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Review

Advances in the role of baicalin and baicalein in colon cancer: mechanisms and therapeutic potential

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Abstract
Colorectal cancer (CRC) remains a malignancy with high incidence and mortality rates worldwide, necessitating the development of more effective therapeutic strategies due to the limitations of current treatments, including drug resistance and adverse effects. *Scutellaria baicalensis*, a traditional Chinese medicinal herb, contains baicalin and baicalein as its primary bioactive flavonoids, which exhibit notable pharmacological properties such as antibacterial, anti-inflammatory, antioxidant, and antitumor effects. Recent studies have demonstrated that baicalin and baicalein show promising antitumor activity in CRC treatment through mechanisms such as scavenging reactive oxygen species, immune regulation, and inhibition of tumor cell proliferation, induction of apoptosis, and modulation of the gut microenvironment. This study further investigates the molecular mechanisms underlying the therapeutic effects of baicalin and baicalein in CRC, aiming to provide new research perspectives and potential clinical applications for the integration of flavonoid-based compounds from *Scutellaria baicalensis* in CRC treatment.

Keywords Colon cancer · Baicalin · Baicalein · Mechanism · Scutellaria baicalensis

1 Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide and ranks as the third most prevalent cancer globally, following breast and lung cancers [1]. Its incidence and mortality rates are continuously rising, posing significant challenges to public health systems [2]. Risk factors for CRC include the consumption of red and processed meats, alcohol intake, obesity, inflammatory bowel disease, and a family history of CRC. Protective factors, on the other hand, include aspirin use, high vitamin D levels, increased folate intake, and regular physical activity [3–5]. Surgical resection remains the primary curative treatment for CRC. However, due to the disease's insidious onset, high aggressiveness, and various influencing factors, many patients miss the optimal treatment window and must rely on adjuvant chemotherapy and other conservative

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approaches [6–8]. Unfortunately, current first-line treatments are often hampered by tumor cell resistance and significant adverse effects [9, 10]. Therefore, exploring novel and more effective therapeutic strategies is critical to improving CRC treatment and prognosis.

Traditional Chinese medicine herb exerts antitumor effects through a multi-target, multi-pathway regulatory mechanism [11–13]. It not only directly inhibits tumor cell proliferation and induces apoptosis but also modulates the immune microenvironment, suppresses inflammation, and improves overall patient health, making it highly valuable for clinical applications [14–16]. *Scutellaria baicalensis*, a traditional Chinese medicinal herb with a long history, contains baicalin and baicalein as its major active constituents [17, 18]. Modern pharmacological studies have revealed that Scutellaria exhibits a wide range of therapeutic effects, including antimicrobial, anti-inflammatory, antioxidant, antitumor, antitussive, cardioprotective, and neuroprotective activities [19–22]. Although direct clinical applications of Scutellaria in cancer treatment are rare, recent advancements in pharmacological research have highlighted the significant antitumor potential of its active flavonoid components [23–26]. Among these, baicalin and baicalein are the most studied flavonoids derived from Scutellaria [27]. These compounds have been shown to possess multiple pharmacological properties, such as antibacterial, antiviral, free radical scavenging, antioxidant, antipyretic, analgesic, anti-inflammatory, antitumor, cardioprotective, neuroprotective, hepatoprotective, and antidiabetic effects [28–34]. Recent studies increasingly demonstrate the promising efficacy of baicalin and baicalein in the treatment of CRC. This review explores the potential molecular mechanisms underlying their therapeutic effects against CRC, highlighting their significant antitumor activities via various pathways. The findings aim to provide novel insights and directions for the integrated treatment of CRC based on these Scutellaria-derived flavonoids.

2 Structure and origin of baicalin and baicalein

Baicalin has a molecular formula of $C_{21}H_{18}O_{11}$ and is the most abundant flavonoid compound found in the traditional Chinese medicine *Scutellaria baicalensis* [35]. It is a glycoside formed by the combination of baicalein and a molecule of glucuronic acid. At room temperature, baicalin appears as a pale yellow powder with a bitter taste. It is sparingly soluble in methanol, ethanol, and acetone, slightly soluble in chloroform and nitrobenzene, and practically insoluble in water but soluble in hot acetic acid [36]. Baicalein, chemically named 5,6,7-trihydroxyflavone, is primarily extracted from the roots of *Scutellaria baicalensis* and has a molecular formula of $C_{15}H_{10}O_5$. It is one of the most abundant compounds in Scutellaria. Its primary sources include the whole herb and roots of *Scutellaria altissima* L. (family Lamiaceae), the leaves and roots of *Scutellaria galericulata* L. (formerly S. scrodiifolia Fisch.), the seeds and bark of *Oroxylum indicum* (L.) Vent. (family Bignoniaceae), and the leaves of *Plantago major* L. (family Plantaginaceae) [37]. Baicalein is soluble in methanol, ethanol, acetone, ethyl acetate, and hot glacial acetic acid, and slightly soluble in chloroform [38]. After entering the body, baicalein is rapidly converted into baicalin and other metabolites in the bloodstream. Conversely, oral administration of baicalin is poorly absorbed in the gastrointestinal tract; it requires enzymatic hydrolysis to baicalein in the intestine before absorption into the bloodstream, where it is promptly reconverted into baicalin [39]. Both baicalin and baicalein exhibit a wide range of pharmacological activities, including antibacterial, antiviral, free radical scavenging, antitumor, and cardiovascular protective effects [38, 40–43]. Baicalin can also absorb ultraviolet radiation, scavenge reactive oxygen species (ROS), and inhibit melanin production, making it applicable not only in medicine but also in cosmetics [44]. Baicalein, on the other hand, demonstrates the ability to reduce cerebrovascular resistance, improve cerebral circulation, increase cerebral blood flow, and inhibit platelet aggregation, and is clinically used in the treatment of post-stroke paralysis [45, 46]. The pharmacological properties of baicalin and baicalein are largely attributed to their capacity to scavenge ROS and interact with various signaling molecules involved in apoptosis, inflammation, autophagy, cell cycle regulation, mitochondrial dynamics, and cytoprotection [47, 48].

3 Anticancer mechanisms against colorectal cancer

3.1 Tumor cell proliferation

Tumor cell proliferation refers to the process in which cancer cells continuously divide and grow through an abnormally active cell cycle, thereby escaping normal regulatory mechanisms. This uncontrolled proliferation leads to tumor growth and expansion [49, 50].

Baicalein exhibits anti-proliferative effects in CRC cells by inducing S-phase arrest and apoptosis via caspase-3/-9 activation [51]. Molecular docking suggests its hydroxyl group interacts with key caspase residues, clarifying its apoptotic

mechanism. Additionally, baicalein inhibits CRC proliferation and reduces ROS levels by upregulating peroxiredoxin 6 (PRDX6), with PRDX6 silencing reversing these effects [52].

Wang et al. [53] synthesized a Ruthenium-Baicalein Complex, which induced apoptosis in HT-29 cells via the p53-dependent pathway and regulated AKT/mTOR and WNT/β-catenin signaling. In vivo, it reduced aberrant crypt foci and hyperplastic lesions while enhancing antioxidant enzymes. Li et al. [54] found that baicalin induced S-phase arrest, inhibited CRC cell proliferation, invasion, and migration by regulating CDKN2A and related pathways, and suppressed tumor growth in vivo via p-AKT, CDK4, and inflammatory cytokine inhibition. Cai et al. [55] demonstrated that baicalin upregulated miR-139-3p to downregulate CDK16, thereby halting the cell cycle. Jia et al. [56] showed that baicalin suppressed CRC proliferation and induced apoptosis by upregulating DKK1, inhibiting β-catenin and c-Myc, and downregulating miR-217 (Fig. 1).

3.2 Tumor cell apoptosis

Tumor cell apoptosis refers to the activation of programmed cell death pathways through intrinsic or extrinsic signals, leading to the elimination of cancer cells and suppression of tumor progression [57, 58].

Labuz et al. [59] reported that baicalein inhibited proliferation and induced apoptosis in CRC cells, though its effects were weaker in drug-resistant LoVo/Dx cells due to P-glycoprotein overexpression. Kim et al. [60] demonstrated that baicalein suppressed tumor growth in a mouse xenograft model via G1-phase arrest, Bax/Bcl-2 modulation, and PI3K/Akt inactivation. In another study by the same research group [61], baicalein was found to inhibit the proliferation of HCT-116 cells in a concentration-dependent manner and to induce apoptosis. The mechanisms involved included morphological changes and PARP cleavage, indicating its role in triggering apoptotic pathways. Dou et al. [62] found that baicalin induced senescence by inhibiting hTERT, with MAPK/ERK and p38 signaling involved in apoptosis. Su et al. [63] showed that baicalein upregulated DEPP and Gadd45α, activating the MAPK pathway and forming a JNK/p38 feedback loop. Jiang et al. [64] revealed that baicalein activated γ-H2AX and AKT, partially protecting cancer cells, while PI3K-AKT or γ-H2AX inhibition enhanced cytotoxicity. Tao et al. [65] found that baicalin downregulated c-Myc and oncogenic miRNAs, inducing apoptosis and tumor regression in vivo. Ma et al. [66] showed that baicalin suppressed Sp1 and survivin, triggering caspase-3-mediated apoptosis via intrinsic and extrinsic pathways (Fig. 2).

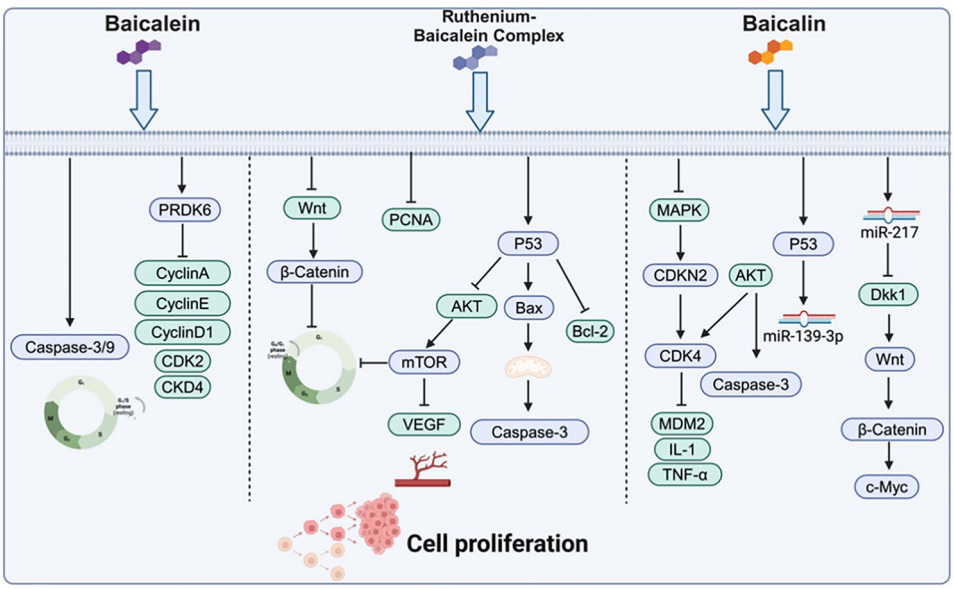

Fig. 1 Mechanism of baicalein and baicalin suppressing proliferation in colorectal cancer. Baicalein induces S-phase cell cycle arrest and apoptosis through caspase-3 and caspase-9 activation, and modulates ROS levels by upregulating PRDX6. The ruthenium-baicalein complex enhances apoptosis and inhibits tumor proliferation by regulating the p53-dependent apoptotic pathway and modulating AKT/mTOR and WNT/β-catenin signaling pathways. Baicalin further suppresses CRC cell proliferation, migration, and invasion by regulating CDKN2A, MAPK, p-AKT, and CDK2, while inducing apoptosis through caspase-3 activation. Additionally, baicalin upregulates miR-139-3p, inhibits CDK16, and reduces miR-217 expression, affecting the Wnt pathway via DKK1 inhibition

3.3 Tumor cell invasion and migration

Tumor cell invasion and migration refer to the process by which cancer cells break through the basement membrane and traverse surrounding tissues or vessel walls to spread distantly, forming metastatic lesions. These are critical features of tumor malignancy [67, 68].

The activation of epithelial-mesenchymal transition (EMT) is a pivotal process in cancer cell metastasis. During EMT, epithelial cells acquire mesenchymal properties, enhancing their motility and migratory capacity [69]. Yang et al. [70] demonstrated that baicalin significantly inhibits the growth, migration, and invasion of CRC cells, induces apoptosis, and arrests the cell cycle, exhibiting potent antitumor effects both in vitro and in vivo. Mechanistically, baicalin exerts its effects by modulating the TGFβ/Smad signaling pathway. This modulation inhibits cell cycle progression, EMT, and cancer stemness (CSC), including reducing CSC marker expression and suppressing spheroid formation. Additionally, baicalin induces p53-independent apoptosis and inhibits TGFβ1-induced EMT (Fig. 3).

3.4 Tumor cell autophagy

Autophagy plays a dual role in tumors, facilitating tumor survival by maintaining cellular homeostasis while also suppressing tumor progression by eliminating damaged components and inducing cell death [71].

Phan et al. [72] discovered that baicalein dose-dependently reduces the viability of various CRC cell lines. When combined with chloroquine, an autophagy inhibitor, the inhibitory effects on HT-29 and HCT-116 cells were significantly enhanced. The combination treatment increased the expression of the autophagy marker LC3-II and induced apoptosis through the caspase-3 pathway (Fig. 4).

3.5 Regulation of immunity

Tumor immunity refers to the process by which the host innate and adaptive immune systems recognize and eliminate tumor cells. The immune system plays a crucial role in regulating inflammatory responses; chronic inflammation

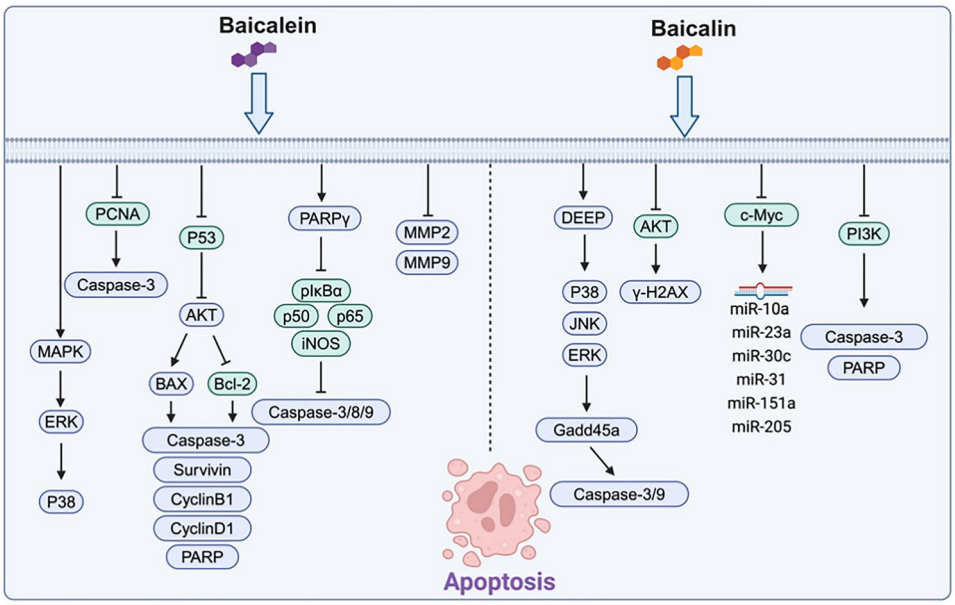

Fig. 2 Baicalein and baicalin significantly influences apoptosis in colorectal cancer cells. Baicalein induces cell cycle arrest, apoptosis, and senescence through various pathways, including inhibition of PI3K/Akt signaling, downregulation of Bcl-2, upregulation of Bax, and activation of the MAPK pathway. It also triggers apoptosis through caspase activation and morphological changes, and increases DNA damage response markers like γ-H2AX. Baicalein's cytotoxicity is enhanced by inhibiting the PI3K-AKT pathway or reducing γ-H2AX expression. In drug-resistant CRC cells, baicalein's effect is reduced due to P-glycoprotein overexpression. Additionally, baicalein downregulates c-Myc and miRNAs, and induces apoptosis through the intrinsic and extrinsic pathways, including Sp1-mediated survivin regulation

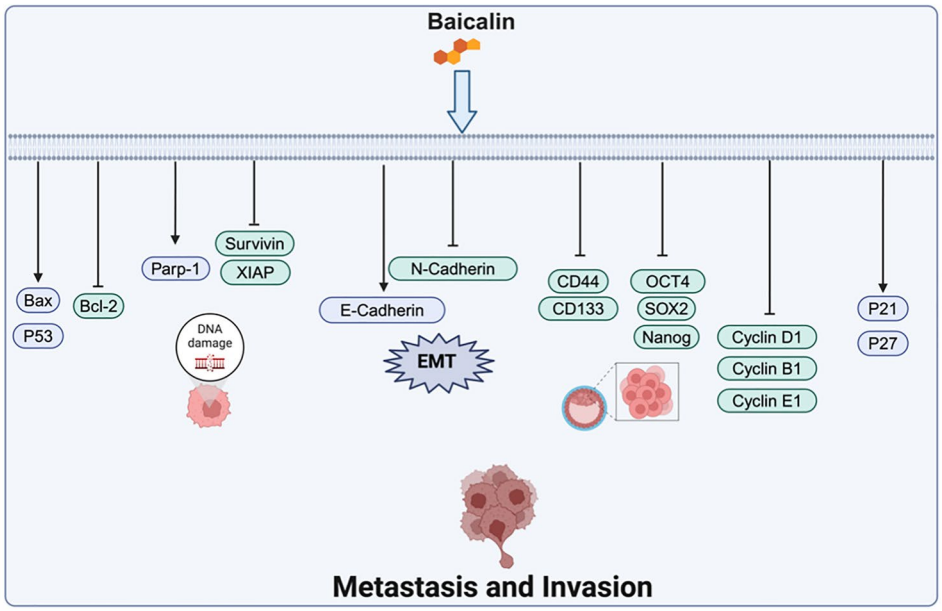

Fig. 3 Baicalin inhibits colorectal cancer metastasis by targeting key migration and invasion pathways. It exerts its antitumor effects by modulating the TGFβ/Smad signaling pathway, which inhibits EMT, cell cycle progression, and cancer stemness (CSC). Baicalin reduces CSC marker expression and suppresses spheroid formation. Additionally, baicalin induces p53-independent apoptosis, inhibits CRC cell growth, migration, and invasion, and effectively arrests the cell cycle

often contributes to tumor progression by activating pro-inflammatory cytokines, immune cell infiltration, and dysregulated signaling pathways [73, 74].

KIM et al. [61] conducted studies using AOM and DSS to induce colorectal tumors in mice and found that baicalein significantly reduced tumor incidence. Mechanistic analysis revealed that baicalein exerts anti-inflammatory effects by activating PPARγ and inhibiting NF-κB activation.Wang et al. [75] demonstrated that oral administration of baicalein significantly prolonged the survival of *Apc*$^{Min/+}$ mice, reduced tumor count, and lowered levels of inflammatory cytokines

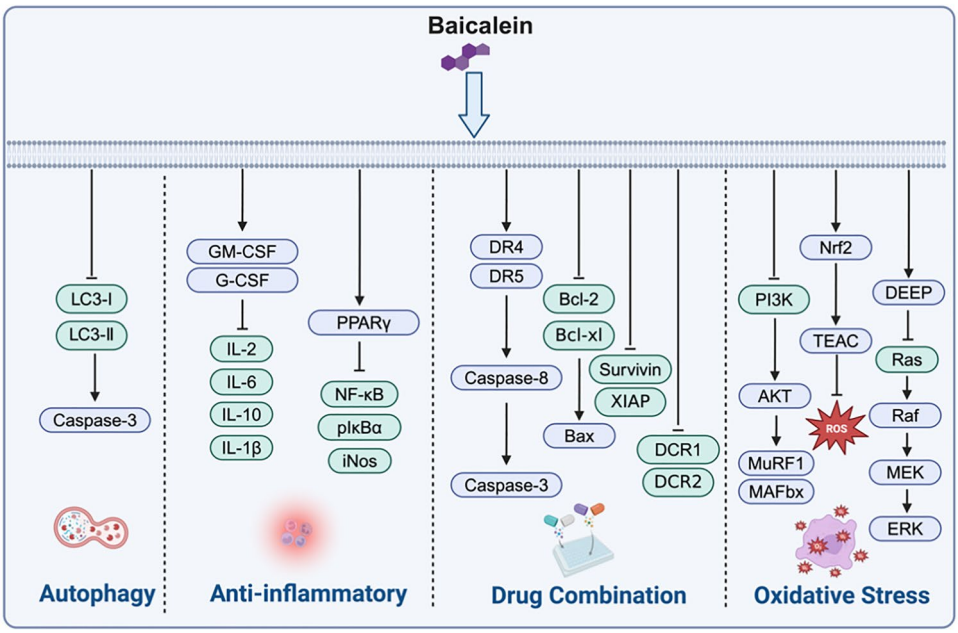

Fig. 4 Baicalein exerts multiple mechanisms in CRC by inducing autophagy, inhibiting inflammation, enhancing drug sensitivity, and regulating oxidative stress. It reduces CRC cell viability and, when combined with chloroquine, enhances apoptosis via LC3 and caspase-3. Baicalein reduces tumor incidence, prolongs survival, and inhibits inflammatory cytokines by activating PPARγ, suppressing NF-κB, and inducing apoptosis. It also enhances TRAIL-induced apoptosis by upregulating DR5 through CHOP activation. Additionally, baicalein mitigates cachexia, promotes cellular senescence, and inhibits tumor growth in CRC by regulating AKT phosphorylation, reducing Nrf2 phosphorylation, and upregulating DEPP with antioxidant effects

such as IL-1β, IL-2, IL-6, IL-10, G-CSF, and GM-CSF. These effects were mediated through the suppression of intestinal inflammation and the induction of cancer cell apoptosis (Fig. 4).

3.6 Enhancing drug sensitivity

Enhancing the sensitivity of tumor cells to chemotherapeutic agents can improve therapeutic efficacy and reduce dose-dependent side effects. This can be achieved by inhibiting resistance mechanisms, promoting apoptosis, and improving drug accumulation [76, 77].

Taniguchi et al. [78] demonstrated that baicalein overcomes cancer cell resistance to TRAIL and significantly enhances TRAIL-induced apoptosis. In SW480 CRC cells, baicalein increased TRAIL sensitivity by upregulating the expression of death receptor 5 (DR5). This DR5 upregulation was dependent on the activation of the CHOP binding site. Yu et al. [79] found that baicalin effectively alleviates resistance to anti-PD-1 therapy by modulating gut microbial metabolites, particularly short-chain fatty acids (SCFAs). Oral administration of baicalin enhanced the efficacy of fecal microbiota transplantation (FMT) combined with anti-PD-1 therapy. In mouse models, baicalin enriched gut bacteria such as Akkermansia and Clostridia_UCG-014, elevated SCFA levels, improved the PD-1^+ ($CD8^+$ T cells/Treg) ratio, and increased levels of IFN-γ^+ and TNF-α^+ $CD8^+$ T cells in the tumor microenvironment (Fig. 4).

3.7 Oxidative stress

Oxidative stress, driven by the excessive production of ROS, causes cellular damage, induces DNA mutations, and leads to genomic instability. It also activates pro-inflammatory and tumor-promoting signaling pathways, playing a critical role in tumorigenesis, progression, and drug resistance [80, 81].

Song et al. [82] found that baicalein significantly alleviates weight loss, skeletal muscle atrophy, and white adipose tissue reduction in cachexia mice. This effect was achieved by suppressing muscle protein degradation and enhancing AKT phosphorylation. Additionally, baicalein effectively mitigated muscle wasting by inhibiting key components of the ubiquitin–proteasome system, such as F-box-only protein 32 and muscle RING finger protein 1. Havermann et al. [83] reported that while baicalein did not significantly affect Nrf2 ubiquitination, proteasomal activity, or transcriptional regulation, it reduced Nrf2 phosphorylation by inhibiting protein kinases. Furthermore, baicalein derivatives showed distinct activities: Negletein demonstrated Nrf2 activation, while Oroxylin A primarily exhibited free radical scavenging effects. Wang et al. [84] revealed that baicalin promotes cellular senescence and inhibits tumor growth in CRC by upregulating DEPP expression, activating the Ras/Raf/MEK/ERK and p16^INK4A/Rb signaling pathways. Its antioxidant effects played a crucial role in this process. Exogenous DEPP expression significantly enhanced senescence-associated β-galactosidase (SA-β-Gal) activity, whereas DEPP knockdown reversed the antitumor effects of baicalin (Fig. 4).

4 Discussion

Baicalin and baicalein exhibit significant anti-CRC activities through various mechanisms (Table 1). In terms of inhibiting tumor cell proliferation, they effectively suppress the growth of CRC cells by inducing cell cycle arrest, activating caspase-dependent apoptotic pathways, and regulating key signaling molecules such as p53, AKT/mTOR and WNT/β-catenin [51, 52, 54]. For promoting apoptosis, baicalin and baicalein activate both intrinsic and extrinsic apoptotic pathways by modulating signaling pathways like MAPK, PI3K/AKT and related microRNAs [85, 86]. They also upregulate genes such as Gadd45α and DEPP, establishing a positive feedback loop to enhance apoptotic effects [59–63]. Additionally, these compounds inhibit tumor cell invasion and migration [70], promote autophagy [72], modulate the immune-inflammatory microenvironment [61], enhance chemosensitivity [78, 79], and reduce ROS production by regulating oxidative stress [82–84]. Collectively, these findings highlight the promising therapeutic potential of baicalin and baicalein in CRC treatment. Further studies are warranted to elucidate their precise molecular mechanisms and explore their clinical application value.

Despite the growing body of research highlighting the anticancer potential of baicalin and baicalein in various malignancies, their mechanisms of action require further elucidation. The variability in sensitivity among different cell types to baicalin and baicalein remains unclear, and their application in drug-resistant tumors needs optimization [87–89]. Moreover, the high polarity of baicalin prevents it from crossing the lipid bilayer via passive diffusion, resulting in poor

Table 1 Possible mechanisms, real modules, targets, doses and reference of Baicalin and Baicalein in Colon Cancer

Baicalin/Baicalein	Possible mechanisms	Real modules (animal/cell)	Targets	Doses	References
Baicalein	Cell proliferation, apoptosis	Cell: HCT-116, SW480, HT-29 Animal: Xenograft nude mice	Caspase-3, caspase-9, S phases	87.3 μM, 30 mg/kg	[51]
Baicalein	Cell proliferation	Cell: DLD-1, SW480, HaCaT	PRDK6, cyclin A, cyclin D1, cyclin E, CDK2, CDK4, G1 phase	50 μM	[52]
Ruthenium-Baicalein Complex	Cell proliferation, apoptosis	Cell: HT-29 Animal: Swiss albino mice	p53, mTOR, AKT, caspase-3, VEGF	30 μM, 100 mg/kg	[53]
Baicalin	Cell proliferation, invasion, migration, apoptosis	Cell: MC38, CT26 Animal: male C57BL/6 mice	S phase, CDKN2A, MAPK, p-AKT, caspase-3, caspase-9	60 μM, 100 μM, 50 mg/kg	[54]
Baicalin	Cell proliferation	Cell: SW480, HCT-116, CT26 Animal: Male BALB/c nude mice	miR-139-3p, CDK16	60 μM, 50 mg/kg	[55]
Baicalin	Cell proliferation	Cell: DLD1, HCT-116	miR-217, DKK1, Wnt, β-catenin, c-Myc	40 μM	[56]
Baicalein	Cell apoptosis, proliferation	Cell: LoVo	PCNA, caspase-3	100 μM	[59]
Baicalein	Cell apoptosis	Cell: HT-29 Animal: Male nude mice	G1 phase, Bcl-2, Bax, P53, AKT, Caspase-3, Cyclin B1, Cyclin D1, PARP	100 μM, 10 mg/kg	[60]
Baicalein	Cell apoptosis, metastasis, anti-inflammatory	Cell: HCT-116 Animal: Male ICR mice	Caspase-3/8/9, MMP-2, MMP-9, PPARγ, plκBα, iNOS, p50, p65	100 μM, 10 mg/kg	[61]
Baicalein	Cell apoptosis, migration	Cell: HCT-116, HT-29, SW480 Animal: NOD-scid IL2Rγ^{null} immunodeficient mice	MAPK, ERK, p38	50 μM, 50 mg/kg	[62]
Baicalein	Cell apoptosis	Cell: HCT-116	DEEP, JNK, ERK, p38, Gadd45a, Caspase-3, Caspase-9	40 μM	[63]
Baicalein	Cell apoptosis	Cell: RKO, HCT-116	AKT, γ-H2AX, securin, ERK2	60 μM	[64]
Baicalin	Cell apoptosis	Cell: HT-29	miR-10a, miR-23a, miR-30c, miR-31, miR-151a, miR-205, c-Myc, BCL-2, Caspase3, PTEN, HIC1, E2F2, PDCD4, E-cadherin	150 μM	[65]
Baicalin	Cell apoptosis	Cell: SW480	sp1, PARP, caspase-3	50 μg/ml	[66]
Baicalein	Cell autophagy, apoptosis, proliferation	Cell: HT-29, COLO, HCT-116, LoVo, SW480, SW620	LC3-I, LC3-II, Caspase-3	100 μM	[72]
Baicalin	Cell invasion and migration, apoptosis, proliferation	Cell: FHC, RKO, HCT-116	Caspase-3/8/9, Parp-1, XIAP, NF-κB, Survivin, Bcl-2, Bax, p53, Akt, Cyclin D1, Cyclin E1, Cyclin B1, P21, P27, CD44, CD133, OCT4, SOX2, Nanog, E-Cadherin, N-Cadherin	100 μM	[70]
Baicalein	Anti-inflammatory, cancer cell death	Cell: HT-29 Animal: Male C57BL/6 J-*Apc*^{Min}/J, female C57BL/6 J mice	IL-1β, IL-2, IL-6, IL-10, GM-CSF, G-CSF	100 μM, 30 mg/kg	[75]
Baicalein	Enhancing chemotherapy drug sensitivity, cell apoptosis	Cell: SW480	DR5, DR4, CHOP, caspase-3/8/9/10, DCR1, DCR2, Bcl-2, Bcl-xl, Bax, survivin, XIAP	20 ng/mL (TRAIL) + 40 μM (Baicalein)	[78]

Table 1 (continued)

Baicalin/Baicalein	Possible mechanisms	Real modules (animal/cell)	Targets	Doses	References
Baicalein	Oxidative stress	Cell: CM, CT26 Animal: Male BALB/c mice	PI3K, AKT, MuRF1, MAFbx	10 μM, 20 mg/kg	[82]
Baicalein	Oxidative stress	Cell: HCT-116	Nrf2, TEAC, DCF	50 μM	[83]
Baicalin	Oxidative stress, cell proliferation	Cell: HCT-116, SW480	DEEP, Ras, Raf, MEK, ERK	40 μM	[84]

intestinal absorption [90]. Although several formulations have been developed to enhance the bioavailability of baicalin, an ideal preparation has yet to be established. Consequently, its low solubility and bioavailability pose significant challenges to clinical application. Currently, the safety of baicalin has been evaluated in only a limited number of clinical trials and volunteer studies, leaving its safety profile uncertain and warranting cautious use. Additionally, the lack of comprehensive preclinical and clinical trial data hampers the translation of baicalin and baicalein into clinical practice. Future research should prioritize precise identification of their molecular targets, detailed pharmacokinetic and toxicological assessments, and exploration of synergistic effects with other anticancer agents. These efforts are essential for facilitating the widespread clinical application of baicalin and baicalein in cancer treatment.

5 Conclusion

Baicalin and baicalein exhibit strong anti-CRC effects by inhibiting proliferation, inducing apoptosis, and modulating key pathways like p53, AKT/mTOR, and WNT/β-catenin. They also suppress invasion, promote autophagy, enhance chemosensitivity, and reduce oxidative stress, highlighting their therapeutic potential. However, challenges such as variable sensitivity, poor bioavailability, and limited clinical data hinder their application. Future research should focus on optimizing pharmacokinetics, identifying precise targets, and evaluating their synergy with other therapies to facilitate clinical translation.

Author contributions Lexin Li wrote the manuscript and drew the pictures. Xuyang Cui collected and organize literature. Yiming Chen and Zhanyu Lin proofread the manuscript. Xiaoyu Zhang and Yong Zhu are fully responsible for the study designing, research fields, drafting, and finalizing the paper.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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