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Scutellaria baicalensis and Cancer Treatment: Recent Progress and Perspectives in Biomedical and Clinical Studies

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Abstract: *Scutellaria baicalensis* (Huangqin in Chinese) is a major traditional Chinese medicine (TCM) herb, which has a long history of use in the treatment of a variety of symptoms correlated with cancer. In the past decade, the potential of *S. baicalensis* and single compounds derived from it as anticancer agents targeting various pathways has received extensive research attention. Specifically, the proliferation and metastases inhibiting properties of the single compounds in cancer have been studied; however, the underlying mechanisms remain unclear. This review summarizes the various mechanisms, pathways and molecular targets involved in the anticancer activity of *S. baicalensis* and its single compounds. However, the aim of this review is to provide a more thorough view of the last 10 years to link traditional use with modern research and to highlight recently discovered molecular mechanisms. Extracts and major flavonoids derived from *S. baicalensis* have been found to possess anticancer effects in multiple cancer cell lines both *in vitro* and *in vivo*. Further investigation is warranted to better understand the underlying mechanisms and to

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discover novel targets and cancer therapeutic drugs that may improve both the survival and quality of life of cancer patients.

Keywords: *Scutellaria baicalensis*; Baicalein; Baicalin; Wogonin; Oroxylin A; Anticancer; Review.

Introduction

Cancer is a serious threat to human well-beings and is a leading cause of death worldwide (DeSantis *et al.*, 2014). In the last half century since the introduction of chemotherapy for tumor treatment, natural products have become an important source of antineoplastic drugs and anticancer drug discovery (Ocana *et al.*, 2011). Although chemotherapy provides survival benefits to millions of patients, drug resistance and unpleasant side effects limit its application, emphasizing the urgent need for novel anticancer drugs (Ocana *et al.*, 2011). Many natural products have been suggested and developed from herbs used in folk medicine, including traditional Chinese medicine (TCM). Due to its long history of clinical practice and numerous historical case study reports, TCM is an advantageous resource for identifying bioactive anticancer natural compounds. In the past decades, *in vitro*, *in vivo* and clinical studies have demonstrated the potential of TCM for novel cancer interventions as well as for improving patients' quality of life, gastrointestinal distress, and cancer-related fatigue. The increasing research attention and progress in identifying natural products will provide a new chemical bank for anticancer drug discovery for future clinical applications.

Scutellaria baicalensis Georgi, also known as Chinese skullcap or Huangqin, is a perennial herb of the Lamiaceae family (Haniadka *et al.*, 2012; Tuan *et al.*, 2015) whose root is one of the 50 fundamental herbs used in TCM (Li *et al.*, 2016; Chen *et al.*, 2017). First documented in Shennong Bencao Jing circa 100 BC, *S. baicalensis* had frequently been cited in many other compilations. In Chinese herbology, it exhibits effects of clearing heat, drying dampness, purging fire, and removing toxins, and its root has been recognized in the treatment of jaundice, hepatitis, diarrhea, and infections of the respiratory and gastrointestinal tracts in China for more than 2000 years. In the past few decades, clinical applications of *S. baicalensis* have included diseases such as inflammation, hypertension, cardiovascular disease, and tumors (Chang *et al.*, 2016; Wang *et al.*, 2017). The effects of *S. baicalensis* are closely related to its antipyretic, anti-inflammatory, antimicrobial, antitumor, and other pharmacological effects.

More than 40 flavonoids have been separated and identified from *S. baicalensis*. The more intensively studied substrates include baicalein, baicalin, wogonin, wogonoside and oroxylin A. The traditional decoction of *S. baicalensis* extracted using hot water yields approximately 26% baicalin, 10% wogonin-glucuronide, 2% baicalein, and 0.2% wogonin, whereas commercial decoctions using alcohol–water extraction of the raw herb root yield more baicalin and more baicalein and wogonin. Much progress has been made in elucidating the mechanism of the anti-inflammatory and antipathogenic effects of *S. baicalensis*

in the past five years. With respect to cancer treatment, recent studies have shown that *S. baicalensis* inhibits tumor growth by targeting apoptotic pathways, the MAPK pathway, the PI3K-Akt-mTOR signaling pathway, and tumor-associated macrophages (TAMs) (Tan *et al.*, 2015).

In this review, we focus on the anticancer effects of *S. baicalensis* extract and its derived single compounds, including underlying molecular mechanisms, *in vivo* studies, and clinical applications. Electronic databases including MEDLINE (via PubMed), AMED, CINAHL, and China Journals Full Text Database (via CNKI) were extensively searched from inception through till March 2016. The terms and keywords for searching included *S. baicalensis*, Huangqin, *Scutellaria*, baicalin, baicalein, wogonin, oroxylin A, anticancer, neoplasm, and mechanism. No language restriction was imposed, but the most relevant studies were published in English and Chinese. The traditional use, pharmacology and anticancer effects of *S. baicalensis*, the underlying molecular mechanisms of its derived single compounds, and their clinical applications in combination with other herbal medications are discussed.

The Use of *Scutellaria baicalensis* as an Antineoplastic Agent in Decoctions

Scutellaria baicalensis is an important component in many traditional herbal prescriptions used in daily TCM practice. The most well-known prescriptions, such as PHY906, *Huanglian Jiedu* decoction (HLJDT), and Sho-Saiko-To, have received extensive attention in evidence-based studies. These classic decoctions are usually used to treat tumor-related symptoms, and some possess anticancer effects. In addition to classic decoctions, modern herbal mixtures have shown promising anticancer activity. For example, PC-SPES, which contains eight herbs, is widely accepted for hormone-naïve end-stage prostate cancer due to its significant efficacy in inhibiting cancer cell growth via cell-cycle arrest and reduction of androgen receptors and prostate-specific antigen (PSA) expression (Hsieh *et al.*, 2002). Modern biomedical advancements have opened up the use of herbal medication beyond traditional applications in recent years.

Pharmacokinetic Concerns Associated with *Scutellaria baicalensis* and its Active Components

An *in vivo* study of *S. baicalensis* and its single compounds revealed that predominantly conjugates of baicalin, wogonin and oroxylin A were found in plasma, whereas both aglycones and conjugates were found in all other types of tumor studied (Kimura and Sumiyoshi, 2013). The active ingredients in the *S. baicalensis* extract are absorbed in the gastrointestinal tract and reach effective levels in the blood (Zhang *et al.*, 2003). Baicalein inhibits tumor growth, but its hepatic toxicity should be taken into consideration (Wu *et al.*, 2013). However, due to the complexity of whole herb extraction and different extraction methods, herbal extraction may or may not fairly represent the actual contributions of individual components to biological activity *in vivo*.

Pharmacology of the Antineoplastic Properties of *Scutellaria baicalensis* and its Active Components

The aqueous extract of *S. baicalensis*, which is the most common clinically applied form in TCM, dose-dependently inhibits cell growth in hematopoietic malignancies and solid tumors (Table 1). In addition, *S. baicalensis* selectively inhibits malignant cell growth without significantly influencing non-tumorigenic cells (Zhang *et al.*, 2003), such as normal human lung fibroblasts, even at a high concentrations (Zhang *et al.*, 2003). These results reveal different sensitivities of various cancer cell lines to this herb and support the effective and broad-spectrum anticancer activity of *S. baicalensis*.

Induction of Cancer Cell Apoptosis

Apoptosis, or programmed cell death, involves degradation of caspases through the activation of either the intrinsic (mitochondrial) or extrinsic (death receptor) pathway (Kuo *et al.*, 2009). The ability to evade apoptosis is characteristic of cancer cells. The intrinsic apoptotic pathway involves a change in mitochondrial permeability by Bcl-2 related proteins and the release of cytochrome c (Cyto-C), which in turn activates the caspase cascade and leads to cell apoptosis (Kuo *et al.*, 2009). *Scutellaria baicalensis* and its derived single compounds time- and dose-dependently induce cleavage of mitochondrial-dependent caspases and upregulate p53, Bax, and Cyto-C, leading to loss of $\Delta\Psi m$ and reduced Bcl-2 levels in cell lines with different degrees of sensitivity (Kuo *et al.*, 2009) (Table 1). For example, among prostate cancer cell lines with different degrees of androgen sensitivity, androgen-independent DU145 cells were the most sensitive to baicalin treatment, whereas androgen-dependent LNCaP cells were most resistant. The extrinsic apoptotic pathway involves various forms of direct signal transduction, such as the Fas-Fas ligand and tumor necrosis factor receptor apoptosis-inducing ligand (TRAIL), which lead to the initiation of the caspase cascade. Wogonin specifically sensitizes cancer cells to TNF-induced cytotoxicity without showing significant toxicity to normal cells (Yang *et al.*, 2011; He *et al.*, 2012; Yang *et al.*, 2013a). The combination of wogonin and TRAIL exerts enhanced antitumor effects *in vivo* through down-regulation of anti-apoptotic proteins via reduced cFLIP levels and ROS-mediated induction of p53 and Puma (Yang *et al.*, 2013a). Further experiments are required to explore the effects of possible gene regulation and flavonoid-induced apoptosis to improve management of human cancers. Taken together, these results imply that *S. baicalensis* and its derived single compounds may amplify the intrinsic apoptosis pathway and regulate tumor progression. Details are shown in Fig. 1.

The p53-Mediated Apoptotic Pathway

p53 is a critical tumor suppressor gene that controls apoptosis and is either mutated or inactivated in at least 50% of tumors, and loss of wild-type p53 function leads to tumor development in humans (Lee *et al.*, 2008, 2012; Dai *et al.*, 2013). Based on the activation of p53 in a tumor being cytotoxic, various therapeutic rationales targeting p53 are currently

Table 1. Pharmacological Action of *Scutellaria baicalensis*

Cancer Type	Cell Line	Drug Choice	Pharmacological Action	Pathway Involved	Reference
Bladder	5637	Baicalein (25, 50, 75, 100 μM; 24, 48 H)	Growth inhibition; G_1 phase arrest, S phase arrest, antimigration and invasion	p-GSK3β (ser9), p-ERK (thr202/tyr204), p-p38 (thr180/tyr182)↑; p65NF-κB (nuclear), MMP-2, MMP-9, cyclin B1, cyclin D1, p-Akt (thr308) ↓	Wu *et al.* (2013)
		Scutellaria baicalensis ethanol (70%) extraction (baicalin-deprived-fraction) (50, 100 μg/ml; 48, 72 H)	Growth inhibition, S and G_2/M phase arrest, apoptosis	N/A	Wang *et al.* (2010a)
		Oroxylin A (100, 150, 200 μM; 48 H)	Inhibits glycolysis, glucose uptake, intracellular ATP content, lactate production, SIRT-3-mediated cyclophilin D deacetylation	ROS, cleaved-SIRT (mitochondria), HKII (cytosol)↑; HKII (mitochondria), cyclonphilin D↓	Wei *et al.* (2013)
		Wogonin (10, 20, 40 μM; 24 H)	Inhibits tumor angiogenesis, migration	VEGF secretion, HIF-1α, Cdk4, EGFR, surviving↓; PDH1, PHD2, PHD3, VHL↑	Song *et al.* (2013)
		Wogonin (50, 100, 150, 200 μM; 48 H)	Growth inhibition IC_{50} = 100 μM (48 H), apoptosis (mitochondrial), ROS generation	Cleavage PARP, Bax, p-ERK1/2, p-p38↑; procaspase-9, -8, Bcl-2, Bid↓	Yu *et al.* (2011)
	MCF-7/DOX	Wogonin (20, 40, 60 μM; 24 H)	Enhance cell sensitivity to doxorubicin IC_{50} of DOX=218.5 ± 0.01, 140.5 ± 0.03, 83.6 ± 0.02, respectively	Nrf2 (nucleus; total), HO-1, NQO1↓	Zhong *et al.* (2013)
	MDA-MB-231	Baicalein (2, 10, 50 μM; 12, 24 H)	Inhibits cell migration, adhesion, and invasion	MMP-2, -9, p-Akt, p-ERK, p-P38, p-JNK↓	Wang *et al.* (2010b)

Table 1. (*Continued*)

Cancer Type	Cell Line	Drug Choice	Pharmacological Action	Pathway Involved	Reference
		Oroxylin A (1, 4, 16 μM; 24 H)	Growth inhibition, inhibits adhesion, invasion and migration	TIMP-2, PKCδ (cytosol)↑; MMP-2, -9, p-ERK1/2, c-Fos, c-Jun; PKCδ (membrane)↓	Lu *et al.* (2012b)
		Oroxylin A (100, 150, 200 μM; 48 H)	Inhibits glycolysis, glucose uptake, intracellular ATP content, lactate production, SIRT-3-mediated cyclophili D deacetylation	ROS, cleaved-SIRT (mitochondria), HKII (cytosol)↑; HKII (mitochondria), cyclonphilin D↓	Wei *et al.* (2013)
		Wogonoside (100 μM; 1 H-15 H)	Growth inhibition, autophagy, formation of autolysosomes, accumulation of acidic vesicles, formation of autophagy vacuoles	LC3-I, p-motor, p-P70S6K, p-ERK1/2, p-P38↓; LC-3II, Beclin-1↑	Sun *et al.* (2013)
Cervix	HeLa	Oroxylin A (5, 20, 80 μM; 36 H)	Growth inhibition $IC_{50} = 19.4 \pm 0.7$ μM (48 H); apoptosis	Pro-caspase-3, -8, -9, PARP, Bcl-2↓	Li *et al.* (2009)
		Wogonin (20 μM ± TNF 20 ng/ml; 48 H)	Sensitize TNF-induced apoptosis, inhibits catalase activity, induce intracellular H_2O_2 accumulation	caspase-3, caspase-8, cleaved-PARP↑; p-NF-κB p65, c-FLIP↓	Yang *et al.* (2011)
	SW480	Baicalein (10, 20, 40, 80 μmol/L; 24 H) ± TRAIL (20 ng/mL)	Growth inhibition, apoptosis, sensitize TRAIL-induced apoptosis	pro-caspase-3, -8, -9, -10↓; cleaved-caspase-3, -8, -9, -10, cleaved-PARP, CHOP, DR5↑	Taniguchi *et al.* (2008)
Endometrium	HEC-1B	*Scutellaria baicalensis* aqueous extract (200 μg/mL; 96 H)	Growth inhibition $IC_{50} = 46.78$ μg/ml (120H); Antimigration and invasion; G_1 phase arrest, apoptosis	Caspase-3, p27, IkBα↑; Cyclin D1, Cyclin D3, NFκB p50, p-IκBα, MMP-9, CXCR4↓	Kavandi *et al.* (2013)

Table 1. (*Continued*)

Cancer Type	Cell Line	Drug Choice	Pharmacological Action	Pathway Involved	Reference
	Ishikawa		Growth inhibition $IC_{50} = 76.08\,\mu g/ml$ (120H); Antimigration and invasion, G_1 phase arrest, apoptosis		
Esophagus	EC-109	Baicalein (10, 20, 40 μM; 48 H)	Growth inhibition, inhibit colony formation, apoptosis,	Bcl-2, pro-caspase-3, -9, PARP, p-Akt, NF-κB, p-IκB-α, mTOR, p-mTOR↓; Bax, cleaved-caspase-3, -9, cleaved-PARP↑	Zhang *et al.* (2013a)
Gallbladder	SGC996	Baicalein (7.5, 15, 30 μmol/L; 24 H, 48 H)	Growth inhibition, apoptosis, anti-invasion, S phase arrest	Cyclin A↑; cyclin B1, cyclin D1, MMP-9, MMP-2↓	Liu *et al.* (2015)
	GBC-SD				
		Wogonin (1, 5, 10 μM; 24 H)	Growth inhibition, anti-invasion, apoptosis	MMP-2, MMP-9, p-ERK1/2, ERK1/2↓; Maspin↑	Dong *et al.* (2011)
Glial	U251	Wogonin (12.5, 25, 50, 100 μM; 24 H)	Growth inhibition, apoptosis, sub-G_1 arrest	Bax, Bak, GRP78, GRP94, calpain1, p-elF2α, Cleaved-casepase-3, cleaved-PARP↑; Bcl-2, Bcl-xL, pro-caspase-3, -9↓	Tsai *et al.* (2012)
	U87-MG	Wogonin (1, 5, 10, 25, 50 μM; 24 H)	Growth inhibition $IC_{50} = 50\,\mu M$ (24 H), apoptosis, G_1 phase arrest	Acetyl-CoA carboxylase, CDK4, p-mTOR$^{(Ser1682)}$, p-4EBP, survivin↓; p-AMPKα, p-ACC, p53, p21, p27, ROS, cleaved-PARP-1, caspase-3, -8, -9↑	Lee *et al.* (2012)
Head and neck	SCC-25	*Scutellaria baicalensis* aqueous extract (15, 150, 750 μg/ml; 72 H)	Growth inhibition $IC_{50} = 150\,\mu g/ml$ (72 H), G_0/G_1 phase arrest	PGE_2, COX-2↓	Zhang *et al.* (2003)

Table 1. (*Continued*)

Cancer Type	Cell Line	Drug Choice	Pharmacological Action	Pathway Involved	Reference
Leukemia	CCRF-CEM	Wogonin (10, 25, 50, 100 μM; 24 H)	Apoptosis	Mcl-1, CDK9, Bcl-2, p-Ser^2, p-Ser^5↓	Polier *et al.* (2011)
		Wogonin (25, 50, 100 μM; 24 H)	Growth inhibition, apoptosis (intrinsic)	ΔΨm↓; cleaved-caspase-3, -9, Ca^{2+} (cytosol), H_2O_2, Place↑	Baumann *et al.* (2008)
	HL-60	*Scutellaria baicalensis* aqueous extract (20–120 μM; 24 H)	Growth inhibition, apoptosis, reduce telomerase activity	Cleaved-caspase-3↑; Bcl-2, hTERT, hTP1, c-Myc↓	Huang *et al.* (2010)
		Oroxylin A (40 μM; 48 H)	Growth inhibition IC_{50} = 37.8 μM (48 H), G_1 phase arrest	C/EBPβ, p21, PPARγ↑; cyclin E, cyclin D1, CDK4, pRB, phosphorylated RXRα↓	Hui *et al.* (2014)
Lymphoma	Daudi	*Scutellaria baicalensis* aqueous extract (100, 200 μg/ml; 72 H)	Growth inhibition IC_{50} = 360 μg/ml (72 H), G_2/M phase arrest	p53, ETS1, Cdc25B, p63, EGFR, ERK1/2, XIAP, HIF-2α, Cdc25C↓; Cyclin E↑	Ye *et al.* (2009)
		Oroxylin A (12.5, 25, 50 μM; 36H)	Inhibit glucose metabolism under hypoxia	HIF-1α, LDHA, PDK1, HKII↓	Dai *et al.* (2016)
	J5	Baicalein (75 μM; 24 H, 48 H)	Growth inhibition, G_2/M phase arrest, apoptosis, DNA damage, promote ROS and Ca^{2+} production	cleaved-caspase-3, p53, p27, p21, shk2, Wee1, Bax↑; Cdc25c, cyclin B1, cdc2, cytochrome c (mitochondrial), Apaf-2, pro-caspase-9, AIF, Endo G, pro-caspase-3, Bcl-2, GPR78, GADD153, ΔΨm↓	Kuo *et al.* (2009)
	SK-Hep1	Baicalein (1, 5, 10 μM; 24 H)	G_0/G_1 cell cycle arrest, antimigration and invasion	MMP-2, MMP-9, uPA, p50/p65 translocation, pIKB-β, PKCα, p38↓	Chiu *et al.* (2011)
Lung	A549	*Scutellaria baicalensis* aqueous extract (10, 50, 100, 250, 500 μg/ml; 24 H)	Growth inhibition; G_1/S phase arrest, anti-invasion	Cyclin D1, CDK4, MMP-2↓	Park *et al.* (2011)

Table 1. (*Continued*)

Cancer Type	Cell Line	Drug Choice	Pharmacological Action	Pathway Involved	Reference
		Wogonin (14, 25, 35 μg/ml; 48 H)	Growth inhibition, apoptosis	ΔΨm, HDAC1, HDAC2, Mcl-1, c-Myc (protein), Skp2, XIAP, surviving, GSK3β↓; cleaved-PARP, c-Myc (mRNA)↑	Chen *et al.* (2013b)
	L929	Baicalin (50, 100 μM; 72 H)	Growth inhibition, apoptosis	Active caspase-3, SOD↑; HIF-1α, VEGF↓	Du *et al.* (2010)
Lymphoma	LLC CA46	Baicalin (40 μM; 24, 48, 72 H)	Growth inhibition, IC_{50} = 10 μM 48 H, induce apoptosis, intrinsic mitochondrial apoptotic pathway	Bax, cleaved-caspase-3, -9, cleaved-PARP↑; Bcl-2, PARP, p-Akt, NF-κB, pIκB, p-mTOR↓	Huang *et al.* (2012)
Marrow	RPMI-8826	*Scutellaria baicalensis* ethanol (70%) extract (1, 10, 50 μg/ml; 24 H) Baicalein (1, 10, 50 μg/ml; 24 H) Baicalin (1, 10, 50 μg/ml; 24 H) Wogonin (1, 10, 50 μg/ml; 24 H)	Growth inhibition, reduced side population cells	ABCG2↓	Lin *et al.* (2013)
		Wogonin (35.2, 176.0, 264.0, 352.0 μM; 24 H)	Growth inhibition IC_{50} = 143.2 μM (24 H), sub-G_1 arrest, apoptosis,	p-Akt(Ser473), Bcl-2↓; Bax↑	Zhang *et al.* (2013b)
Mucoepidermoid	Mc3	Baicalin (40 μg/ml; 72 H)	Growth inhibition, G_0/G_1, G_2/M arrest, apoptosis	ΔΨm↓	Xu *et al.* (2011)
Nasopharyngeal carcinoma	NPC-TW039	Wogonin (50 μM; 24 H)	Growth inhibition, apoptosis, autophagy	cleaved-PARP↑; p-mTOR, p-P70S6K, LC3 I/II cleavage, p-Akt↓	Chow *et al.* (2012)

Table 1. (*Continued*)

Cancer Type	Cell Line	Drug Choice	Pharmacological Action	Pathway Involved	Reference
Oral	SAS	*Scutellaria baicalensis* aqueous extract (100 μg/mL; 12, 24 H)	Growth inhibition, adhesion inhibition, inhibit proteolytic activities, apoptosis, G_1 phase arrest, anti-angiogenesis	$ERK_{1/2}$, cleaved-PARP, active-p38↑; CDK4, cyclin D1, Bcl-2↓	Sato *et al.* (2013)
Osteosarcoma	MG-63	Baicalein (50, 100 μmol/l; 24 H)	Growth inhibition, apoptosis, G_1 phase arrest, antimigration and invasion	Caspase-3, -8, -9, Bax, Bim↑; Bcl-2, cyclin D1, CDK4, MMP-2, MMP-9, CXCR4↓	Zhang *et al.* (2013c)
	U-2 OS	Wogonin (75 μM; 6, 12, 24, 48 H)	Growth inhibition, sub-G_1 arrest, apoptosis	ΔΨm, Bcl-2↓; intracellular Ca^{2+}, ROS, Bad, Bax, cleaved-caspase-3, -8, -9, AIF, Endo G, Fas/CD95, GADD153, GRP78, ATF-6α, Calpain 1, Calpain 2, caspase-4↑	Lin *et al.* (2011)
Ovarian	A2780/CP70	Baicalein (20, 40, 80 μM; 24 H)	Growth inhibition, LD_{50} = 24.3 μM (24 H)	HIF-1α, c-Myc, p-Akt↑; NF-κB, VEGF↓	Chen *et al.* (2013a)
		Baicalin (20, 40, 80 μM; 24 H)	Growth inhibition, LD_{50} = 55.2 μM (24 H)	HIF-1α↑; c-Myc, NF-κB, VEGF↓	
	OVCA420	*Scutellaria baicalensis* aqueous extract (200 μg/mL; 96H)	Growth inhibition IC_{50} = 45.73 μg/ml (120H); antimigration and invasion, G_1 phase arrest, apoptosis	Caspase-3, p27, IkBα↑; Cyclin D1, Cyclin D3, NFκB p50, MMP-9, CXCR4↓	Kavandi *et al.* (2015)
Pancreas	BxPC-3	Baicalein (5, 15, 50 μM; 24 H)	Growth inhibition, apoptosis	Cyto c (cytosolic), cleaved-caspase-3, -7, cleaved-PARP↑; Cyto c (mitochondria), Mcl-1, Bcl-2↓	Takahashi *et al.* (2011)

Table 1. (*Continued*)

Cancer Type	Cell Line	Drug Choice	Pharmacological Action	Pathway Involved	Reference
Prostate	PC-3	Baicalein (10, 20, 40, 80 μmol/L; 24 H) ± TRAIL (20ng/mL)	Growth inhibition, apoptosis, sensitize TRAIL-induced apoptosis, overcome TRAIL resistance	DR5↑	Taniguchi *et al.* (2008)
		Scutellaria baicalensis aqueous extract (0.15mg/ml; 72 H)	Growth inhibition $IC_{50} = 0.15$ mg/ml (72 H), G_0/G_1 phase arrest, PSA secretion inhibition	PGE_2, COX-2, cyclin D1↓	Ye *et al.* (2007)
		Baicalein (13 μmol/L; 24, 72 H)	Growth inhibition $IC_{50} = 13$ μmol/L (72 H), anti-androgenic, G_1 phase arrest	AR, PSA↓	Bonham *et al.* (2005)
		Wogonin (42 μmol/L; 24, 72 H)	Growth inhibition $IC_{50} = 42$ μmol/L (72 H), anti-androgenic, G_1 phase arrest	PSA↓	Bonham *et al.* (2005)
Sarcoma	S180	Wogonin	Growth inhibition $IC_{50} = (7.37 \pm 1.53) \times 10^{-5}$M (48 H)	N/A	Wang *et al.* (2006)
Skin	A431	Baicalein (10, 20, 40 μM; 12, 24, 48 H)	Growth inhibition, anti-invasion, antimigration	p-Ezrin, Ezrin↓	Wu *et al.* (2011)
Stomach	MGC-803	Wogonin (100 μM ± 5-FU 40μM; 48 H)	Growth inhibition, potentiates anticancer effect of low dose 5-FU, apoptosis	Bax, cleaved-PARP, NF-κB↑; Bcl-2, p-IκB↓	Zhao *et al.* (2010)

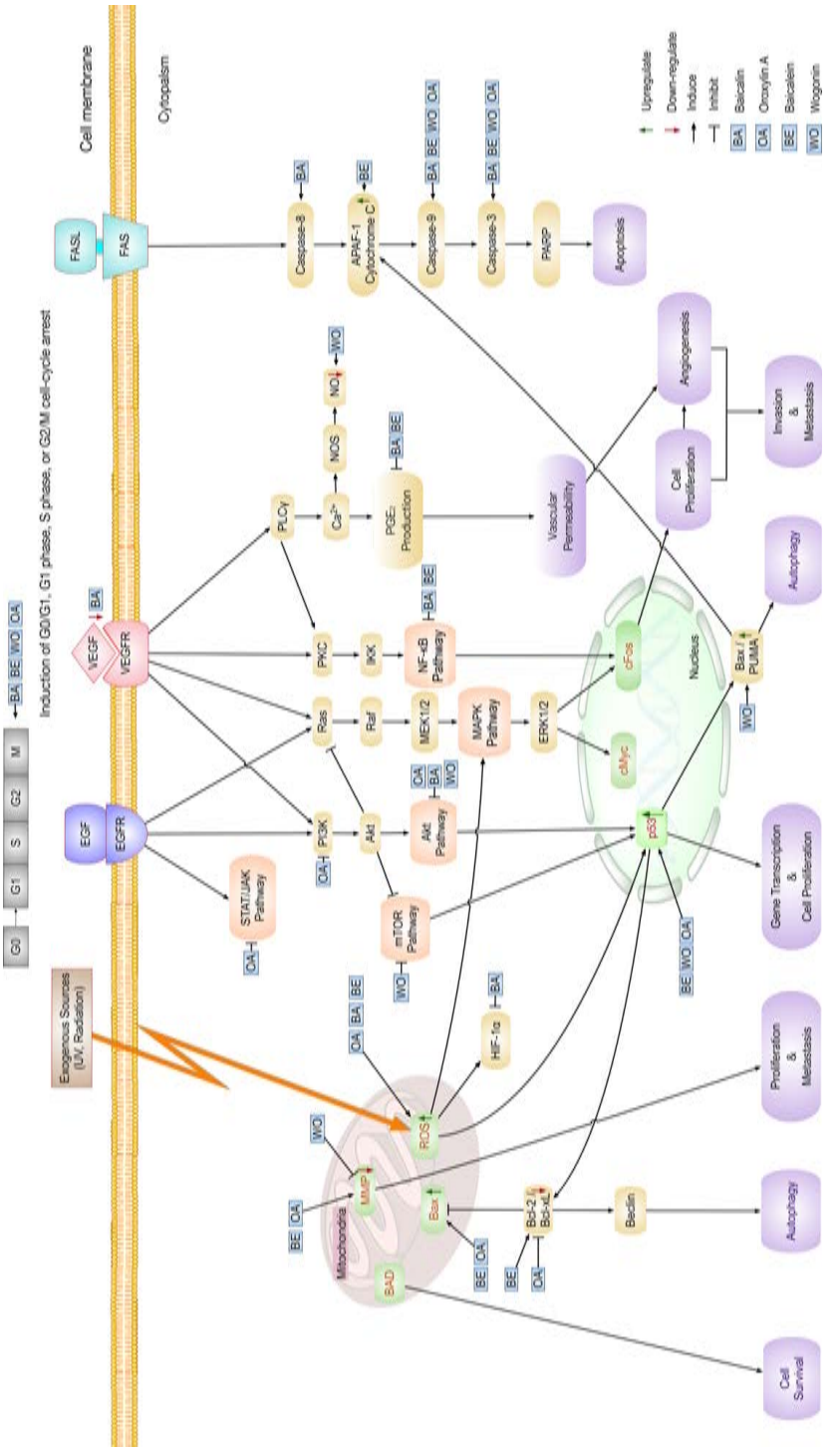

Figure 1. Schematic diagram illustrates the molecular mechanism that is responsible for the anticancer effect of *S. baicalensis* derived flavones.

under investigation (Lee *et al.*, 2008, 2012; Dai *et al.*, 2013). In human hepatoma J5 cells, baicalein promotes p53 levels and p53-independent $p21^{WAF1/CIP1}$ repression to induce apoptosis. In addition, in HepG2 cells, oroxylin A induces p53 protein expression and modulates glucose metabolism without inducing severe apoptosis (Dai *et al.*, 2013). Other studies have demonstrated that wogonin is associated with increased intracellular levels of $p21^{Cip-1}$, $p27^{Kip-1}$, p53, and PUMA, oligomerization of Bax, mitochondrial cyto C release, and activation of caspases (Lee *et al.*, 2008, 2012). The p21 protein inhibits cyclin-dependent kinase compounds, especially CDK4/6–cyclinD, thus arresting the cell-cycle in the G0/G1 phase (Lee *et al.*, 2008). Hence, wogonin regulates cancer apoptosis by modulating p53 signaling.

Inhibition of Cancer Cell Proliferation and Survival

The PI3k-Akt-mTOR Pathway

The PTEN/PI3K/AKT/mTOR pathway is essential for the survival and proliferation of human cells (Parajuli *et al.*, 2011). GSK-3 is a downstream signaling molecule of Akt and mediates the tumor-promoting activities of Akt (Parajuli *et al.*, 2011). Baicalin, baicalein, and wogonin, specifically downregulate anti-apoptotic and upregulate apoptotic components of the PI3K/Akt pathway via impairment of nuclear NF-κB and the anti-apoptotic protein Bcl-2 (Wu *et al.*, 2013). Oroxylin A suppresses the PI3K-PTEN-Akt-mTOR signaling pathway and Integrinβ-related pathways. These results suggest that the Akt/GSK-3/NF-κB signaling pathway might be a major target for the antitumor activity of *Scutellaria* flavonoids (Parajuli *et al.*, 2011). HLJDT induces apoptosis in myeloma cell lines via a mitochondria-mediated pathway and reduces IL-6 dependent or independent proliferation of myeloma cell lines (Ma *et al.*, 2005; Liu *et al.*, 2010). We recently determined that HLJDT activates AMPK, thereby leading to the inactivation of eEF2 (Ma *et al.*, 2005; Wang *et al.*, 2015b; Liu *et al.*, 2015), and hence inhibits cancer development and progression.

The Ras/Raf/MEK/ERK (MAPK) Pathway

The Ras/Raf/MEK/ERK (MAPK) pathway is frequently found to be dysregulated in cancer and may engage in cross-talk with autophagy (Hu *et al.*, 2015). The breast cancer cell line MCF-7 is highly sensitive to wogonin through the activation of the ERK/p38 MAPK signaling pathways (Wang *et al.*, 2010a; Yu and Kim, 2011). In MDA-MB-231 cells, wogonoside regulates MAPK signaling, induces autophagy and inhibits cell growth by inhibiting mTOR activity (Yu *et al.*, 2011). Moreover, baicalin dose-dependently induces autophagy and apoptosis in SMMC-7721 cells (Zou *et al.*, 2012) by upregulating Beclin 1, a key regulator of autophagy (Zou *et al.*, 2012). Thus, baicalin inhibits tumor progression through the MAPK signaling pathway and its cross-talk with autophagy.

Regulation of Oxidative Stress in Cancer Cells

Reactive oxygen species (ROS) serve as signaling molecules to activate AMPK, which inhibits cell proliferation and tumorigenesis. Wogonin induces apoptosis by generating ROS and modulating p53 levels through AMPK activation, and oroxylin A treatment produces similar effects (Lee *et al.*, 2012). In lung cancer cells, baicalin enhances SOD activity, inhibits HIF-1α, increases ROS, and reduces superoxide anion (Du *et al.*, 2010). These findings suggest that *S. baicalensis* augments exogenous sources, such as UV and radiation, induces ROS generation, and inhibits tumorigenesis.

Regulation of Inflammation in Cancer Cells

The relationship between inflammation and cancer has become a hot topic in cancer research. Current studies suggest many cytokines, growth factors and free radicals released during the process of inflammation can trigger cancer-related gene transcription and tumorigenesis (Li-Weber, 2009; Chandrashekar *et al.*, 2012; Yao *et al.*, 2014). COX-2 is overexpressed in inflammation and cancer and is associated with carcinogenesis, cancer invasion, metastasis, chemo- and radio-resistance and poor prognosis (Lu *et al.*, 2012a). *Scutellaria baicalensis* aqueous extract significantly decreases PGE2 dose-dependently by inhibiting COX-2 activity and suppresses tumor cell growth without arresting non-tumorigenic cell growth both *in vitro* and *in vivo* (Zhang *et al.*, 2003; Li-Weber, 2009; Kimura and Sumiyoshi, 2013). Wogonin and oroxylin A were recently shown to significantly inhibit LPS-induced iNOS and COX-2 gene expression and PGE2 production in leukemia, possibly through the NF-κB pathway. In all phases of tumorigenesis, inflammatory events alter the local microenvironment via the release of growth factors, chemokines, and cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor-necrosis factor alpha (TNFα) (Yang *et al.*, 2013b; Yao *et al.*, 2014). Oroxylin A prevents inflammation-related tumor growth through the down-regulation of inflammatory gene expression by inhibiting NF-κB signaling and significantly suppresses IL-6 secretion, possibly through IL-6/STAT3 signaling (Yang *et al.*, 2013b; Yao *et al.*, 2014). These results provide a molecular basis for the use of *S. baicalensis* to treat inflammatory disorders as well as cancers. However, the exact connection at the molecular level between inflammatory disorders and carcinogenesis remains unclear.

In Vitro and *In Vivo* Inhibition of Cancers by *Scutellaria baicalensis* and its Single Compounds

Suppression of Tumor Growth

Notably, the anticancer activities of *S. baicalensis*, whether the herb is used alone or in a decoction, have been reported in recent years both *in vitro* and *in vivo* (Li-Weber, 2009). As shown in Table 2, tumor models in tissues such as the liver and lungs have been studied *in vivo*. As reported by Ikemoto *et al.* in 2000, *S. baicalensis* aqueous extract can significantly inhibit bladder tumor growth in MBT-2-implanted mice (Ikemoto *et al.*, 2000).

Table 2. *In vivo* Studies

Drug	Animal	Implantation	Dosage	Effect	Reference
Scutellaria radix	Nude mice	Flank s.c. injection of MiaPaCa-2 cells	*Scutellaria baicalensis* dried 50% ethanol extract, mixed with diet, average of 1.49 g/kg/day for 13 weeks	Plasma contained conjugates, predominantly; Oroxylin A was the highest in the pancreas (63%), followed by the tumor (54%)	Lu *et al.* (2012a)
Baicalin	C57BL/6 mice	Right flank s.c. injection of LLC cells	Oral gavage, 100 mg/kg, once daily for 4 weeks	Tumor mass↓; median survival times↑; serum SOD activity↑; in tumor: MDA↑, HIF-1α, VEGF↓; peri-tumor lung: MDA↓, HIF-1α, VEGF↑	Du *et al.* (2010)
	C57BL/6 mice	Right flank s.c. injection of A549 cells	Oral gavage, 100 mg/kg, once daily for 4 weeks	Tumor mass↓; median survival times↑; serum SOD activity↑; in tumor: MDA↑, HIF-1α, VEGF↓; peri-tumor lung: MDA↓, HIF-1α, VEGF↑	Du *et al.* (2010)
	BALB/c nu/nu nude mice	Flanks or backs s.c. injection of SW620 cells	i.p. 50 mg/kg, 7 times a week for 28 days	Tumor mass↓; no obvious toxicity or reduction of body weight	Chen *et al.* (2012)
	BALB/c nude mice	Colon orthotropic implantation of tumor tissue block	Intragastric infusion 50, 100, 200 mg/kg, twice/day for 28 days	No significant differences in primary tumor weights and vascular densities of the primary tumors; no significant differences in tumor metastasis; survival rate↑	Yang *et al.* (2013a)
	C57BL/6 mice	Intravesical instillation of MB49	0.8 mg/mouse for 9 times	Slightly reduced tumor size; serum GOT↑	Wu *et al.* (2013)

Table 2. (*Continued*)

Drug	Animal	Implantation	Dosage	Effect	Reference
	C57BL/6 mice	Flank s.c. injection of SK-Hep1 cells	i.p. 5, 10, 20 mg/kg/day for five days	Significant dose- and time-dependent tumor growth inhibition	Chiu *et al.* (2011)
	C57BL/6 mice	s.c. implantation of LNCaP 35 tumor bits	Oral (in corn oil) 20 mg/kg/day, 5 of 7 days for 4 weeks	Tumor growth inhibition	Bonham *et al.* (2005)
	Swiss albino mice	B(a)P-induced lung cancer: B(a)P (50 mg/kg body weight) dissolved in corn oil orally twice a week for four successive weeks	Oral (in corn oil)12 mg/kg, once/week for 16 weeks	Protective effects on lung surface; tumor multiplicity↓; tumor load↓; serum CEA↓; serum CYFRA 21–1↓	Naveenkumar *et al.* (2012)
				Anticarcinogenesis; anti-inflammation; MMP-2, MMP-9, COX-2, NF-κB, TNF-α, IL-1β, iNOS↓	Chandrashekar *et al.* (2012)
Oroxylin A	C57BL/6 mice	Intraperitoneal injection of AOM to induce colitis-associated cancer	Oral gavage, 150, 100, 200 mg/kg/day, seven days prior to CAC induction for 14 weeks	Tumor development↓; tumor growth↓; IL-6↓	Yang *et al.* (2013b)
	C57BL/6 mice	Tail vein injection of B16-F10 melanoma cells	i.v. 20, 40, 80 mg/kg/every other day for 21 days	The number of metastatic modules↓; MMP-2, -9↓	Lu *et al.* (2012b)
	BALB/c nu/nu nude mice	Right axillary fossa s.c. injection of HeLa cells	i.v. 80 mg/kg/2days, 14days in total	Tumor weight↓	Li *et al.* (2009)

Table 2. (*Continued*)

Drug	Animal	Implantation	Dosage	Effect	Reference
	Mice	U937 xenografts	i.p. oroxylin A, i.p, (80 mg/kg, 3 times/week)	Tumor weight↓	Hui *et al.* (2014)
Wogonin	BALB/c nude mice	s.c. injection of HCT116 cells	i.v. 60 mg/kg/2days for 3 weeks	Tumor growth↓; HIF-1α, PI3K/Akt↓	Wang *et al.* (2014)
	H-2^{q}Rag$^{-/-}\gamma c^{-/-}$ immunodeficient mice	Right dorsal flank s.c. injection of CEM cells	i.p. 200 mg/kg(dissolved in DMSO and diluted in olive oil), once/day for 14 days	Tumor growth↓; $LD_{50} = 3.9$ g/kg	Baumann *et al.* (2008)
	C3H/He mice	s.c. transplantation of solid-type LM8	Oral gavage, 25 or 50 mg/kg body weight, 2 times/day for 35 days	Tumor growth↓; antilymphangiogenesis; HIF-1α, PCNA index, CD31, LYVE-1, LPS-induced COX-2, VEGFC-induced p-VEGFR-3↓	Kimura *et al.* (2013)

Serum samples taken from a single healthy person 6 h after oral administration of 1 g of *S. baicalensis* water extract in 180 mL of water showed the greatest antiproliferative effects on bladder cancer cell *in vitro* (Ikemoto *et al.*, 2000). One study demonstrated that baicalin, by inhibiting IL-6, TNF-α, and NF-κB expression, can effectively ameliorate anorexia and prevent skeletal muscle atrophy in a cancer-induced cachexia model (Aung *et al.*, 2003). *Scutellaria baicalensis* markedly decreases the expression of CXCR4 and MMP-9 in ovarian and endometrial cancer cells (Kavandi *et al.*, 2015). *Scutellaria baicalensis* crude ethanol extract and pure active compounds altered apoptosis in a population of A549, SK-LU-1, and SK-MES-1 lung cancer cells without affecting normal human lung fibroblasts (Gao *et al.*, 2011). In a mouse pancreatic cancer model, after administration of *S. baicalensis* extract in-feed for 13 weeks, oroxylin A was found highest in the pancreas (63%), followed by the tumor (54%), and plasma contained predominantly conjugates forms of flavones (Lu *et al.*, 2012a). Notably, heat-processed *S. baicalensis* extract possesses cytotoxicity against lung cancer cells, whereas the whole *S. baicalensis* extract does not significantly inhibit proliferation (Wang *et al.*, 2013a).

Inhibition of Tumor Angiogenesis and Metastasis

Angiogenesis plays an important role in tumor growth and metastasis and is tightly regulated by many cytokines, such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs). Baicalin and wogonin reduce the expression and activity of VEGF, suppress angiogenesis and have promising impacts on cancer cell viability and proliferation both *in vitro* and *in vivo* (Lu *et al.*, 2012b; Song *et al.*, 2013; Chen *et al.*, 2015). KDR/Flk-1 may be the target responsible for the antiangiogenic activity of oroxylin A (Gao *et al.*, 2010). Furthermore, oroxylin A reduces the activity and expression levels of MMP-2 and MMP-9 (Gao *et al.*, 2010; Dai *et al.*, 2013). In addition, our recent study showed that the Gegen Qinlian decoction comprising of four herbs: Radix *Puerariae*, *S. baicalensis*, *Rhizoma Coptidis*, and Radix *Glycyrrhizae*, suppresses neo-angiogenesis of human renal carcinoma via the inhibition of MMP-2. In particular, *S. baicalensis* is the major active component and down-regulates MMP-2 activity (Wang *et al.*, 2015a). In A549 lung cancer cells, *S. baicalensis* aqueous extract has a strong protective effect against MMP-2-mediated metastasis and cell proliferation through down-regulation of cyclin D1 (Park *et al.*, 2011). In addition, baicalein inhibits gallbladder cancer cell growth and metastasis via the down-regulation of zinc finger X-linked protein (Liu *et al.*, 2015). Together, these results suggest that *S. baicalensis* and its derived single compounds are potential antimetastasis therapeutic drugs.

Regulation of the Tumor Microenvironment

The plasticity of tumor-associated macrophages (TAMs) is influential in cancer development, and repolarization of TAMs toward the M1 phenotype characterizes an immunocompetent microenvironment favoring tumor regression (Tan *et al.*, 2015). Many studies have revealed that carcinogenesis involves a process of macrophage infiltration into the

tumor microenvironment, followed by macrophage polarization by tumor-favoring factors (Tan *et al.*, 2015). Our previous studies have revealed that baicalin suppresses HCC growth both *in vitro* and *in vivo* by inducing TAMs and M2-like macrophage repolarization to M1-like macrophages. Mechanistically, baicalin initiates autophagic degradation of TRAF2 in TAMs and activates the RelB/p52 pathway, thereby inducing the polarization of M1-like macrophages (Tan *et al.*, 2015). Consequently, baicalin may inhibit HCC development (Tan *et al.*, 2015).

Scutellaria baicalensis and its Decoction in Combination with Cancer Chemotherapy

Potential Synergistic Interactions for Side-Effect Reduction

Despite significant progress in the field of cancer treatment in recent years, chemotherapy- and radiation-induced side effects such as nausea and vomiting remain major problems affecting approximately 70% to 80% of patients. The anti-oxidant properties of *S. baicalensis* may be responsible, at least in part, for attenuating the cisplatin-induced nausea and vomiting, possibly by binding to 5-HT_{1A} receptors. *Scutellaria baicalensis* pretreatment decreased cisplatin-induced kaolin intake in the rat model of simulated nausea by inducing serotonin (5-hydroxytyptamine, 5-HT) release. In addition, the combination of *S. baicalensis* and Qing-Shu-Yi-Qi-Tang, which has high anti-oxidant activity, improved cachectic symptoms and stimulated antitumor immunity in a rat HCC model receiving 5-fluorouracil (5-FU) chemotherapy (Wang *et al.*, 2012). These results are consistent with the TCM understanding of this herb.

Experimental evidence also suggests that simultaneous administration of paclitaxel and oroxylin A or wogonin has synergistic antiproliferative effects and induces apoptosis MCF-7 human breast cancer cells (Zhong *et al.*, 2013). Baicalein protects against doxorubicin-induced cardiotoxicity by reducing mitochondrial oxidant injury and JNK activation, indicating that baicalein may be a useful adjunctive therapy for doxorubicin-based chemotherapy with preexisting cardiomyopathy or heart failure (Chang *et al.*, 2011). In addition, baicalein alleviated cancer-induced bone pain via inhibition of the expression of IL-6 and TNF-α and activation of p-p38 and p-JNK MAPK signals in the spinal cord in a rat mammary gland carcinoma model (Hu *et al.*, 2015). TCM has been recognized as a new source of anticancer drugs or chemotherapy adjuvants, and *S. baicalensis* is promising for relieving chemotherapy side effects.

Potential Actions in Drug-Resistant Reversal and Chemotherapy Sensitizing

Increases in the therapeutic index and chemotherapeutic drug efficacy in chemo-resistant cell lines have also drawn research attention. Baicalein significantly enhances the oral bioavailability of tamoxifen, which might be due to inhibition of the CYP3A-mediated metabolism of tamoxifen (Li *et al.*, 2011). Baicalein also increases the sensitivity of gastric cancer AGS cells to 5-FU treatment under hypoxia and suppresses hypoxia-enhanced glycolytic flux via regulation of the PTEN/AKT/HIF-1α signaling pathway. Wogonin may

be a potential adjuvant therapy for drug-resistant human non-small lung cancer (NSCLC) based on the inhibition of the over-expression of dihydrodiol dehydrogenase (DDH), which is an indicator of poor prognosis and chemo-resistance in NSCLC. Wogonin reverses drug resistance in MCF-7/DOX cells via the Nrf2-mediated cellular protection response. At weakly toxic concentration, oroxylin A dramatically increases paclitaxel-induced apoptosis and reverses chemo-resistance by inhibiting Integrinβ1 and its related pathways in the CAM-DR model of HCC (Zhu *et al.*, 2012). Wogonin shows antiproliferative activity in carboplatin- and paclitaxel-resistant ovarian cancer cells and sensitizes the cells to chemotherapy (Chen *et al.*, 2011). Similarly, wogonin possesses synergistic effects with either paclitaxel or 5-FU in gastric cancer (Zhao *et al.*, 2010b; Wang *et al.*, 2013b). Wogonin enhances etoposide-induced apoptosis in cancer via the inhibition of P-glycoprotein, overcomes IL-6-induced adriamycin resistance in human non-small lung cancer cells, and enhances the cytotoxicity of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (He *et al.*, 2012; Yang *et al.*, 2013a). Similarly, in leukemia HL-60 and Jurkat cells, wogonin accelerates etoposide-induced apoptotic cell death and may be a potential agent for reducing adverse reaction to etoposide (Lee *et al.*, 2007, 2009). 5-FU combined with oroxylin A exhibits stronger apoptotic induction in HepG2 cells than either of the single drugs by modulating the metabolic enzymes of 5-FU and apoptosis-related proteins (Zhao *et al.*, 2010a). In the colon cancer HT-29 cell line, oroxylin A and 5-FU synergistically inhibit proliferation *in vitro* and *in vivo* by modulating the COX-2 signaling pathway (Ha *et al.*, 2012). Wogonin also sensitizes cisplatin-induced apoptosis in both A549 cells and HeLa cells through caspase- and ROS-dependent mechanisms and induces H_2O_2 accumulation (He *et al.*, 2012).

Scutellaria baicalensis containing PHY906 enhances the therapeutic effects of anticancer agents as an adjuvant to chemotherapy, as examined with promising results in clinical studies for colorectal, liver, and pancreatic cancers, without altering the pharmacokinetics of the chemotherapeutic agents (Liu and Cheng, 2012). PHY906 increases the therapeutic indexes of many drug combinations, including 5-FU/LV, CPT-11/5-FU/LV, oxaliplatin/5-FU/LV, and gemcitabine/oxaliplatin (Liu and Cheng, 2012). Moreover, PHY906 can also potentiate the anticancer effect of sorafenib, and its major ingredient, *S. baicalensis*, is one of the main active components via targeting the inflammatory tumor microenvironment in HepG2 xenograft models. To date, the PHY906 clinical program has launched five trials in three different types of cancers, including advanced colorectal cancer, advanced hepatocellular carcinoma and advanced pancreatic cancer, in both the US and Taiwan (Liu and Cheng, 2012).

Discussion

Molecular Understanding of the Anticancer Effect of Scutellaria baicalensis and its Active Components

TCM, which is characterized by multi-ingredient, multi-target therapies with low adverse effects, is being increasingly recognized as a new source of anticancer drug discovery.

Although the recognition of the pathological nature of cancer has not been as clear in the thousand years of clinical practice of TCM physicians as in Western medicine, tumors were frequently described as heat, dampness or toxin-induced lumps in the body with corresponding treatment approaches that included clearing heat, drying dampness, and removing toxins (Tang *et al.*, 2009). Clues and implications of *S. baicalensis* in the treatment of diseases with symptoms similar to tumors, such as diarrhea, vomiting, fever, and bleeding, can be derived from the TCM view of this herb (Tang *et al.*, 2009). These clinical applications can easily be linked to the modern concept of anti-infection or anti-inflammation, as specified in the Chinese Pharmacopoeia, which has led to the development of *S. baicalensis* as a natural antibiotic, anti-inflammatory and anticancer agent. Accumulating evidence demonstrates that *S. baicalensis* extracts and their major flavonoids possess anticancer, antiproliferative, antimetastatic, and anti-angiogenic effects against multiple cancer cell lines both *in vitro* and *in vivo*.

Notably, *S. baicalensis* exerts broad effects on cell signaling networks and targets many components in the complex and dysregulated signaling network. Pathway Array analysis and Genes2Networks analysis may play important roles in identifying useful targets for the development of effective cancer therapies. Different components of *S. baicalensis*, its major flavonoids and other compounds found in trace amounts might act on different targets in this complex signaling network, resulting in a synergistic antiproliferative effect (Tuan *et al.*, 2015; Kavandi *et al.*, 2015). Future studies of the effects of individual components of *S. baicalensis* on the complex signaling network are warranted.

Scutellaria baicalensis Components as Adjuvants for Cancer Chemotherapy

Although studies have demonstrated the synergistic effect of *S. baicalensis*-derived flavones and chemotherapeutic drugs both *in vitro* and *in vivo*, the potential hepatotoxicity of these flavones and the potential alteration of pharmacodynamics and pharmacokinetics of chemotherapeutic drugs should be taken into careful consideration. For example, baicalein induces hepatic toxicity by increasing aspartate aminotransferase (AST) values, and the isolated compounds may exert effects in non-malignant cells, such as healthy immune cells (Wu *et al.*, 2013). Future clinical studies are warranted for the development of novel anticancer therapeutics and the validation of the clinical application of *S. baicalensis* and its derived flavones.

Herbal decoctions are widely used in TCM and contain various herbs rather than specific components. In addition, quality management of pesticide residues is suboptimal. For example, PHY906 has better effects than traditional Huangqin Tang used alone, indicating a need to consider potential interactions between herbs that may occur after heat processing (Liu and Cheng, 2012). It would be helpful to compare the bioactivity of different components of *S. baicalensis* extracts, for example, between baicalein and wogonin, under the same experimental conditions. Thus, there is a need to understand the underlying mechanisms and precise analyses of active ingredients within the extracts. Although *S. baicalensis* has long been used in daily TCM practice and in dietary supplements, clinical trials, especially well-designed randomized controlled trials are needed

to confirm its clinical effects and potential as a drug candidate for cancer treatment and chemoprevention. Identifying the major active anticancer components of herbal decoctions is an urgent need. Issues about the oral administration of herbal remedies should be considered because the bioactivity of a given compound could be altered by the intestinal microbiota. Thus, further investigation on the effects of the gut microbiome on compound metabolites is needed to understand the pharmacological actions of *S. baicalensis*.

Clinical Trials

In recent years, herbal therapies have drawn increasing attention as alternative cancer treatments, but contamination and quality control remain important concerns for the utilization of herbal decoctions. From 1997–2002, PC-SPES, a *S. baicalensis* containing herbal formula, was studied in phases I and II clinical trials in patients with progressive prostate cancer and androgen-independent prostate cancer, respectively (Small *et al.*, 2000). This eight-herb combination with antimutagenic and anti-oxidant activities contains multiple chemical components that inhibit DNA topoisomerase and protein kinase. However, it cannot be determined whether the activity of PC-SPES *in vitro* or *in vivo* is due to a single component because the ethanoic extracts of complex herbal mixtures may not adequately reflect the actual pharmacological contributions of individual components *in vivo* (Shabbir *et al.*, 2008). Although PC-SPES usage was well tolerated and early-phase clinical trials showed therapeutic benefits, the analyzed compounds were poorly standardized and regulated, with variable quantities of synthetic drugs in the PC-SPES capsules (Small *et al.*, 2000). Therefore, the product was later withdrawn from the market in 2002 due to concerns about quality control. In 2008, a phase I clinical trial was conducted using PC-Spes2, which was prepared under strict and independent quality control, in patients with hormone-refractory prostate cancer and demonstrated activity and safety. PHY906, also known as KD-18, enhances the therapeutic effects of anticancer agents as an adjuvant to chemotherapy and has been examined in phases I and II clinical studies for colorectal, liver, and pancreatic cancers. Promising results were obtained, with no alteration of the pharmacokinetics of the chemotherapeutic agents used. To date, the PHY906 clinical program has launched more than five trials in three different types of cancer including advanced colorectal cancer, advanced hepatocellular carcinoma and advanced pancreatic cancer in both the US and Taiwan.

Challenges Ahead

Studies have reported that specific glycyrrhetinic acid (GA) binding sites are present on the cellular membranes of rat hepatocytes *in vitro* (Yuan *et al.*, 2013). Other studies have indicated that GA-modified nano-carriers have higher affinities for human hepatic or hepatic carcinoma cells, indicating that GA modification and GA-modified wogonin liposomes are good candidates for the targeting of hepatic carcinoma cells (Tian *et al.*, 2014). GA-modified wogonin liposomes can actively and specifically target the liver, resulting in decreased tumor weight as well as improving bio-distribution, tumor-specific

accumulation and therapeutic efficacy. These effects are a result of the increased receptor-mediated uptake of liposomes in liver cells, which produces better anticancer effects *in vivo* compared with passively targeted liposomes (Tian *et al.*, 2014). These results suggest that structure modification may allow more specific targeting of tumors and, consequently, enhanced therapeutic outcomes, and this mechanism warrants further study. There is also a lack of new methods, such as genomics and proteomics approaches, computer-aided molecular design and analog prediction of cell response, to study the effects of *S. baicalensis* flavonoids. The development of *S. baicalensis* as a more effective anticancer agent remains challenging.

The distribution of *S. baicalensis* derived wogonin and baicalin to tumors after oral administration needs to be further studied. Baicalin is rapidly converted to its aglycone, baicalein. Wogonin is observed to wogonin-7-D-glucuronide through glucuronide conjugation in the liver, and consequently large amounts of wogonin-7-D-glucuronide and a small amount of wogonin are observed in the blood stream. Therefore, it seems likely that the bioavailability of wogonin alone may be low after oral administration. While the current use of polyherbal mixtures or decoctions in hospitals is increasing in China (Carmady and Smith, 2011), debate and skepticism concerning the lack of scientific evidence on their efficacy and safety remain in the Western scientific world. Furthermore, extensive analyses of the chemical constituents of *S. baicalensis* and their pharmacokinetic and pharmacodynamics properties are needed. Further studies are required to clarify the antitumor and antimetastatic actions of the metabolites of *S. baicalensis*-derived flavones.

Summary

Given the increasing prevalence of cancer worldwide, there is an urgent need to improve the therapeutic activity and selectivity of anticancer agents. This review demonstrates that (1) the cell viability and proliferation of various cancer cell lines are sensitive to treatment with *S. baicalensis*-derived flavones; (2) the decreased proliferation is associated with the induction of apoptosis and autophagy; (3) inflammatory COX-II expression and PGE2 production are decreased with *S. baicalensis* treatment; (4) *S. baicalensis* treatment is associated with multiple pathways, including the Akt, MAPK, mTOR, and NF-κB pathways; (5) *S. baicalensis* and its derived flavones possess anti-angiogenic and antimetastatic properties; and (6) the expression of oncogenes, including cMyc, NF-κB, and HIF-α, is inhibited, whereas tumor suppressor genes such as p53 are induced by *S. baicalensis* and its derived flavones. It is important to note that *S. baicalensis* exerts broad effects on cell signaling networks, specifically acting on the key proteins, and may target many components of the complex and dysregulated cancer signaling network. Pathway Array and Genes2Networks analyses may play an important role in identifying useful targets for the development of effective cancer therapies. It is possible that different components of *S. baicalensis*, its major flavonoids and other compounds found in trace amounts act on the different targets in this complex signaling network, resulting in synergistic antiproliferative effects. Future study of the effects of individual components of *S. baicalensis* on the complex signaling network is warranted.

In the process of identifying novel therapeutic targets, we deepen our understanding of malignant biological behavior and the molecular mechanisms of tumor growth. These advances have not only contributed to further improving the clinical trials of drugs, but have also spawned a number of landmark discoveries. Novel therapeutic agents targeting specific signaling pathways have promising anticancer effects, but adverse effects such as gastrointestinal burden and toxicities require close monitoring to avoid termination of treatment and failure to effectively control tumor proliferation. Agents targeting multiple signaling pathways may not only possess more potent anticancer effects, but also inevitably carry greater adverse effects. Investigation into the underlying pathophysiological mechanisms of these adverse effects is also important. Achievements in combination therapy have been made in recent years, and we believe that new molecular therapies will also show very encouraging results. However, in addition to obtaining these benefits, further research is inevitably needed to resolve difficulties, such as potential drug combinations, order of administration, treatment goals, assessment of long-term effects, and the development of molecular-targeted drugs. In an adjuvant treatment program, the goal of treatment for metastatic disease is to improve quality of life and prolong survival time for patients.

In conclusion, *S. baicalensis* extracts and the major flavonoids of *S. baicalensis* have anticancer effects in multiple cancer cell lines both *in vitro* and *in vivo*. The exact mechanisms are not yet fully understood, and further investigation is needed not only to further elucidate the mechanism of action, but also to discover novel targets for cancer therapies and promising cancer therapeutic drugs. *Scutellaria baicalensis* is promising for anticancer therapy and should be developed into novel treatments for clinical trials.

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