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## Anticancer properties of baicalein: a review

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### Abstract

The constituents of many traditional Chinese herbal remedies are currently at the forefront of modern cancer research. Baicalein, a bioactive flavone widely used in nutraceuticals and pharmaceuticals, has shown great potential in the treatment and prevention of cancer without causing severe side effects. Baicalein induces cancer cell apoptosis and cause cell cycle arrest. It shows inhibitory effects on angiogenesis, metastasis and inflammation, all of which are necessary for the promotion and progression of cancer. This review presents an overview of the anti-cancer effects and mechanisms of baicalein. In addition, the bioavailability of baicalein and approaches to improve it are summarized. Treatments of baicalein in combination with other anti-cancer agents are also mentioned.

### Keywords

Baicalein; Apoptosis; Angiogenesis; Metastasis; Bioavailability

### Introduction

Herbal plants have long been utilized to prevent and treat diseases. Nowadays, many people still rely on herbal nutraceuticals for their primary health care. More than 50% of the drugs currently in clinical application are of natural product origin (Sithranga Boopathy and Kathiresan 2010). *Scutellaria baicalensis* Georgi is a species of flowering plant in the Lamiaceae family. The dried root of *Scutellaria baicalensis* Georgi is widely and historically used in Traditional Chinese Medicine (Li-Weber 2009). Flavonoids, a class of secondary metabolites commonly found in plants, are one of the most important bioactive components in the root of *Scutellaria baicalensis* Georgi. Epidemiological studies have found a significant correlation between the dietary intake of flavonoids and a reduced risk of cancer, inflammation and heart disease (Li-Weber 2009). Over 50 flavonoids have been isolated from the root of *Scutellaria baicalensis* Georgi, including baicalein, baicalin, wogonin, norwogonin, oroxylin A and  $\beta$ -sitosterol. Baicalein (5,6,7-trihydroxyflavone, Fig. 1), one of four major flavonoids existed in the root of *Scutellaria baicalensis* Georgi (Kim et al. 2013), is an important active constituent responsible for the physiological activity of *Scutellaria baicalensis* Georgi (Mehendale et al. 2007). Previous researches have shown that baicalein

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exerts numerous biological activities, such as anti-cancer, anti-inflammation, anti-cardiovascular diseases, anti-bacterial or viral infection, and anti-neurodegenerative diseases. Studies have demonstrated that baicalein suppresses cancer cell proliferation, induces apoptosis and cell cycle arrest in human breast, prostate, hepatocellular, myeloma and T24 bladder cancer cells (Chen et al. 2014b; Li et al. 2013a). Baicalein inhibits migration and invasion of human breast cancer cells, hepatoma cells and skin cancer cells (Chiu et al. 2011; Wang et al. 2010b; Wu et al. 2011). Like most flavonoids, baicalein is hydroxylated at the C-5 position, which is vital for its extensive pharmacological effects (Moon et al. 2006). This review focuses on various anti-cancer effects and mechanisms of baicalein, as well as the future use of baicalein in modern medicine.

## Extraction

To isolate baicalein from over 781 compounds contained in extracts of *Scutellaria baicalensis* Georgi, various extraction methods have been implemented, such as high-speed counter-current chromatography, dynamic microwave-assisted extraction, and on-line continuous flow ultrasonic extraction. There is much debate as to which extraction method is most efficient for medical use (Li et al. 2011b). Traditional extraction method and supercritical fluid extraction (SFE) method are two of the widely-used methods in extracting baicalein.

A traditional procedure used for baicalein extraction is to ground the dried roots of *Scutellaria baicalensis* Georgi to fine powder, extract with 70% ethanol for two hours, and collect the filtrate. Repeat the extraction and filtration steps a few more times (Lin et al. 2013). The filtrate was then vacuum lyophilized and examined using high performance liquid chromatography (HPLC).

SFE is another commonly used extraction method for baicalein because of its quick yields and cost efficiency. Methanol and ethanol are generally used as the solvent in SFE as they are low-toxic and yield the most efficient results (Li et al. 2011b). The solvent and ground *Scutellaria baicalensis* Georgi is actively mixed for approximately 24 hours at room temperature followed by repeated extraction and removal of the solvent. Then, the extracts are recrystallized. The purity of the extracted flavonoids are tested using the HPLC method (Chen and Chen 2013).

## Effect on apoptosis

Apoptosis is an ordered and orchestrated cellular process that occurs in physiological and pathological conditions (Wong 2011). The morphological changes of apoptosis include blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. Unlike necrosis, apoptosis produces apoptotic bodies that phagocytic cells are able to engulf and quickly remove before the contents of the cell can spill out onto surrounding cells and cause damage. Resisting apoptosis is a key process in cancer development and progression. Cancer cells that avoid apoptosis continue to proliferate uncontrollably, which results in an increased tumor mass. Therefore, apoptosis is a popular target of many treatment strategies (Kasibhatla and Tseng 2003). Apoptosis is

predominantly initiated through mitochondria-mediated (intrinsic) and receptor-mediated (extrinsic) pathways (Li-Weber 2009). The intrinsic apoptotic pathway is characterized by permeabilisation of the mitochondria, release of Cytochrome c into the cytoplasm and activation of the Caspase cascade through Caspase-9. The extrinsic apoptotic pathway is activated by the binding of membrane death receptors with their ligands, such as the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and CD95L, leading to initiation of the Caspase cascade through Caspase-8. In some cases, extrinsic and intrinsic pathways can crosstalk and be linked together.

Baicalein has shown potent apoptosis-inducing properties in various types of cancer. It initiates apoptosis through both the mitochondria-mediated (intrinsic) and receptor-mediated (extrinsic) pathways (Li-Weber 2009). The mechanisms are diverse.

One of the mechanisms is that baicalein directly modulates the components of intrinsic and extrinsic apoptotic pathway. Bcl-2 family comprises a group of structurally related proteins that play a fundamental role in the intrinsic apoptotic pathway. Bcl-2 family protein can be either pro-apoptotic (for example, Bax, Bad, Bak) or anti-apoptotic (for example, Bcl-2, Bcl-xL, Mcl-1, and Bcl-w). The ratio of pro- to anti-apoptotic Bcl-2 family proteins determines cell fate. In SCC-4 human tongue cancer cells, baicalein successfully induced apoptosis by elevating levels of pro-apoptotic agents (Bax) and lowering the level of anti-apoptotic protein Bcl-2 (Lin et al. 2007). The increasing ratio of pro- to anti-apoptotic Bcl-2 family proteins caused release of Cytochrome c and other apoptogenic proteins from the mitochondrial membrane to cytosol, lead to activation of Caspase cascade, and finally initiated apoptosis in the target cells (Zhang et al. 2013b). Death receptor 5 (DR5) and other TRAIL receptors, components of the extrinsic apoptotic pathway, were significantly increased at protein and mRNA levels by baicalein in cancer cells in comparison with normal cells, showing great promise in serving as a therapeutic agent (Taniguchi et al. 2008).

Another mechanism is that baicalein regulates the apoptotic pathway via radical oxygen species (ROS). ROS play an important role in a variety of normal biochemical functions and abnormal pathological processes (Pelicano et al. 2004). When overexpressed, ROS can create oxidative stress and eventually cause mitochondrial dysfunction (Lee et al. 2011). Due to this, ROS production is a mechanism shared by all non-surgical therapeutic approaches for cancer, including chemotherapy, radiotherapy and photodynamic therapy (Wang and Yi 2008). Like other flavonoids, baicalein can be either anti-oxidant or pro-oxidant, depending on its metabolism and concentration. It is reported that baicalein generated ROS, subsequently caused endoplasmic reticulum (ER) stress, activated Ca<sup>2+</sup>-dependent mitochondrial death pathway, finally triggered apoptosis (Lee et al. 2008; Lin et al. 2007). Baicalein also enhanced apoptosis via ROS-mediated Bcl-2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) expression (Ye et al. 2015). Besides, baicalein-induced ROS generation up-regulated DR5 expression and then activated the extrinsic apoptotic pathway in human prostate cancer cells (Taniguchi et al. 2008).

Affecting upstream signal pathways of the apoptotic pathways is also an important mechanism. Mitogen-activated protein kinases (MAPKs) are a highly conserved family of serine/threonine protein kinases, mainly including the extracellular signal-regulated kinase 1

and 2 (ERK 1/2), the c-Jun N-terminal kinases 1-3 (JNK 1-3)/ stress activated protein kinases and p38 isoforms. MAPK pathways involve in fundamental cellular processes such as proliferation, apoptosis, and survival. It is activated when an extracellular messenger or ligand binds to a membrane-bound receptor, which in turn activates RAS-GTP and triggers a phosphorylation cascade. The MAPK pathway finally reaches an activator protein in the nucleus which can generate the expression of growth factors, cyclins, and/or, cytokines (Gao et al. 2010). The p38 MAPK pathway is often targeted by anti-cancer drugs as it induces and mediates apoptosis through the activation of different Caspases (Moon et al. 2006). Baicalein enhanced phosphorylation of p38 MAPK, diminished protein level of survivin, a member of the inhibitor of apoptosis (IAP) gene family, in bladder, lung, and breast cancer cells (Moon et al. 2006). Baicalein, together with baicalin, increased apoptosis by activating Caspases-3 and Caspase-9, down-regulating Bcl-2 and up-regulating Bax or p53 through the ERK/p38 MAPK pathway (Zhou et al. 2009).

p53 is a tumour suppressor protein that regulates the expression of a wide variety of genes involved in apoptosis, growth inhibition and cell cycle arrest. Baicalein induced apoptosis through up-regulating p53 in A549, SK-LU-1 and SK-MES-1 human lung cancer cell lines. In HT-29 colon cancer cells, baicalein triggered apoptosis via Akt activation in a p53-dependent manner (Kim et al. 2012).

The phosphoinositide 3-kinase(PI3K)/Akt pathway is an intracellular signaling pathway which plays a critical regulatory role in diverse cellular processes, such as angiogenesis, metabolism, growth, proliferation, and survival (Hemmings and Restuccia 2012). Baicalein can slow down cancer development by inhibiting the function of four different isoforms of PI3K (Kong et al. 2011). Once treated with baicalein, EC-109 esophageal squamous carcinoma cells yielded drastically decreased expression of nuclear transcription factor kappa-B (NF- $\kappa$ B) and phosphorylation of Akt, mTOR and I $\kappa$ B in a time-dependent manner (Zhang et al. 2013a). Through the decreased expression of NF- $\kappa$ B, a transcription factor that serves to promote cell survival and impair apoptotic activity, baicalein successfully overcame the PI<sub>3</sub>K/Akt pathway and induced apoptosis in cancerous cells (Zhou et al. 2009).

Platelet-type 12-Lipoxygenase (12-LOX) is found to be involved in the progression of human cancers and the inhibitor of 12-LOX offers a target for the prevention of cancer (Leung et al. 2007). Baicalein is known as a 12-LOX inhibitor. By inactivating 12-LOX, baicalein reduced the levels of anti-apoptotic proteins Bcl-2 and Mcl-1, and increased the levels of the pro-apoptotic protein Bax (Tong et al. 2002a; Tong et al. 2002b). It markedly induced the release of Cytochrome c from mitochondria into the cytosol and activated Caspase-9, Caspase-7, and Caspase-3, concomitant with cleavage of the Caspase-3 substrate poly(ADP-ribose) polymerase (Tong et al. 2002a; Tong et al. 2002b), finally caused apoptosis.

### Effect on cell cycle

Cell cycle is the series of events that take place in a cell leading to its division and duplication. In actively dividing eukaryote cells, cell cycle is composed of four stages: Gap 1

phase (G1), Synthesis phase (S), Gap 2 phase (G2) and Mitosis phase (M). There are different checkpoints all along the cell cycle to verify whether the processes at each phase of the cell cycle have been accurately completed before progression into the next phase. The cell cycle checkpoints are made up of cyclin-dependent kinases (CDKs), CDK subunits (Cyclins), and CDK inhibitors (CDKIs) as well as phosphorylated retinoblastoma protein (p-Rb) (Cheng et al. 2012). When cells fail to overcome cell cycle checkpoints, cell cycle arrest is triggered. G1 arrest may slow growth and induce cell death. G2/M arrest may increase the cytotoxicity of chemotherapy and be associated with enhanced apoptosis (Tyagi et al. 2002). Cancer represents a dysregulation of cell cycle, resulting in uncontrolled cell proliferation. Inducing cell cycle arrest can help to inhibit cancer. Baicalein causes cell cycle arrest during different phases based on types of cancer (Lee et al. 2005). Baicalein induces G1/S arrest due to increased Cyclin E expression, a major factor in the regulation of the G1/S checkpoint of the cell cycle, accompanied by reduced levels of Cdk 4 and Cyclin D1 in human lung squamous carcinoma (CH27) cells (Lee et al. 2005) and osteosarcoma cells (Lin et al. 2007). In prostate cancer cells, baicalein induced G0/G1 arrest via decreasing cyclin D1, cyclin D3 and phosphorylated retinoblastoma (pRB) protein (Pidgeon et al. 2002). In Hep G2 and Hep J2 hepatoma cells, baicalein treatment dramatically caused S-phase arrest (Chen et al. 2000). The underlying mechanisms include DNA damage in the early stages, inhibition of growth stimulating factors, and the induction of CDK inhibitors such as p21 or p27 (Chen et al. 2000). In bladder cancer cells, baicalein induced G2/M arrest by affecting cyclin B1 and phospho-Cdc2 (Thr161), two vital proteins for the initiation of mitosis (Chao et al. 2007). In addition, baicalein along with other extracts halted the cell cycle during the S and G2/M-phases in MCF-7 human breast cancer cells by suppressing 17 $\beta$ -estradiol-induced transactivation of estrogen receptor  $\alpha$  (Po et al. 2002; Wang et al. 2010a).

## Effect on angiogenesis

Angiogenesis is a fundamental step in the transition of tumors from a benign state to a malignant one. Angiogenesis is a multi-step physiological neovascularization produced through the development of new capillary blood vessels from previously established vessels, carried out through factors such as the vascular endothelial growth factor (VEGF) (Liu et al. 2003). Neovascularization is required for the growth of solid tumors and can be controlled by the pro-oncogene c-Myc, which ensures VEGF expression through HIF-1 (Chen et al. 2013a; Liu et al. 2003).

Baicalein displays repressive effect on angiogenesis. When cultured with conditioned medium from baicalein and baicalin-treated cancer cells, the average number and length of sprouts formed by the endothelial cell aggregates was significantly decreased in a dose-dependent manner (Miocinovic et al. 2005). It can partially be attributed to the baicalein-induced reduction of angiogenic related protein. In ovarian cancer cells, baicalein effectively lowered the protein level of VEGF, c-Myc, HIF- $\alpha$ , and NF $\kappa$ B (Chen et al. 2013a). In BV2 microglia, baicalein suppressed expression of hypoxia-induced HIF-1 $\alpha$  and hypoxia responsive genes, including inducible nitric oxide synthase (iNOS), COX-2, and VEGF, by inhibiting ROS and PI3K/Akt pathway (Hwang et al. 2008). In addition, baicalein influenced phosphorylation of VEGF receptor 2 and ERK in human umbilical vein endothelial cells (HUVECs), which lead to the failure of new blood vessel formation (Ling et al. 2011).

Interestingly, baicalein can be utilized as a pro-angiogenic agent in certain cases (Cho et al. 2008). Baicalein was revealed to promote HIF-1 genes and the growth of new blood vessels by reducing ubiquitination and asparaginyl hydroxylation of HIF-1 $\alpha$  (Cho et al. 2008). It is possible that baicalein could work as both a pro-angiogenic and anti-angiogenic agent depending on the dosage and cell types (Cho et al. 2008).

### Effect on metastasis

Metastasis is the process by which cancer cells spread from the place where it first started to other parts of the body. It is a pivotal factor for poor prognosis. In fact, for many cancers it is the metastatic recurrence, not the primary tumor that ultimately proves to be fatal. Metastasis consists of multiple steps which are regulated by a series of proteases, including matrix metalloproteinases (MMPs), cathepsins and plasminogen activator (PA), all of which damage the extracellular matrix (ECM) (Chen et al. 2013b), allowing cancer cells break away from the primary tumor tissue and migrate to other tissues.

Baicalein inhibits invasion and migration in various cancer cells, mainly via reducing the expression and proteinase activity of matrix metalloproteinases (Chandrashekar et al. 2012; Kim et al. 2013; Wu et al. 2013; Zhang et al. 2013b), and/or increasing the expression of tissue inhibitors of metalloproteinase (TIMPs) (Chen et al. 2013b; Zhang et al. 2014b). MAPK pathway is a crucial target of baicalein (Chen et al. 2013b; Wang et al. 2010b; Yan et al. 2015; Zhang et al. 2014b). By diminishing phosphorylated levels of ERK, p38 and JNK, baicalein significantly inhibited the expression and secretion of MMP-2/9 in MDA-MB-231 cells (Wang et al. 2010b). Likewise, baicalein reduced expression and proteinase activity of MMP-2/9 and increased expression of TIMP-1/2 by impairing phosphorylation of p38 in glioma cells (Zhang et al. 2014b). In hepatocellular carcinoma cells, baicalein inhibited the phosphorylation of MEK1 and ERK1/2, leading to decreased expression and proteinase activity of MMP-2/9 and urokinase-type plasminogen activator (u-PA), as well as increased expression of TIMP-1 and TIMP-2 (Chen et al. 2013b). Although playing an important role in regulating metastasis in many cancer cells, MAPK pathway is not the only target of baicalein. Baicalein suppressed the TGF- $\beta$ /Smad4 signaling pathway and reduced the expression of the metastasis-associated N-cadherin, vimentin, ZEB1 and ZEB2 in gastric cancer cells (Chen et al. 2014a). Moreover, baicalein inhibited E2-induced migration, adhesion and invasion by interfering with 17 $\beta$ -estradiol (E2)-induced novel G protein-coupled estrogen receptor (GPR30)-related signaling (Shang et al. 2015). Ezrin (Tang et al. 2015; Wu et al. 2011) and zinc finger protein X-linked (ZFX) (Liu et al. 2015) were also involved in the anti-metastatic mechanisms of baicalein.

### Effect on inflammation

Inflammation is part of the biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation can be classified as acute and chronic. Chronic inflammation leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process. In many cases cancer is a direct effect of chronic inflammation (Li-Weber 2009). Inflammation orchestrates the microenvironment around

tumors, contributing to proliferation, survival and migration. Baicalein has historically been applied as an herbal anti-inflammatory therapy in China (Li et al. 2006). When used as an agent against 7,12-dimethylbenz[a]anthracene (DMBA) / 12-O-tetradecanoylphorbol-13-acetate (TPA)-mediated skin tumorigenesis, baicalein significantly inhibited the production of inflammatory cells, such as mast cells, macrophages, and neutrophils (Ma et al. 2013), all of which tend to assist in tumor growth and progression and are not effective sites to launch an attack against the tumor (Liu et al. 2010). In benzo(a)pyrene [B(a)P]-induced lung cancer bearing animals, administration of baicalein significantly counteracted B(a)P-induced increase of mature mast cell numbers and cytokines such as TNF- $\alpha$ , interleukin-1 $\beta$ , iNOS and NF $\kappa$ B (Chandrashekar et al. 2012). Baicalein were also found to inhibit the multifunctional cytokine Interleukin-6, suggesting it would serve as an anti-inflammatory treatment and provide a therapeutic effect on multiple myeloma patients (Liu et al. 2010). One of the possible anti-inflammatory mechanisms of baicalein is it reduces prostaglandin E2 (PGE2) release and arachidonic acid (AA) liberation through inhibiting MAPK-cytosolic phospholipase A2 (cPLA2) pathway (Nakahata et al. 1998).

## Bioavailability and improvement

A lot of flavonoids display remarkable anti-cancer activity in cell models, however, it is still unknown how viable and readily available they work in human body. The upmost concern is poor bioavailability. Like other flavonoids, baicalein undergoes serious first-pass metabolism in intestine and liver in human and rats, which is responsible for its low bioavailability, predominantly in the form of glucuronidation, sulfation and methylation (Li et al. 2011b; Zhang et al. 2011b). UDP-glucuronosyltransferase (UGT) 1A9 demonstrated the fastest formation rate of baicalein in human liver preparations (Zhang et al. 2007). The efflux of conjugated metabolites which are produced intracellularly was mediated by membrane transporters, including multidrug resistance associated proteins (MRPs), breast cancer resistance protein (BCRP), human organic anion-transporting polypeptide (OATP) 2B1 and OATP1B3 (Zhang et al. 2011b). According to a Phase I, randomized, double-blind, single-dose trial of baicalein carried out in 72 healthy adults (Li et al. 2014), the maximum plasma concentration that the drug achieved after dosing (C<sub>max</sub>) ranged from 5.82 to 108.17 ng/mL after oral administration of 100-2800 mg baicalein.

To improve bioavailability of baicalein, one of the methods is to prepare it in the form of nanocrystal or with delivery systems. Baicalein nanocrystal showed rapid and extensive absorption. Its C<sub>max</sub> was much higher and half-life was much longer than free baicalein (Tsai et al. 2012; Zhang et al. 2011a). Complexation with delivery systems could enhance the solubility and dissolution of baicalein (Huang et al. 2014; Liang et al. 2013; Liu et al. 2006; Liu et al. 2012; Zhang et al. 2014a). Delivery systems improved the pharmacokinetic properties of baicalein, leading to an increase in relative bioavailability. For example, when embedded with self-microemulsifying drug delivery system (SMEDDS), the drug release rate was significantly higher. The absorption of baicalein from SMEDDS resulted in about 200.7% increase in relative bioavailability than that of the baicalein suspension in rats by oral administration (Liu et al. 2012).

Another way to solve this problem is to co-treat baicalein with compounds sharing the same metabolic pathways with baicalein, or UGT and SULT inhibitors. These compounds may interfere with the metabolism and absorption of baicalein. Acetaminophen, (–)-epicatechin, piperine and curcumin were proven to produce a dose-dependent inhibition on the glucuronidation and sulfation of baicalein (Fong et al. 2012). Among them, curcumin and high-dose (–)-epicatechin were demonstrated to subsequently increase the absorption of baicalein (Fong et al. 2012).

Modification of baicalein molecules to create analogs is also a strategy. Several baicalein derivatives were proven to have stronger cytotoxicity than baicalein. Baicalein derivatives, which were synthesized by introducing a group to C6-OH and a nitrogen-containing hydrophilic heterocyclic ring to C7-OH, exhibit more potent cytotoxicity than baicalein against HepG2, A549, and BCG-823 cancer cell lines (Luo et al. 2014). Baicalein derivatives with one geranyl group, baicalein sulfated derivatives, baicalein benzyl derivatives, and baicalein amino acid derivatives also showed a significant increase in cytotoxicity compared with baicalein (Ding et al. 2011; Li et al. 2013b; Neves et al. 2011; Wang et al. 2014a). Modified with O-alkylation and O-acylation, singly or in combination, on the ring A of baicalein evaluated the effects of their inhibitory activities against multidrug-resistant tumor cell lines and P-gp 170. Higher pro-oxidant property (Wang et al. 2014a), new target pathways (Ding et al. 2011) and more resistant to membrane transporters may be responsible for the enhanced anti-cancer efficacy of baicalein derivatives.

## Combination treatments

Baicalein enhances the cytotoxicity and/or bioavailability of certain cancer therapy drugs. A synergistic therapeutic effect were observed when treated baicalein in combination with silymarin, vincristin or dexamethasone (Chen et al. 2009; Chen et al. 2013c; Otsuyama et al. 2007). In addition, baicalein was demonstrated to increase the cytotoxicity of cisplatin through enhancing gap junction intercellular communication (Wang et al. 2014b). Baicalein can increase the oral bioavailability of tamoxifen by inhibiting cytochrome P450 (CYP) 3A4-mediated metabolism of tamoxifen in the small intestine and/or liver, and P-glycoprotein (P-gp) efflux pump in the small intestine, reducing total body clearance in rats after an oral administration of baicalein and tamoxifen (Li et al. 2011a). Similarly, via inhibiting both P-gp and the CYP3A subfamily in the intestine and/or liver, the area under the curve (AUC<sub>0-∞</sub>) and the C<sub>max</sub> of doxorubicin were significantly greater and higher, respectively in the presence of baicalein (Shin et al. 2009). The absolute and relative bioavailability of doxorubicin were also obviously increased compared with that of the control group (Shin et al. 2009).

## Conclusion

Cancer proves to be one of greatest challenges in modern medicine. Present cancer treatments are usually with side effects and can be harmful to the healthy cells in the body. Baicalein, a flavonoid extract from the dried root of *Scutellaria baicalensis* Georgi, has the potential to decrease cancer growth and retard cancer promoting processes, such as angiogenesis, metastasis, and inflammation, without impairing normal cells. However, low



bioavailability limits the application of baicalein. Improvement of baicalein bioavailability and combination treatment with other anti-cancer agents have shown some promise which could lead to a broader use of this flavonoid as a anti-cancer agent candidate. So far, most anti-cancer effects of baicalein have been observed in vitro or in animal models. In the future, more clinical trials should be carried out to investigate the anti-cancer activity of baicalein in human body and provide more evidence for its pharmacological use.

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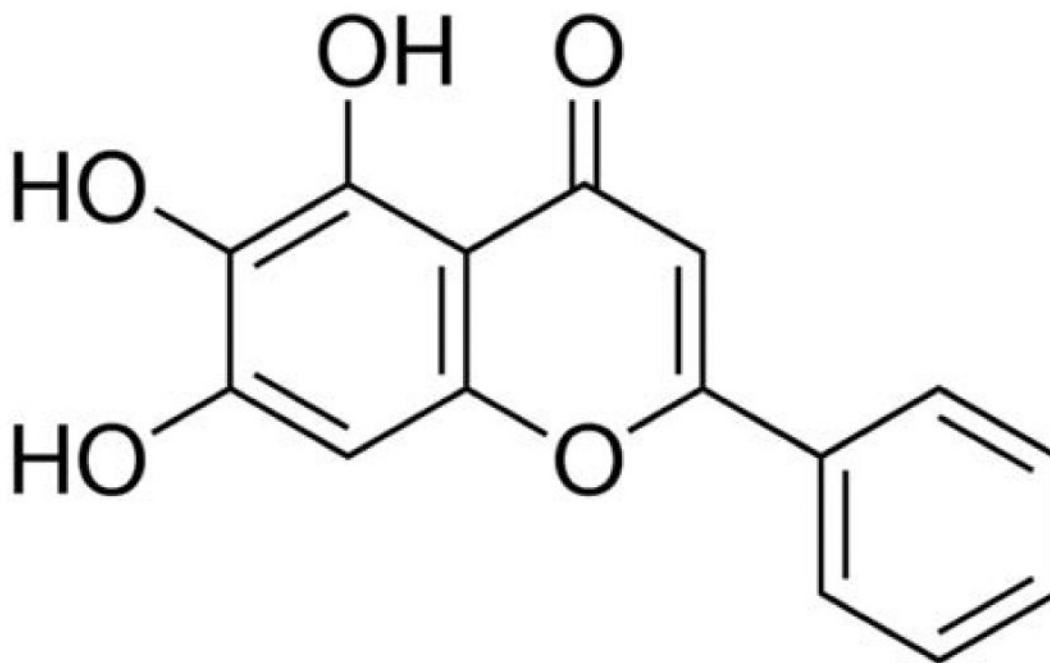
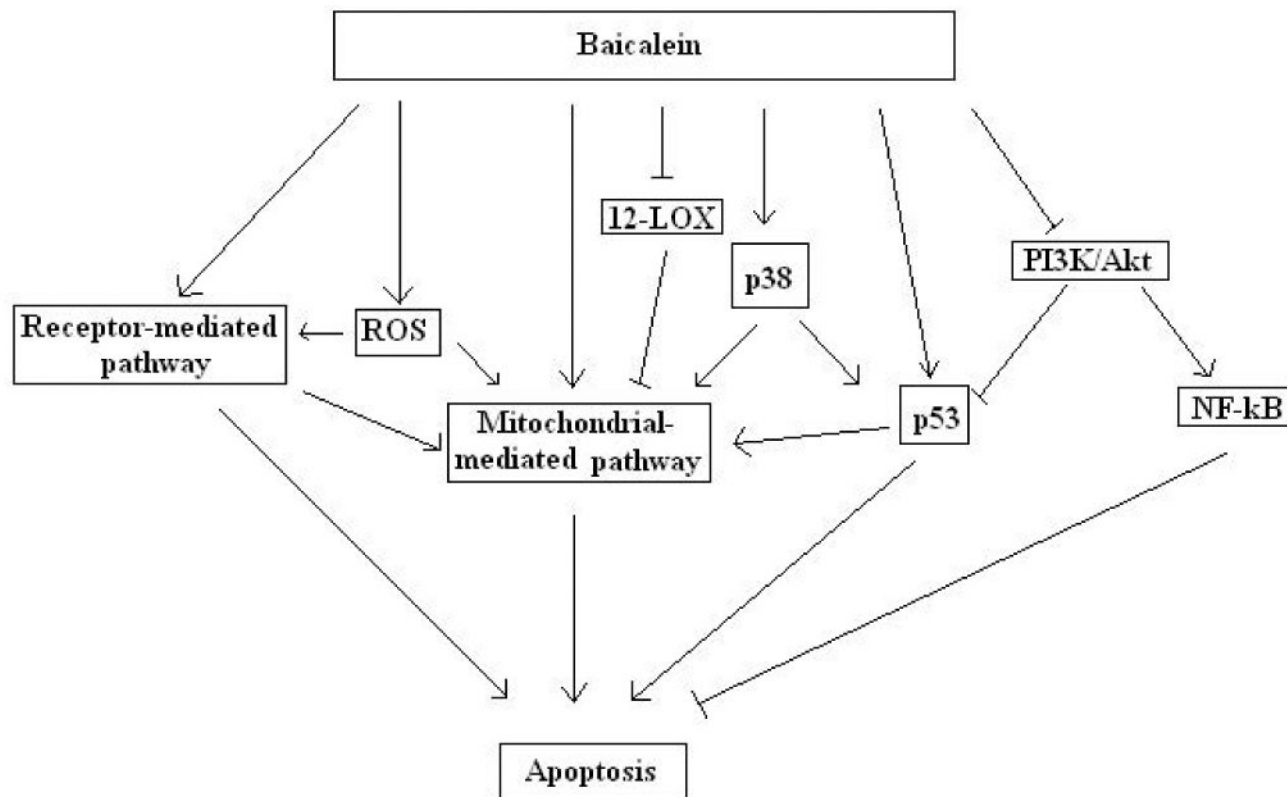
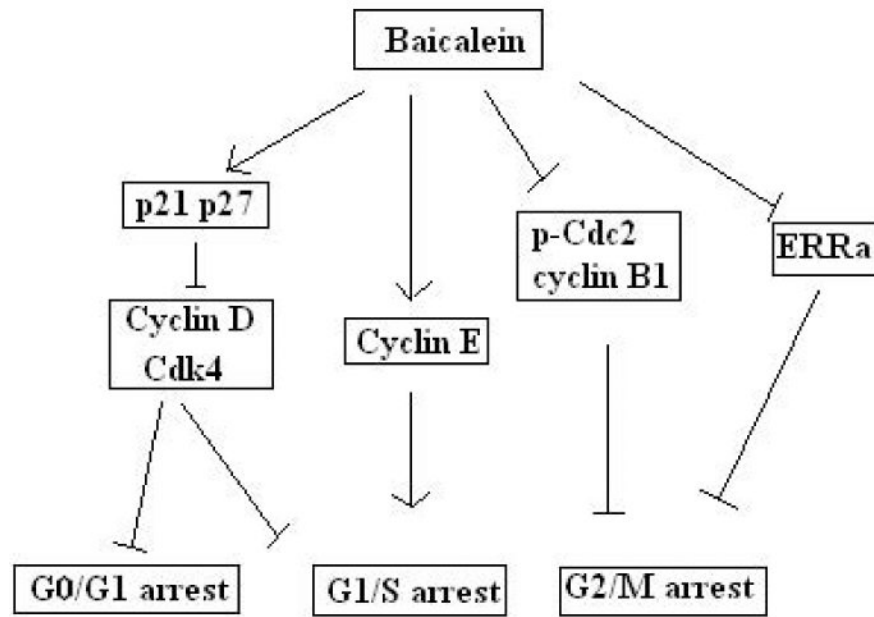


Fig. 1. Chemical structure of baicalein

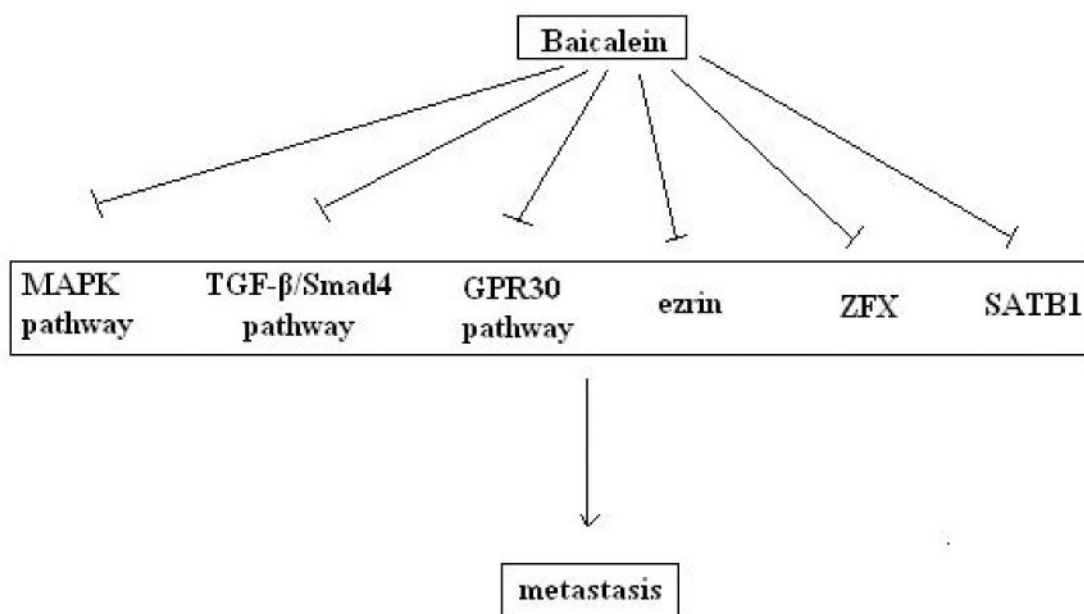


**Fig. 2.** Baicalein induced apoptosis in cancer cells through multiple mechanisms, such as increasing reactive oxygen species (ROS) level, inactivating 12-Lipoxygenase (12-LOX), inhibiting PI3K/Akt and its down-stream proteins, as well as up-regulating tumor suppressors p38 and p53.



**Fig. 3. Baicalein induced cell cycle arrest in cancer cells mainly via inhibiting cyclin-dependent kinases (CDKs) and cyclins, and up-regulating CDK inhibitors (CDKIs)**





**Fig. 4.** Baicalein reduced metastasis of cancer cells by targeting the MAPK pathway, TGF-β/Smad4 pathway, GPR30 pathway, ezrin, Zinc finger protein X-linked (ZFX) or special adenine-thymine (AT)-rich DNA-binding protein 1 (SATB1).

Table 1

## Physical and biochemistry characteristics in each group

	NC	DN	DV	DL	DLV
BW (g)	368.67±9.74	283.14±14.87	330.33±6.74	314.34±30.03	298.67±1.76
KW (g)	1.12±0.09	1.62±0.17 <sup>a</sup>	1.05±0.08	1.60±0.06	1.54±0.03
KW/BW (×10 <sup>-3</sup> )	3.02±0.16	5.78±0.61 <sup>bb</sup>	3.19±0.27	5.22±0.63 <sup>a</sup>	5.17±0.12 <sup>a</sup>
SBP (mmHg)	152.60±3.46	151.50±4.16	157.70±3.28	160.30±1.45	155.80±3.79
DBP (mmHg)	83.40±2.65	89.20±1.76	77.00±3.79	85.60±4.10	79.50±4.18
FPG (mmol/L)	6.40±0.24	21.59±5.72	19.05±2.76	24.24±2.67	23.67±6.03
TG (mmol/L)	0.45±0.06	1.73±0.10 <sup>a</sup>	0.49±0.13 <sup>c</sup>	1.76±0.24 <sup>bb</sup>	1.80±0.12 <sup>bb</sup>
TC (mmol/L)	2.40±0.11	2.51±0.23	2.31±0.16 <sup>c</sup>	2.56±0.20	2.38±0.25
SA (g/L)	28.02±1.64	24.90±2.87	29.09±1.48	23.17±2.84	24.69±1.38
Ca (mmol/L)	2.73±0.19	2.68±0.26	2.76±0.25	1.72±0.07	1.68±0.12
PTH ng/L	2.73±0.012	3.22±0.15	3.02±0.14	6.02±0.24 <sup>bc</sup>	5.79±0.65 <sup>bc</sup>
25(OH)D (nmol/L)	23.47±0.73	21.50±0.62 <sup>bb</sup>	23.71±0.32 <sup>c</sup>	25.15±0.53 <sup>b</sup>	24.43±0.81 <sup>b</sup>

NC, control group; DN, diabetic nephropathy group; DV, DN+1,25(OH)2D<sub>3</sub> group; DL, DN+ lenti-shVDR group; DLV, DN+lenti-shVDR+1,25(OH)2D<sub>3</sub> group; BW, body weight; KW, kidney weight; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; SA, serum albumin; Ca, serum calcium; PTH, serum parathyroid hormone.

<sup>a</sup>  $P < 0.05$  vs. NC group;

<sup>b</sup>  $P < 0.05$  vs. DV group;

<sup>c</sup>  $P < 0.05$  vs. DN group.