradigms, Scutellaria baicalensis has great potential to complement existing anticancer strategies, providing a holistic approach to combat tumor heterogeneity and therapeutic resistance.

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