Review

Scutellaria baicalensis: Bioactive Components, Bioactivities and Therapeutic Potential

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Article history: Received 18 July 2015, Received in revised form 23 August 2015, Accepted 25 August 2015, Published 30 August 2015.

Abstract: Traditional Chinese medicines have a long history of clinical application. However, their therapeutic mechanisms are still largely unknown. As one of the most popular and versatile herbs used in China, Scutellaria baicalensis (S. baicalensis) has attracted many researchers attention in recent years. Studies revealed that the herb possesses numerous bioactivities, including antitumor, antiallergic, neuroprotective, anti-inflammatory, cardiovascular protective, hepatoprotective, antiviral and antibacterial activities. This review summarizes current knowledge about bioactive components, bioactivities and therapeutic potential of S. baicalensis based on latest literature, aiming to provide insights for further study and application of this famous herbal medicine.

Keywords: Scutellaria baicalensis; baicalin; baicalein; bioavailability; anticancer; neuroprotection; cardioprotection.

1. Introduction

Scutellaria baicalensis Georgi, also known as baikal skullcap or Chinese skullcap, is a perennial herb in the Labiatae family. It has a native distribution in Asia, including China, Japan,
Korea, Mongolia and Russian Far East area. The wild plants grow in sunny grass slopes, waste and cultivated areas at the elevation between 100 to 2000 meters. It blooms purple flowers from July to August and fruits from August to September.

Radix *Scutellariae* (Huang Qin in China) is the root of *S. baicalensis*. It is one of the 50 fundamental herbal medicine used in China and has a long history of over 2000 years, which was first recorded in “Shen Nong's herbal classic” (200-300 A.D.). The described functions of Huang Qin in traditional Chinese medical classics were to clear heat, relieve dryness, discharge fire, detoxicate, stop bleeding and prevent miscarriage. It is made into decoction pieces by steamed or boiled in water or by fried with yellow wine. In folk medicine, decoctions of Huang Qin have been empirically used against various diseases, including fever, bronchitis, ulcers, hepatitis and other inflammatory diseases. Besides, it is often used in combination with other herbs to treat gastrointestinal and respiratory infection, cardiovascular disorders and gynecologic diseases. According to the current Chinese Pharmacopoeia (2010), Huang Qin is contained in more than 170 herbal formulas, and it is a key ingredient of Xiaochaihu Granule, Niuhuang Jiedu Tablets and Shuanghuanglian Oral Liquid.

The present review focuses on recent discoveries concerning the bioactive components, bioactivities and therapeutic potential of *S. baicalensis*. The underlying mechanisms of action were discussed based on recent discoveries.

2. Biologically Active Components of *S. baicalensis*

*S. baicalensis* is a rich source of polyphenols, especially flavonoids, which are the main bioactive substances in this herb. Besides, it contains a wide variety of terpenoids, alkaloids, phytosterols, essential oils and polysaccharides. To date, more than 150 different polyphenols including flavones, flavonols, flavanones, flavanonols, chalcones, and biflavones have been isolated and identified from *S. baicalensis* (Seo et al., 2013). Among them, baicalin, wogonoside, oroxyloside and their aglycons, baicalein, wogonin, and oroxylin A (Fig. 1) were reported to be the main biologically active components. Furthermore, baicalin is regarded as the most important determinant of the quality of Huang Qin. According to Chinese Pharmacopoeia (2010), the content of baicalin in Huang Qin should not be lower than 9% as measured by HPLC.

The total phenolics and flavonoids content of the roots are 60.52 GAE mg/g in aqueous extracts and 46.85 GAE mg/g in ethanol extracts (Zhang et al., 2011a). The distribution of polyphenols is not even in different tissues of *S. baicalensis*. A recent study evaluated polyphenol mixtures isolated from different parts of the herb (root, stem, leaf and flower) via HPLC-MS/MS. There were total 46 compounds identified from *S. baicalensis* (root 23, stem 14, leaf 17, flower 18). And the content of polyphenols (mg/kg, fresh sample) was the highest in the root (1715.7±0.5), followed by leaf
(885.0±0.5), flower (622.4±0.2) and stem (307.4±0.1) (Seo et al., 2013). These findings are consistent with previous reports, which help to explain why the main part of the plant that is consumed is the root extract.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Structure</th>
<th>MW</th>
<th>Concentration in dry root (μg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baicalin</td>
<td>OH O-Glucuronic acid</td>
<td>446.37</td>
<td>73.8-131.5</td>
</tr>
<tr>
<td>Wogonoside</td>
<td>H O-Glucuronic acid OMe</td>
<td>460.39</td>
<td>-</td>
</tr>
<tr>
<td>Oroxyloside</td>
<td>OMe O-Glucuronic acid</td>
<td>460.39</td>
<td>-</td>
</tr>
<tr>
<td>Baicalein</td>
<td>OH OH H</td>
<td>270.24</td>
<td>6.8-15.9</td>
</tr>
<tr>
<td>Wogonin</td>
<td>H OH OMe</td>
<td>284.27</td>
<td>4.4-14.3</td>
</tr>
<tr>
<td>Oroxylin A</td>
<td>OMe OH H</td>
<td>284.26</td>
<td>-</td>
</tr>
</tbody>
</table>

**Figure 1.** Chemical structure of major bioactive flavonoids in *S. baicalensis*.

### 3. Bioavailability and Pharmacological Action

As a widely prescribed herbal medicine, the metabolic process of main components in *S. baicalensis* has been extensively investigated. *In vitro* study showed that main components in water extract of Huang Qin were stable when incubated with artificial gastric (pH=1.5) and intestinal (pH=6.8) juices (Jung et al., 2012; Xing et al., 2014). Recently, researchers evaluated repeated administration of *S. baicalensis* decoction (2g/kg) on the pharmacokinetics and distribution of flavonoids in rats. The free form of baicalein and wogonin were mainly found in lung, kidney and liver, but undetectable in serum. On the contrary, the glucuronides/sulfates of baicalein and wogonin were the primary form in serum (Hou et al., 2011). These results provided evidence for the use of these
flavonoids. For example, baicalin, a glucuronide of baicalein, might benefit cardiovascular disorders, whereas baicalein and wogonin might be used to treat diseases in liver, lung or kidney. Besides, several studies showed that after orally administration of water extract of Huang Qin, the four flavones, namely baicalin, wogonoside, norwogonoside and oroxyloside, were converted to their aglycons by human intestinal bacteria. And the metabolites displayed stronger anti-complementary, anti-inflammatory and anti-bacterial activities, which may help to explain the use of *S. baicalensis* in treatment of gastrointestional infection (Jung et al., 2012).

However, the clinical application of baicalin and baicalein are limited due to their low bioavailability. It was reported that both baicalin and baicalein could form intra-molecular hydrogen bonds, which led to poor solubility in water. The absolute bioavailability after oral administration of baicalin and baicalein to rat was 2.2% and 27.8%, respectively. This challenges pharmaceutical researchers to improve the absorption and bioavailability. A novel baicalin-loaded nanoemulsion was developed to improve the oral bioavailability of baicalin. *In vitro* release studies showed sustained release property of the nanoemulsion. In the rat model, after orally administration at a dose of 100 mg/kg baicalin, the nanoemulsion significantly increased the AUC of baicalin up to 7-fold higher than that of free baicalin suspension (Zhao et al., 2013). There was also report that baicalin-loaded liposomes elevated the bioavailability and peak concentration up to 3.04 and 2.83-fold that of the control after oral administration in rat. Besides, the tissue distribution analysis suggested that the liposomes increased the baicalin concentration in the kidney, liver and lung (Wei et al., 2014).

Drug-drug interaction can lead to adverse drug effects. Inhibition of enzymes involved in drug metabolism, such as cytochrome P450 (CYP) is thought to participate in this process. The CYP3A subfamily is the most abundant isoforms of CYP and metabolizes nearly 60% of drugs used in clinical activities. Previous reports suggested that baicalin could inhibit CYP3A activity. A recent study investigated the roles of baicalin in the metabolism of midazolam, a drug commonly used as probe for CYP3A activity. Results showed that baicalin decreased the clearance and increased AUC of medazolam in a dose dependent manner in rats, and further research revealed that the inhibition of CYP3A resulted in the pharmacokinetic changes of midazolam (Tian et al., 2013). Furthermore, another study suggested that baicalin could competitively displace nifedipine from plasma proteins and suppress its metabolism in liver by inhibiting CYP3A activities in rats. So, doctors might need to be cautious to prescribe baicalin to patients taking these drugs (Cheng et al., 2014a).

4. Therapeutic Potential and Possible Mechanisms

*S. baicalensis* and its bioactive components have shown numerous pharmacological activities, including anti-inflammatory, antitumor, neuroprotective, cardiovascular protective, hepatoprotective,
antiallergic, antiviral and antibacterial activities.

4.1. Anticancer Effects

Many natural products and their derivatives have been proved to possess potent anticancer activities. In fact, 69% of anticancer drugs approved were developed through screening natural products from plants, animals and microorganisms. For example, paclitaxel, vincristine, and etoposide are plant derived agents that currently used in cancer therapy. As a widely used and multipurpose herbal medicine in China, *S. baicalensis* and its constituents have also been extensively explored for potential anticancer activities. The data showed that the herb could selectively inhibit tumorigenesis and tumor growth and may be a promising anticancer candidate in drug development. This review summarizes recent discoveries about the anticancer activities of *S. baicalensis* according to different mechanisms of function.

4.1.1. Inducing apoptosis

Apoptotic deficiency is highly involved in tumorigenesis. Targeting this process as a therapeutic strategy is a hot topic in anticancer drug development. The activation of apoptosis involves two different pathways, the death receptor-mediated extrinsic pathway and the mitochondria-mediated intrinsic pathway.

The initiation of the extrinsic pathway requires the binding of the tumor necrosis factors (i.e., TNF-α, TRAIL) to their corresponding receptors. A number of NF-κB target genes can negatively regulate TNF-induced apoptosis. Studies found that baicalein treatment suppressed the activation of NF-κB, thus sensitized HCT-116 human colorectal cancer cells to death triggered by TNF (Kim et al., 2013). Wogonin was also able to enhance TNF-induced apoptotic death in the same way in cancer cells derived from cervical, ovarian and lung (Yang et al., 2011). And treatment of wogonin was reported to enhance TRAIL-induced cytotoxicity to A549 nonsmall-cell cancer cells (Yang et al., 2013).

The mitochondria mediated pathway is triggered by intrinsic signals, such as DNA damage, growth factor deprivation, ROS and Ca^{2+} overload. Wogonin treatment could significantly increase the intracellular H_{2}O_{2} level, which directly or indirectly gave rise to mitochondria-mediated apoptosis in human hepatoma HepG2 and glioma U87/U251 cancer cells (Tsai et al., 2012; Wei et al., 2010). In addition, wogonin treatment was reported to upregulate pro-apoptotic factors (Bax, p53, capase-3) and downregulate anti-apoptotic factors (Bcl-2, survivin) in several cancer cell lines including human breast cancer MCF-7, myeloma RPMI8226, myelogenous leukemia HL-60 and colorectal cancer HT-29 cells (Huang et al., 2012a; Jung et al., 2012; Zhang et al., 2013a). The PI3K/Akt signaling pathway
is negatively related to mitochondria-mediated apoptosis. Treatment of CA46 lymphoma cells with baicalein was found to block the PI3K/Akt pathway and induced apoptosis in these cells (Huang et al., 2012b). Besides, baicalein treatment was reported to inhibited human osteosarcoma cell proliferation by induction of Bax/Bcl-2 mediated apoptosis (Zhang et al., 2013a).

4.1.2. Inhibiting metastasis

Metastasis is a hallmark of malignant tumors and plays an important role in clinical progression. Metastasis requires the degradation of extracellular matrix (ECM) by matrix metalloproteinases (MMPs, especially MMP-2 and MMP-9). *S. baicalensis* and its main active components (baicalein, wogonin, oroxylin A) have all been found to be able to inhibit cell migration by suppressing MMP-2 and MMP-9 in various types of cancer cells (Cheng et al., 2014b; Park et al., 2014; Zhang et al., 2013a). A study showed that baicalein could also promote the expression of tissue inhibitors of metalloproteinases (TIMPs), and in turn contribute to the inhibition of metastasis (Zhang et al., 2014). It was reported that hypoxia induced epithelial-mesenchymal transition (EMT), which made tumor cells more invasive. Oroxylin A treatment was found to block hypoxia-induced EMT in three tumor cell lines: MCF-7, DU145, and HepG2 (Cheng et al., 2014b). Previous studies reported that maspin is a potent suppressor of metastasis. In a study using human gallbladder carcinoma GBC-SD cells, wogonin significantly upregulated maspin, which might be critical to the inhibition of cell migration (Dong et al., 2011).

4.1.3. Interfering cell cycle

Cell cycle dysregulation results in uncontrolled cell proliferation. The G1/S transition is a rate-limiting step. It is reported that wogonin (50 μM) induced G1/G0 phase arrest in glioma cells by downregulating cyclin D1, CDK2, CDK4 and simultaneously increasing p27 expression (Wang et al., 2013). Similar action was observed in osteosarcoma cells, baicalein treatment triggered G1 cell cycle arrest through reducing the expression of cyclin D1 and CDK4 (Zhang et al., 2013a). Another rate-limiting step in cell cycle is the G2/M transition. Baicalein could induce both G0/G1 and G2/M phase arrest in human mucoperidermoid carcinoma cell line Mc3. Securin is an anaphase inhibitory protein during cell division and its overexpression is involved in cancer cell proliferation (Jiang et al., 2010). A study found that baicalein (40-80 μM) significantly suppressed securin expression in various types of tumors.

4.1.4. Promoting differentiation

Promoting malignant cells’ maturation is a new strategy to cure tumors. Researchers showed
that wogonin could promote differentiation in glioma cells. Wogonoside was found to have similar effects in AML cells (Chen et al., 2013a). In addition, it was reported that side population (SP) cells, a source of cancer stem cells, are responsible for the recurrence of cancers. And *S. baicalensis* extract, as well as baicalein and wogonin, could markedly decreased the proportion of SP cells in human multiple myeloma cells (Lin et al., 2013a).

### 4.1.5. Reversing drug resistance

Multidrug resistance (MDR) is a serious obstacle in chemotherapy. Several studies found that wogonin could reverse MDR in numerous types of cancer cells. For example, wogonin enhanced the sensitivity of MCF-7/DOX cells to DOX (doxorubicin). It also potentiated anticancer effect of etoposide by inhibition of P-gp in Jurkat, HL-60, A549, and NCI-H226 cancer cells. In addition, it was reported to ameliorate adverse effects such as myelosuppression of etoposide (Enomoto et al., 2011). Another bioactive components of *S. baicalensis*, oroxylin A, significantly enhanced the cytotoxicity of 5-FU by downregulating its key metabolic enzymes (Zhao et al., 2010). Study also found the component could reverse adriamycin resistance through inhibition of the CXCL12/CXCR4 axis (Wang et al., 2014). These results suggested that wogonin and oroxylin A might be potential adjunctive agent in cancer therapy.

### 4.1.6. Other effects

Autophagy deficiency contributes to spontaneous tumorigenesis. Evidence suggested that baicalin and wogonoside inhibited cancer cell viability probably through induction of autophagy (Lin et al., 2013b; Sun et al., 2013). Two studies suggested that the mechanisms of wogonin’s antitumor effects were also related to the block of angiogenesis and lymphangiogenesis (Kimura et al., 2013; Song et al., 2013a). In cancer cells, there is a shift in energy production from mitochondrial oxidative phosphorylation to aerobic glycolysis. And oroxylin A blocked the glycolysis to inhibit the growth of MDA-MB-231 and MCF-7 human breast carcinoma cell lines (Wei et al., 2013).

### 4.2. Neuroprotective Effects

The root of *S. baicalensis* Georgi has been used as an herbal therapy to treat ischemia stroke. Numerous studies suggested that the antioxidant, antiapoptotic, anti-inflammatory abilities of *S. baicalensis* as well as its active components (i.e. baicalin, baicalein, wogonin, oroxylin A) are beneficial to the treatment neurological disorders. Among the active components of *S. baicalensis*, baicalin and its aglycone baicalein attracted more attention in the search for neuroprotective compound. It is noteworthy that baicalin can pass through the blood-brain barrier, which makes it a
promising therapeutic agent on the CNS.

4.2.1. Neurodegenerative diseases

Accumulating evidences suggest that oxidative stress, ER stress and apoptosis are highly involved in neurodegenerative diseases, such as Alzheimer’s disease (AD) and Parkinson disease. In cultured PC12 cell, a cell line commonly used in brain disease studies, baicalein (5-40 μmol) significantly inhibited H2O2 induced apoptosis, ROS production and lipid peroxidation (Zhang et. al., 2010). Likewise, the pretreatment of baicalein (12-200 μM) protected PC12 cells against oxidative damage caused by 6-OHDA (1 mM for 8h), an analogue of dopamine (Zhang et al., 2012). In another study using HT22 murine hippocampal neuronal cells, flow cytometric analysis showed that after preincubation with baicalein (50 μmol), apoptotic death caused by thapsigargin and brefeldin A, two ER stress inducers, was reduced from 63.84% to 28.96% and 55.27% to 26.20%, respectively (Choi et al., 2010). Besides, in the rotenone model of Parkinson’s disease, baicalein could also reverse rotenone-induced apoptosis in dopaminergic SH-SY5Y cells, as measured by MTT assay, the pre- and subsequent co-treatment of baicalein (25-100 μM) increased cell viability equal to or even more than the control level (P<0.01) (Song et al., 2012).

AD is characterized by the formation of amyloid plaques. Baicalein could directly interfere the aggregate of Aβ1-42 (Song et al., 2013b). In CHO cells overexpressing wild type human amyloid precursor protein (APP) and in primary culture AD mice (Tg2576) neuron cells, baicalein significantly reduced Aβ production by enhancing APP α-processing. These effects were also verified in AD transgenic mouse model. I.p. daily administration of baicalein (10 mg/kg) for 8 weeks ameliorated AD-like pathology and mitigated cognitive deficits (Zhang et al., 2013b). Besides, baicalin could dose-dependently prevent Aβ1-42 aggregation in SH-SY5Y cells (Yin et al., 2011).

The overactivation of NMDA receptor leads to excitotoxic neuronal cell death, which is associated with various neurodegenerative diseases including AD and Huntington’s chorea. Glutamate is a major excitatory neurotransmitter in brain. In the presence of S. baicalensis extract, glutamate (350 μmol, 20 min) induced excitotoxic neuron cell death was significantly inhibited. And the maximum inhibition was achieved at 100 μg/mL of the extract (Yang et al., 2014).

Chronic cerebral hypoperfusion is associated with vascular dementia (VaD). And in AD and VaD patients, neuron inflammation was observed in pathologically vulnerable regions of brain. Using rat models for AD and vascular dementia, a study found that the daily administration of S. baicalensis extracts at 100 mg/kg alleviated memory impairment induced by chronic cerebral hypoperfusion and LPS infusion (Hwang et al., 2011).

4.2.2. Brain and spinal cord injury

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Previous researches have demonstrated that cerebral ischemia/reperfusion induces a cascade of pathological responses such as oxidative stress, neuron apoptosis, inflammation as well as excitotoxicity.

A study evaluated the protective effects of post-injury baicalin treatment against transient global cerebral ischemia injury in gerbils. Data showed that baicalin (100-200 mg/kg) dramatically reduced neuronal damage. And the neuroprotection of baicalin may be related to inhibition of oxidative stress (measured by level of MDA, SOD, GSH ect.), capase-3 activity and upregulation of BDNF (Cao et al., 2011). Another study also indicated that the peroxynitrite scavenging ability of baicalin may account for the reduced infarct size and apoptotic death in cerebral ischemia-reperfusion rat model (Xu et al. 2013). Brain is known to be more prone to oxygen and glucose deprivation (OGD). In cerebral ischemia/reperfusion injury, OGD activated TLR2 receptor and TNFα, initiating a cascade of inflammatory responses. Baicalin could downregulate TLR2/TNFα and thus protect neuron cells from OGD damage (Li et al., 2012a).

Mounting evidences suggested that NF-κB is a key regulator of inflammation after brain damage. Baicalin (100-200 mg/kg) could attenuate inflammation in focal cerebral ischemic reperfusion injury through downregulation of NF-κB p65 in rats (Xue et al., 2010). Besides, the inhibition of NF-κB by baicalin offered protection against perihematomal edema in a rat model of intracerebral hemorrhage (Zhou et al., 2014). Researchers also found that, after experimental traumatic brain injury (TBI), the administration of wogonin (40 mg/kg) improved both long-term histologic and functional outcomes in mouse TBI. And those beneficial effects may be associated with inhibition of the TLR4/NF-κB pathway (Chen et al., 2012).

Spinal cord injury (SCI) is an emergency with two damage processes. The secondary damage, which involves inflammation and oxidative stress, can exacerbate the primary injury and affect the final neurological deficits. Baicalin has potent anti-oxidative and anti-inflammatory effects. And its administration significantly decreased the edema of spinal cord tissue, the permeability of blood-spinal cord barrier and improved the motor function in a rat model of SCI (Cao et al., 2010).

Previous studies provided evidence that activation of TREK channels have neuroprotective effects in cerebral ischemia through modulating excitability of neuron cells. Both baicalein and wogonin could dose-dependently activate the TREK-2 channel in rat and thereby might be beneficial to neuroprotection (Kim et al., 2011).

4.2.3. Neurogenesis

Neural precursor cells (NPCs) possess self-renewal ability and can replace neurons in damaged or diseased areas in brain. In wogonin (2.46 μM) treated cortical NPCs, there is a twofold (21.46±0.9%) increase of the percentage of differentiated cells compared with control (10.96±0.9%).

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Furthermore, more mature neurons were observed in dil stained hippocampal precursor cells (HiB5 cells) in brain slices from the rat transplanted with wogonin treated HiB5 cells than those untreated. These results suggested that wogonin could facilitate NPCs differentiation both \textit{in vitro} and \textit{in vivo} (Lim et al., 2010).

However, the limitation of utilizing NPCs in the treatment of neurological diseases is that NPCs tend to differentiate into astrocytes, which can inhibit neurite outgrowth and form glial scar. Baicalin was reported to selectively promote neuronal differentiation of NPCs. And its administration enhanced hippocampal neurogenesis and improved learning and memory functions after cerebral ischemic injury in adult rats (Zhuang et al., 2013). The modulation of the signal transducer and activator of transcription 3 (stat3) and basic helix-loop-helix gene (bHLH) families may underlie the selectivity of baicalin (Li et al., 2012b).

Brain derived neurotrophic factor (BDNF) also plays an important role in neurogenesis, neuronal differentiation as well as learning and memory. It is reported that the neuroprotective and memory enhancing effects of oroxylin A (50 μM) is associated with induction of BDNF through stimulating the MAPK-CREB pathway and blocking the activity of GABAA (Jeon et al., 2011).

4.2.4. Epilepsy

It is reported that cells in hippocampus is vulnerable to seizure induced damage, and baicalin treatment could attenuate the neuronal cell loss, apoptosis and degeneration caused by seizures in rat hippocampus (Liu et al., 2012). Besides, baicalin possessed potent anti-convulsant abilities which may be mediated by binding to the GABAA receptor (Yoon et al., 2011). Therefore, baicalin might be a potential therapeutic agent in epilepsy treatment.

4.3. Cardioprotective Activity

4.3.1. Hypertension

Large-conductance Ca$^{2+}$-activated K$^+$ (BK$_{Ca}$) channels is essential to modulate smooth muscle contraction and the diameter of resistance arteries. As such, enhancing the function of BK$_{Ca}$ channel in arterial smooth muscle cells has been considered to provide a pharmacological strategy for treating hypertension. In isolated rat mesenteric artery, baicalin at 30 and 100 μM alleviated KCl-induced contraction in a dose dependent manner. And the mechanism by which baicalin induced relaxation may involve activation of BK$_{Ca}$ channels and inhibition of VDCC channels via upregulating the cGMP/PKG and cAMP/PKA pathways (Lin et al., 2010). In addition, baicalin could directly inhibit the activity of renin, with an IC50 value of 120.36 μM. It is well known that the renin-angiotensin system (RAS) is a key regulator in the pathogenesis of hypertension, which made baicalin a potential
agent for the management of hypertension (Deng et al., 2012).

4.3.2. Cardiac hypertrophy and fibrosis

Hypertension can lead to complications such as left ventricular hypertrophy and diastolic dysfunction. Published literature indicated that myocardial fibrosis may play a key role in this process. The daily administration baicalein (200 mg/kg) to spontaneously hypertensive rats protected against cardiac fibrosis, as shown by histological examination. And the beneficial role of baicalein was operated, at least partly, through the decreased production of collagen myocardial collagen volume fraction (Kong et al., 2011). In addition, targeting Rho kinase (ROCK) is suggested to be a potential anti-fibrotic strategy in the context of preventing and/or treating heart injury. Researchers found that baicalein could inhibit the activations of ROCK1 and ROCK2 with IC50 values of 6.55 and 2.82 μM, respectively. And the treatment of baicalin to angiotensin II stimulated rat heart-derived H9c2 cells effectively suppressed actin stress fiber formation through inhibiting the activity of ROCK (Oh et al., 2012). Furthermore, a study found that baicalin (100 mg/kg/d) potent inhibit MEK-ERK1/2 signaling pathway in response to hypertrophic stimuli. And by doing so, it inhibit cardiac hypertrophy and fibrosis induced by angiotensin II or overload pressure (Zong et al., 2013).

4.3.3. Myocardial infarction

Oxidative stress in cardiomyocytes plays a pivotal role in the pathogenesis of both heart failure and ischemic reperfusion injury. The ROS can cause severe myocardium damage due to less SOD, GSH and catalase in the cardiac system. In a rat model of myocardial ischemia reperfusion, wogonin treatment (10 mg/kg) showed cardioprotective effects by suppressing arrhythmias, inflammation, and apoptosis. These protective effects were achieved by inhibition of oxidative stress, NF-κB, P38 and monocyte chemoattractant protein-1 (MCP-1) (Lee et al., 2011). Lysophosphatidylcholine (lysoPC) is a metabolite from membrane phospholipids in injured cardiomyocytes and plays an important role in cardiac dysfunction during cardiac ischaemia. The treatment of baicalein could inhibit lysoPC induced-apoptosis via decreasing ROS production, Ca^{2+} overload and deactivation of MAPK signaling pathways (Chen et al., 2014). Besides, accumulating evidence has shown that VEGF is also a survival factor which can promote cardiomyocytes survival and reduce infarct size in heart. A study found that both S. baicalensis and baicalin significantly increased VEGF expression through activation of the ERRα pathway (Zhang et al., 2011b).

4.3.4. Atherosclerosis

Previous evidence suggested that VSMCs apoptosis facilitated a series of deleterious consequences in atherosclerosis. Wogonin attenuated lippotoxicity-induced apoptosis by inhibiting the
intracellular accumulation of diacylglycerol (DAG) and subsequent suppression of PKC phosphorylation in cultured vascular smooth muscle cells. This property of wogonin may benefit the treatment of atherosclerosis (Liu et al., 2011).

4.4. Anti-inflammatory Effects

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease and smoke plays a key role in the pathogenesis. In a cigarette smoke induced COPD rat model, the administration of baicalin (80 mg/kg) effectively protected pulmonary function and ameliorated inflammatory responses to cigarette smoke via decreasing inflammatory cells and the production of TNF-α, IL-8, IL-6. Likewise, baicalin treatment suppressed the expression of pro-inflammatory cytokines induced by cigarette smoke extract in type II pneumocytes. The anti-inflammatory effects of baicalin may achieved by the inhibition of NF-κB pathway (Zeng et al., 2010). Another study suggested that the anti-inflammatory ability against cigarette smoke induced COPD may also involve the modulation of histone deacetylase (HDAC) 2 activity (Li et al., 2012).

T-helper-17 (Th17) cells were reported to be implicated in various inflammatory diseases including rheumatoid arthritis. A study reported that baicalin decreased splenic T-helper-17 (Th17) cells proliferation in vivo, thereby inhibited IL-17 mediated inflammation and potently alleviated joint inflammatory destruction in an experimental arthritis model (Yang et al., 2013).

Pregnane X Receptor (PXR) has been considered as an important target for gut inflammation. In the dextran sodium sulfate model of murine colitis, the administration of baicalein reduced the colon histological (inflammation) score as well as the expression of inflammatory mediators (TNFα, IL-6) through a Cdx2/PXR pathway (Dou et al., 2012).

Using the S. aureus-induced mastitis mouse model, a study demonstrated that S. baicalensis (25-100 mg/kg) effectively attenuated pathological damage and cell apoptotic death in mammary glands. Meanwhile, the reduced TLR2 expression, p53 phosphorylation and alteration of apoptosis-related factors were also observed after treatment of S. baicalensis (Guo et al., 2014).

Insufficient apoptosis in active lymphocytes plays an important role in the pathogenesis of autoimmune hepatitis. Baicalein preferentially promoted mitochondria apoptosis in activated lymphocytes in vitro. Additionally, baicalein treatment ameliorated hepatitis and enhanced apoptosis in hepatic mononuclear cells and splenocytes in concanavalin A-challenged mice (Zhang et al., 2013).

A study demonstrated that the aqueous extracts from S. baicalensis effectively attenuated experimental periodontitis in mouse model, and the effect of S. baicalensis is likely due to its Th2-dominance response (Huang et al., 2013).

4.5. Hepatoprotection
Ischemia/reperfusion (I/R) to the liver is a serious problem following many clinical conditions including liver transplantation, trauma, hepatic failure and cancer. Several studies reported the hepatoprotective effects of baicalin against ischemia/reperfusion (I/R) injury. In the I/R injury rat, there was an increase in ALT, TNF-α, IL-6 serum level, iNOS, COX expression, and hepatic lipid peroxidation as well as decrease in hepatic GSH level. The pretreatment of baicalin (200 mg/kg) ameliorated these changes and inhibited NF-κB nuclear localization and apoptosis (Kim et al., 2010). In the rat model of alcoholic fatty liver, the use of baicalin prevented I/R injury via suppressing TLR4-mediated inflammatory responses (Kim et al., 2012). Together, these results showed that baicalin possessed antioxidant, anti-inflammatory and anti-apoptotic abilities, which may account for the liver protection against I/R injury.

Hepatic fibrosis is a wound-healing response caused by chronic liver inflammation, such as hepatitis B and alcoholic liver disease. Untreated fibrosis may lead to liver cirrhosis finally giving rise to organ failure and death. It was reported that baicalin could provide protection against liver fibrosis. Hepatic stellate cell is a well-recognized factor in the development of liver fibrosis. A study found that S. baicalensis extracts induced G2/M cell cycle arrest and apoptosis of hepatic stellate cells via the ERK-p53 pathway in vitro, which led to amelioration of dimethylnitrosamine induced liver fibrosis in rat (Pan et al., 2012). Furthermore, evidence demonstrated that S.baicalensis extracts alleviated LPS-induced liver sinusoidal endothelial cells activation and hepatic stellate cells migration through inhibiting MCP-1. Therefore, S. baicalensis may be a therapeutic agent against liver fibrosis (Chen et al., 2013b).

4.6. Antiallergic Effects

Asthma is characterized by reversible airflow obstruction, airway hyperresponsiveness (AHR), chronic airway inflammation with excessive mucus secretion. The anti-asthma effect of baicalein was evaluated in OVA-sensitized BALB/c mice. Results showed that both pre- and post-treatment of baicalein (10 mg/kg) alleviated asthma features, such as AHR, airway inflammation and remodeling, besides, the airway injury was also ameliorated by baicalein treatment, as assessed by apoptosis of bronchial epithelia and mitochondria dysfunction (Mabalirajan et al., 2013). Previous literature has shown that skullcapflavone II, a flavonoid from S. baicalensis, is a potential bradykinin antagonist. Since bradykinin is involved in the pathogenesis of asthma, a study investigated the therapeutic potential of skullcapflavone II against OVA-induced allergic asthma. In OVA-challenged female BALB/c mice, the oral administration of skullcapflavone (10 or 30 mg/kg/d) significantly inhibited AHR, inflammation, early stage remodeling and Th2 immune responses. Besides, the protective effects of skullcapflavone II were comparable to that of dexamethasone (3 mg/kg/d) and montelukast (30...
mg/kg/d) (Jang et al., 2012).

A recent study evaluated the anti-allergic activity of *S. baicalensis* extract in splenocytes isolated from OVA-sensitized mouse, and found that the extract (3-100 μg/mL) dose dependently decreased the production of IL-4 without affecting cell viability. Researchers next investigated the effects of baicalein, baicalin, wogonin on IL-4 production *in vitro*. Though all the three compounds (10-50 μmol/L) inhibited the production of IL-4 and other cytokines, only wogonin didn’t affect cell viability. Further studies showed that the oral administration of either *S. baicalensis* extract (25 mg/kg) or wogonin (1 mg/kg) for 16 days significantly suppressed OVA-specific IgE, reduced Th1 and Th2 cytokines production in OVA-sensitized mice (Shin et al., 2014a.)

There has been an increase in food allergy in recent years, which is estimated to affect about 5-6% children and 3-4% adults. A study demonstrated that the oral administration of *S. baicalensis* alleviated OVA-stimulated food allergy symptoms (diarrhea, decreased rectal temperature, and anaphylactic shock) and reduced OVA-specific IgE production in OVA-sensitized BALB/c mice through modulating system immune response by enhancing Th1 responses and inhibiting Th2 and Th17 responses. Besides, another study showed that *S. baicalensis* could inhibiting allergen permeation in intestinal via enhancing expression of tight junction-related proteins. Therefore, it was suggested that the oral administration of *S. baicalensis* may benefit the treat of food allergy disorders (Shin et al., 2014b).

4.7. Antibacterial Effects

The antibacterial abilities of many herbal medicines rely on the high concentration of flavonoids. As mentioned above, the transformation of the flavones in *S. baicalensis* extract to their aglycons by intestinal bacteria significantly enhanced the antibacterial activities. Particularly, norwogonin displayed potent inhibitory effects against multidrug-resistant acinetobacter baumannii (MIC 0.256 mg/mL) (Xing et al., 2014). Another study showed that baicalein effectively reversed the ciprofloxacin resistance of methicillin-resistant *Staphylococcus aureus* *in vitro* (Chan et al., 2011).

4.8. Antiviral Effects

The oral treatment of baicalein showed protective effects against influenza A/FM1/1/47 (H1N1) virus infection *in vivo* (Xu et al., 2010). Another research indicated the combination of baicalein with ribavirin could exert a synergistic inhibitory effect against influenza A (H1N1) virus infection in cell culture as well as in mice (Chen et al., 2011). Ethylacetate or chloroform extracts of *S. baicalensis* also exhibited inhibition against neuraminidase activity of influenza A virus (Hour et al., 2013). Besides, both *in vitro* and *in vivo* study showed that baicalein inhibited the infection of Sendai
virus, a parainfluenza virus (Dou et al., 2011).

Extract of *S. baicalensis* (IC50: 86.59–95.19 µg/mL) was found to suppressed infection and replication of dengue virus in Vero cells (Zandi et al., 2013). Studies also shown that baicalein displayed antiviral effects against dengue virus with an IC50 value of about 13.5 µg/mL (Moghaddam et al., 2014).

5. Conclusions

*S. baicalensis* has a 2000-year history of clinical application and is one of the 50 fundamental herbal medicines used in China. Accumulated evidence has linked a wide range of health benefits to *S. baicalensis*, including anticancer and antiallergic effects, protection of cardiovascular and nervous system, as well as inhibition of bacterial and viral infection. The therapeutic potential should be attributed to abundant polyphenols, especially baicalin, wogonoside, oroxyloside and their aglycons. In cancer prevention, bioactive compounds isolated from *S. baicalensis* have been showed to selectively induce apoptosis, inhibit metastasis, interfere in cell cycle and promote differentiation of cancer cells. Furthermore, they could reverse drug resistance and ameliorate adverse effects caused by other chemotherapeutics. The antioxidant and anti-inflammatory properties of baicalin and baicalein provided bases for the protection of cardiovascular and nervous system of *S. baicalensis*. And the modulation of immune systems of wogonin and skullcapflavone II may be beneficial to the treatment of allergic diseases. In the future, the low bioavailability of active compouds (baicalein, baicalin) from the herb and possible interaction with other drugs still require further investigations. In addition, the mechanisms of action of bioactive compounds from *S. baicalensis* should be studied further.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 81372976), Key Project of Guangdong Provincial Science and Technology Program (No. 2014B020205002), and the Hundred-Talents Scheme of Sun Yat-Sen University.

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