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Review

Drug-herb interactions between *Scutellaria baicalensis* and pharmaceutical drugs: Insights from experimental studies, mechanistic actions to clinical applications

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ABSTRACT

Whilst the popular use of herbal medicine globally, it poses challenges in managing potential drug-herb interaction. There are two folds of the drug-herb interaction, a beneficial interaction that may improve therapeutic outcome and minimise the toxicity of drug desirably; by contrast, negative interaction may evoke unwanted clinical consequences, especially with drugs of narrow therapeutic index.

Scutellaria baicalensis Georgi is one of the most popular medicinal plants used in Asian countries. It has been widely used for treating various diseases and conditions such as cancer, diabetes, inflammation, and oxidative stress. Studies on its extract and bioactive compounds have shown pharmacodynamic and pharmacokinetic interactions with a wide range of pharmaceutical drugs as evidenced by plenty of *in vitro*, *in vivo* and clinical studies. Notably, *S. baicalensis* and its bioactives including baicalein, baicalin and wogonin exhibited synergistic interactions with many pharmaceutical drugs to enhance their efficacy, reduce toxicity or overcome drug resistance to combat complex diseases such as cancer, diabetes and infectious diseases. On the other hand, *S. baicalensis* and its bioactives also affected the pharmacokinetic profile of many drugs in absorption, distribution, metabolism and elimination *via* the regulatory actions of the efflux pumps and cytochrome P450 enzymes. This review provides comprehensive references of the observed pharmacodynamic and pharmacokinetic drug interactions of *Scutellaria baicalensis* and its bioactives. We have elucidated the interaction with detailed mechanistic actions, identified the knowledge gaps for future research and potential clinical implications. Such knowledge is important for the practice of both conventional and complementary medicines, and it is essential to ensure the safe use of related herbal medicines. The review may be of great interest to practitioners, consumers, clinicians who require comprehensive information on the possible drug interactions with *S. baicalensis* and its bioactives.

1. Introduction

The practice of herbal medicine has a long history. It remains prevalent worldwide as a primary healthcare with an international market estimated at approximately US$84.5 billion by 2019 [1,2].

Most people consume herbs and hebral products as part of their cultural belief and under the impression that herbs are natural and safe. In addition, their easier availability makes it more accessible in comparison to the conventional medicines which requires a prescription from a general practitioner [3]. Herbs are often self-administered in combination with therapeutic drugs without the knowledge of health practitioners. It was reported that nearly 25% of the U.S. adults concurrently taking a prescription medication together with dietary supplements including herbal medicines [4]. This use pattern raises

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concerns of potential drug-herb interactions as there have been numerous clinical observations and associated adverse reactions. For instance, St. John's wort preparations are known to have clinically important interactions with many conventional drugs (*i.e.* antidepressants, lipid-lowering drugs, antiepileptics) that caused life-threating events in several cases [5]. *Salvia miltiorrhiza* (*Dan Shen*) and *Ginkgo biloba* (ginkgo) have demonstrated to affect hemostasis, which increases the risk of bleeding when used with warfarin [6]. *Panax ginseng* (ginseng) induced mania if co-administered with phenelzine [3]. On the other hand, some of the interactions may be therapeutically beneficial *via* synergism to enhance therapeutic effects or to reduce drug's side effects. A great effort has been made to develop combination therapies with synergistic effect to combat complex and challenging diseases such as cancer, diabetes and infectious diseases. For instance, cancer patients co-administered mushrooms and chemotherapy were less likely to have recurrent cancer, reduced side-effects and higher survival rate [7]. Thus, herb-drug interaction can be a double-edged sword in the clinical practice, which may result in adverse consequences or bring desired clinical outcomes.

Generally, herb-drug interactions occur through two mechanisms: pharmacodynamic (interacting with drug targets) and pharmacokinetic (changing the fate of drug in the body). Pharmacodynamic interactions can be synergistic (enhanced efficacy and/or reduced toxicity), additive (no interaction) or antagonistic effects (reduced efficacy and/or increased toxicity) [8,9]. Pharmacokinetic interactions are more frequently reported, involving modulation of absorption, distribution, metabolism and excretion of drugs, often *via* affecting drug transporters, *e.g.*, P-glycoprotein (P-gp) or biotransformation, cytochrome P450 (CYP450) enzymes. Herb-drug pharmacokinetic interactions raises more concerns and are of clinical significance as changes in drug's pharmacokinetic parameters (*i.e.* C_{max}, T_{max} and AUC) may result in unwanted or toxic effects, especially when the drug has a narrow therapeutic index (*e.g.*, digoxin, warfarin and phenytoin) [10].

Scutellariae Radix, the dry root of *Scutellaria baicalensis* Georgi, is one of the most frequently prescribed herbs in traditional medicine [11]. It is a perennial herb that is native to Siberia, Mongolia and parts of China and Korea. The dried root (known as *Huang Qin* in Chinese) has a long history of medicinal use for the treatment of inflammatory, respiratory and gastrointestinal ailments [12]. *Huang Qin* was first recorded back between 200 and 250 CE in *Shennong Bencaojing* (*The Classic of Herbal Medicine*) for bitter, cold, lung and liver problems [13]. *S. baicalensis* is currently listed in Chinese Pharmacopoeia (2020), European Pharmacopoeia (EP 9.0), and British Pharmacopoeia (BP 2018) [13,14]. A number of scientific studies have demonstrated a broad range of pharmacological actions of *S. baicalensis* including anti-inflammatory, anti-oxidant, anti-microbial, immunomodulatory, anti-cancer and anti-convulsant effects [15]. In a clinical setting, *S. baicalensis* is a common component of hundreds of multi-herb formulae [13], including popular *Xiao Chai Hu Tang* (Chinese), *Sho-saiko-to* (Japanese) and *Lung Fufang* preparations, used for palliative aid of liver viral diseases and cancer, particularly where treatment from conventional therapies was inadequate [13,16].

The pharmacological activities of *S. baicalensis* are attributed to its rich amount of flavonoids, including baicalein, baicalin, and wogonin. However, to date, there is no review on possible drug-herb interactions of *S. baicalensis* and its bioactive compounds with pharmaceutical drugs. Thus we aim to provide a comprehensive evaluation of drug-herb interaction of *S. baicalensis* and its identified bioactives with most up-to-date evidence in English and Chinese literature from the pharmacodynamic and pharmacokinetic perspectives. Extensive search was conducted using PubMed, Google Scholar and CNKI database, with key words including *S. baicalensis, Huang Qin,* and individual compounds identified from the herb, "drug interaction", "synergy" "CYP", "pharmacodynamic interaction", "pharmacokinetic interaction".

2. Phytochemistry of *S. baicalensis*

So far, over 100 compounds have been identified from *S. baicalensis* using various chemical analysis techniques. *S. baicalensis* contains a myriad of flavones, phenylethanoids, amino acids, sterols and essential oils. The main bioactive components in the dried roots are predominantly flavonoids. The major and representative flavonoids included baicalein, wogonoside, wogonin and baicalein which accounted for approximately 5.02% of the total weight of root [17]. Although amounts varied in crude materials, baicalin was found to be the most abundant compound, followed by wogonoside, wogonin, baicalein, wogonin 7-O-glucuronide [17–19]. High-performance liquid chromatography (HPLC) using UV detector methods were initially established and used to separate and identify major flavonoids in *S. baicalensis* including baicalin, baicalein, wogonin, wogonoside, oroxylin A, wogonin-7-glucuronide and oroxylin A 7-O-glucuronide [18,20,21]. A HPLC coupled photodiode array detection and electrospray ionisation tandem mass spectrometry (HPLC-DAD-ESI-MS) method was applied for the chemical fingerprint analysis of 15 samples of *S. baicalensis,* and 20 compounds were separated and their structures were elucidated [22]. Qiao et al. (2016) developed a quick and robust ultra-high performance liquid chromatography coupled with hybrid quadrupole orbitrap mass spectrometry (UHPLC/orbitrap-MS) method, and characterised more than 100 compounds in the *S. baicalensis* extract [23]. Other advanced techniques including infrared spectroscopy, nuclear magnetic resonance, high-speed counter-current chromatography, micellar electrokinetic chromatography and capillary electrophoresis were used for the detection of a wider range of compounds. A summary of the separation methods and identified compounds in *S. baicalensis* are listed in Appendix A.

3. Pharmacodynamic interactions

3.1. Anti-cancer drugs

Synergy is a novel and promising strategy in cancer therapy to identify and exploit combination therapy with conventional chemotherapies to provide a greater efficacy and sensitivity or minimise the adverse side effects and drug resistance [24]. Thus, enormous effort has been made to incorporate the concept of synergy into the development of combination drug treatment for cancers. However, consequential risks are also associated with the concomitant use, particularly for those chemotherapeutic agents with narrow therapeutic window or high toxicity. As such, understanding the molecular actions of bioactives is important in understanding and predicting any potential risks [25].

3.1.1. Interaction with cisplatin

Cisplatin is a platinum compound used as a first line chemotherapy drug for ovarian cancer, testicular cancer, bladder cancer, head and neck cancer, lung cancer, and brain tumours, *etc.* It acts by forming DNA-platinum adducts, which leads to p53-mediated DNA damage, cell cycle arrest and cell death [26,27]. A major drawback in the long term use of cisplatin is the drug resistance due to decreased intracellular concentration, diminished drug uptake, and increased efflux attributed to a variety of cellular self-defence systems [28,29]. Several studies have identified that the down-regulation of activated epidermal growth factor receptor (EGFR)-dependent protein kinase B (PKB or known as Akt)/-phosphoinositide 3-kinase (PI3K) and extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) signalling pathways can overcome cisplatin resistance and increase the anti-cancer effect [30,31]. Reactive oxygen species (ROS) and calcium mediated apoptosis pathways are also essential in the drug sensitivity of cisplatin [32].

Several studies showed that the concomitant use of *S. baicalensis* extract and cisplatin to treat ovarian cancer enhanced efficacy, sensitivity, and reduced side effects of cisplatin [33–36]. Interestingly, the

enhanced activity of *S. baicalensis* acted through alternate molecular targets from that of cisplatin. For example, an ethanol extract of *S. baicalensis* was tested with or without cisplatin in ovarian cancer cell line and cisplatin resistant cell line, and the combination strengthened the anti-cancer effect of cisplatin in both cell lines, especially the resistant cell line, highlighting the benefits of combinational use against chemo-resistance. Moreover, the combination-induced apoptosis was induced *via* autophagy by upregulated expressions of *Atg5* and *Atg12*, which was different from the action of cisplatin on apoptosis *via* the p53 pathway [33]. *S. baicalensis* also sensitised the effect of cisplatin *via* targeting hypoxia-inducible factor 1-α (HIF-1α) [34]. Hussain et al. (2018) showed that the aqueous extract of *S. baicalensis* attenuated HIF-1α levels in ovarian cancer cells by down-regulating the PI3K/AKt and mitogen-activated protein kinases (MEK)/ERK pathways, and thus further reduced the cell growth in four cisplatin sensitive and resistant ovarian cancer cell lines [36]. The anti-oxidant activity of *S. baicalensis* may help to reduce the toxicity of cisplatin. The co-administration of *S. baicalensis* aqueous extract (1 mg/kg and 3 mg/kg, i.p.) and cisplatin showed a significant decrease in cisplatin induced-toxicity compared to cisplatin alone in rats *via* reduced pica and kaolin consumption induced by cisplatin. Such anti-emetic effect was associated with the anti-oxidant activity of *S. baicalensis* [35].

Studies into the interactions between the bioactive compounds in *S. baicalensis* and cisplatin for anti-apoptotic activity revealed diverse molecular actions to strengthen the apoptotic action of cisplatin and overcome its drug resistance. In particular, apigenin and chrysin were found to amplify the signal of cisplatin on the same p53 pathway attributed to the activation of ERK1/2 and MAPK, resulting in a significant cleavage of caspase-3 and caspase-9 and eventually cell death [37,38]. As a major bioactive compound, baicalin (8 μg/mL) attenuated cisplatin (4 μg/mL) resistance in lung cancer cells (A549 and A459 cisplatin-resistant cell lines) with a significantly higher inhibitory rate of cell invasion and proliferation. The elevated expression of microtubule affinity-regulating kinase 2 (MARK2) and p-Akt in A450 cisplatin-resistant cells was markedly lower after the co-treatment of baicalin, highlighting that the decreased cisplatin resistance was associated with the down-regulation of PI3K/Akt pathway. This was consistent with studies that linked the inhibition of PI3K/Akt activation and phosphorylation to reduced cisplatin resistance of cancer cells [39,40]. The enhanced apoptotic activity of the baicalin and cisplatin combination was verified on HepG2.0 liver cancer cells, whereby synergistic interaction was detected with 1–4 mg/mL baicalin plus 0.5–4.0 μg/mL cisplatin [41]. Another major flavonoid in *S. baicalensis*, baicalein, reduced the drug resistance of cisplatin on A549 lung cancer cells by down-regulating PI3K/Akt/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway [42]. Baicalein also increased the early and late apoptosis rate on cisplatin treated MCF-7 breast cancer cells [43]. Scutellarin was found to sensitise the anti-cancer effect of cisplatin on ovarian cancer cells. Although the signalling pathway was not fully investigated, the complex of scutellarin and cisplatin exhibited significant conformational change to the DNA, resulting in higher expressions of p53 and caspase-3 [27]. Wogonin sensitised cisplatin-induced apoptosis in both A549 cells and HeLa cells by promoted expression of intracellular ROS which contributed substantially to the enhanced apoptosis [44].

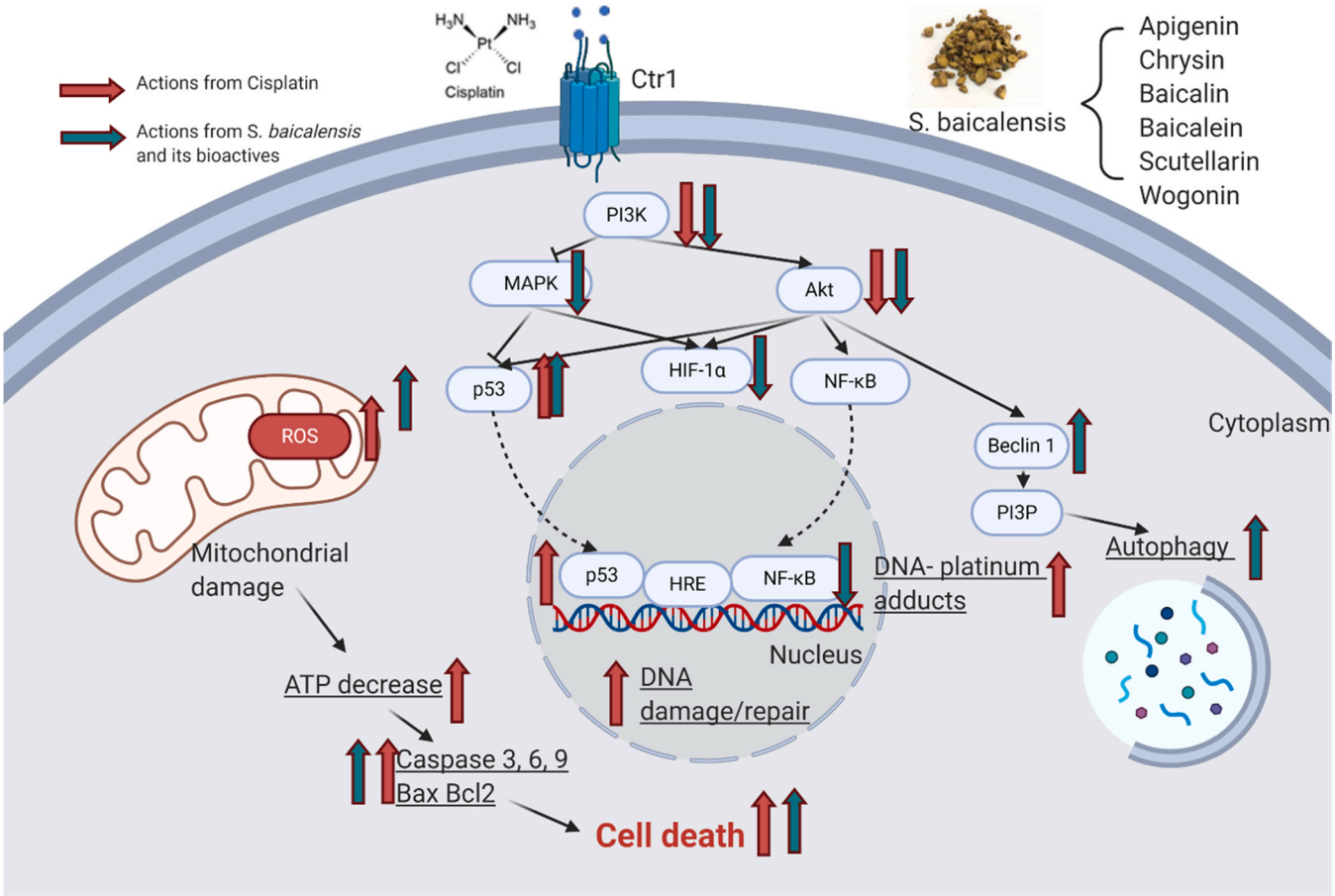

Fig. 1. Interactions of cisplatin with *S. baicalensis* and its bioactives including apigenin, chrysin, baicalein, baicalein, scutellarin and wogonin at the molecular level, which led to enhanced cell death, autophagy and reduced drug resistance. Green arrow represents the molecular actions of *S. baicalensis* and its bioactives, red arrow represents the molecular actions of cisplatin. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Therefore, cisplatin combined with *S. baicalensis* and its various active compounds may be a potential therapeutic approach in overcoming drug resistance and reducing the undesirable side effects. However, clinical studies are warranted to confirm the possible beneficial therapeutic outcome of the combined therapy. Fig. 1 summarises the drug-herb interactions between *S. baicalensis* and its bioactives with cisplatin.

3.1.2. Interaction with fluorouracil

5-Fluorouracil (5-FU) is an anti-metabolite chemotherapy drug that is extensively used for various cancers. However, the drug resistance and cytotoxicity from its metabolites remain a major challenge for its clinical use [45]. After enter the cell, the metabolites of 5-FU are formed and attached to thymidylate synthase which leads to DNA damage *via* the activation of p53 pathway [45]. It also provokes intracellular oxidative stress characterised by the elevated levels of ROS that is known to cause major side effects such as cardiotoxicity [46].

Bioactives from *S. baicalensis* were reported to potentiate the anti-cancer activity and increase the sensitivity of 5-FU *via* strengthening the apoptotic related pathways or elevating mitochondrial ROS activity. Notably, the overall effect of *S. baicalensis* extracts with 5-FU remains lacking, and whether or not the increased oxidative stress would exacerbate the cardiotoxicity of 5-Fu is yet to be determined.

Oroxylin A and scutellarin were shown to promote the apoptotic effect of 5-FU by strengthening the action of 5-FU on the p53 pathway. Oroxylin A combined with 5-FU presented a synergistic effect (combination index<1) in inducing cell death of HepG2 cells when the inhibitory rate was higher than 7.5%. When combined, oroxylin A enhanced the signalling transduction on p53 by 5-Fu, with decreased expressions of apoptotic-inhibitory proteins cyclooxygenase-2 (COX-2), B-cell lymphoma 2 (Bcl-2), and procaspase 3 [47]. Chan et al. (2009) showed that scutellarin potentiated the effect of 5-FU by inducing apoptosis in (p53++) HCT116 human colon cancer cells through the upregulation of p53 pathway and caspase-6 expression [48].

Apigenin enhanced the apoptotic action of 5-FU by inducing oxidative stress. An *in vivo* study found that coadministration for 5 consecutive days of apigenin (20 mg/kg) intensified the anti-tumour effect of 5-FU (20 mg/kg) by inhibiting the growth of hepatocellular carcinoma xenograft tumours [49]. The mechanistic study on human breast cancer MDA-MB-453 cells revealed that apigenin augmented the action of 5-FU on ROS which led to a decreased activity of the mitochondrial membrane potential (DΨm) [49]. Another *in vivo* study reported that apigenin and 5-FU achieved a greater effect in reducing tumour size than individual treatment in Swiss albino mice transplanted with Ehrlich ascites carcinoma cells, which was associated with an increased intracellular ROS level and decreased level of glutathione [50].

The synergistic effect of bioactives of *S. baicalensis* with 5-FU may also involve the regulation of Akt pathway. For instance, apigenin and 5-FU at concentrations > 10 μM exerted an enhanced pro-apoptotic effect *via* the inhibition of Akt expression on breast cancer cells [51,52]. Wogonin was found to decrease the cell survival rate when used with 5-FU on SMMC-7721 hepatocellular carcinoma (HCC) cells with high COX-2 expression, and this was associated with the down-regulation of the PI3K/Akt signalling pathway [53]. Additionally, over-expression and high DNA binding activity of the transcription factor NF-κB had been identified in 5-FU resistant cell lines. Thus, blocking the NF-κB pathway was shown to sensitise cancer cells to 5-FU. Wogonin was

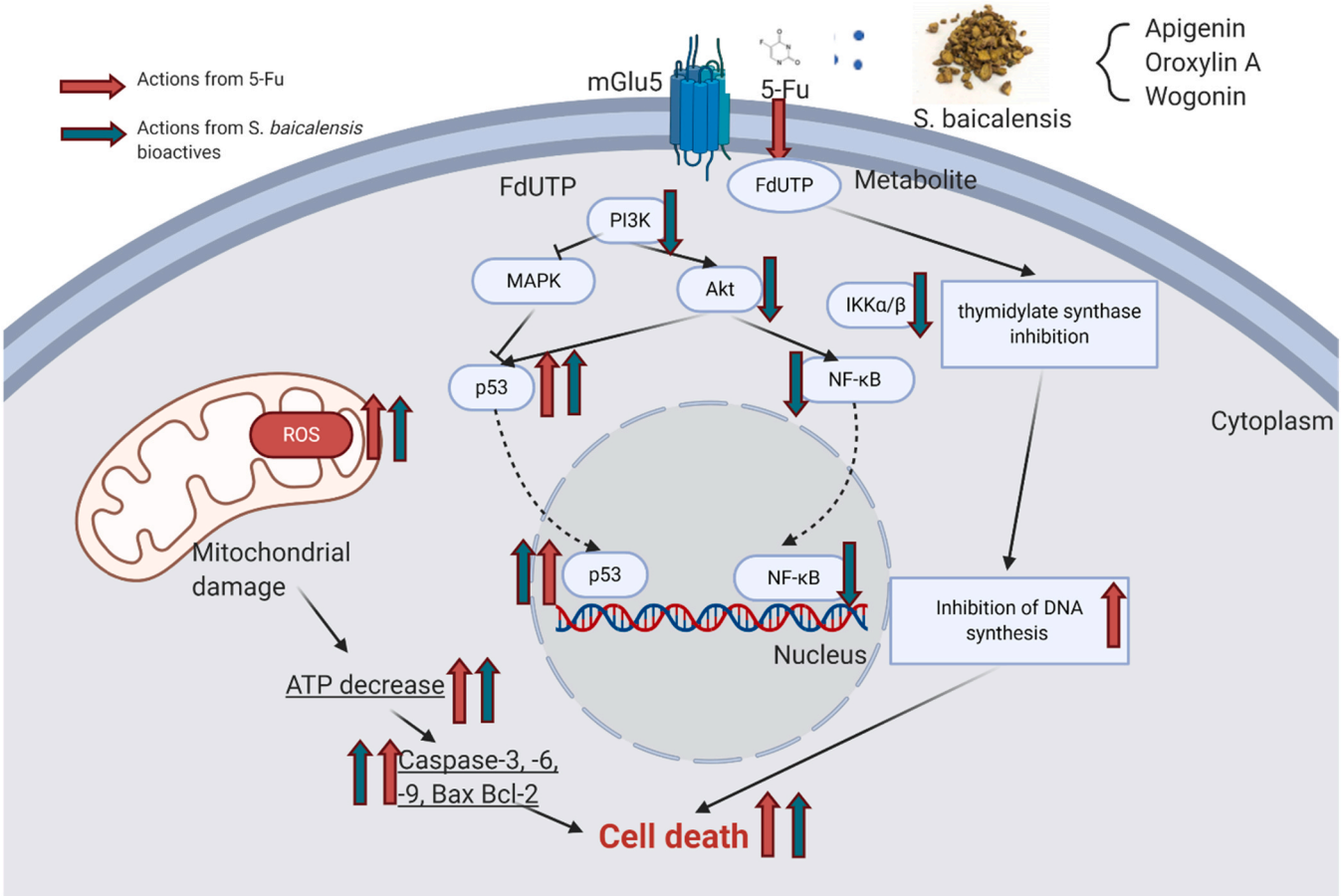

Fig. 2. Interactions of 5-FU with *S. baicalensis* bioactives including apigenin, oroxylin A and wogonin at the molecular level which led to enhanced cell death and reduced drug resistance. Green arrow represents the molecular actions of *S. baicalensis* bioactives, green arrow represents the molecular actions of 5-FU. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

found to down-regulate the phosphorylation of I-κB and suppressed NF-κB translocation to the nucleus before modulating the transcription of downstream genes, and thus the combined use of wogonin and 5-FU enhanced apoptosis of gastric cancer cells [54]. Fig. 2 summarises the drug-herb interactions between *S. baicalensis* and its bioactives with 5-FU.

3.1.3. Interaction with paclitaxel

Pal et al. (2017) showed that combined nanotised apigenin (GO-NA) with paclitaxel enhanced the anti-proliferative effect of paclitaxel in ovarian cancer cells, which was associated with promoted ROS accumulation and mitochondrial depolarisation evoked cell apoptosis [55]. A similar synergistic effect of apigenin and paclitaxel was reported in HeLa cells on apoptosis *via* an over-expression of ROS [56]. These findings suggested that apigenin may synergistically interact with paclitaxel leading to an enhanced anti-cancer activity of paclitaxel.

3.1.4. Other chemotherapy drugs

A number of studies investigated the interactions of *S. baicalensis* and its bioactive compounds with other chemotherapy drugs as summarised in Table 1. In general, *S. baicalensis* aqueous extract and its bioactives exhibited beneficial synergistic interactions with chemotherapy drugs by enhancing the efficacy and sensitivity. The mechanistic actions were mainly associated with strengthening the p53-induced DNA damage, inducing autophagy and downregulation of PI3K/Akt, MAPK and NFκB signalling pathways. However, further study is needed to elucidate how individual components contribute to the overall effect of *S. baicalensis*. Besides, most of the findings were pre-clinical studies, and their clinical implications have yet to be investigated.

3.2. Anti-diabetic drugs

It is well recognised that the management of type II diabetes and related complications requires a long-term treatment to achieve multiple goals. Metformin has long been used as a first line drug for the treatment of type II diabetes for its powerful anti-hyperglycaemic properties and other related bioactivities including alleviation of endothelial dysfunction, reducing oxidative stress, insulin resistance and lipid profiles, and promoting fat redistribution [75]. Rosiglitazone is a third line anti-diabetic drug used as an insulin sensitiser. However, it is associated with risks including increased cardiac complications and stroke which limit its efficacy [76].

3.2.1. Interactions with metformin

Several studies showed that *S. baicalensis* and its bioactive compounds enhanced the anti-diabetic activities of metformin mainly through the anti-oxidant activity. An *in vivo* study suggested that the co-administration of metformin (500 mg/kg) and *S. baicalensis* ethanol extract (400 mg/kg) resulted in significant elevation of plasma and pancreatic insulin levels and reduction of plasma, hepatic triglycerides and cholesterol levels in streptozotocin-induced diabetic rats. The effect was associated with a reduced level of oxidative stress attributed to elevated activities of anti-oxidant enzymes including superoxide dismutase, catalase and glutathione peroxidase [77]. The same team later showed that baicalin (120 mg/kg) contributed mostly to the anti-oxidant activity of *S. baicalensis* which mitigated oxidative stress and enhanced the anti-diabetic effect of metformin (500 mg/kg) in streptozotocin-induced diabetic rats [78]. Furthermore, baicalin and metformin showed a positive interaction in treating dehydroepiandrosterone-induced polycystic ovarian syndrome in rats. After 14 days' injection of metformin (270 mg/kg) with baicalin (50 mg/kg), the combined treatment restored the sex hormone levels including luteinising hormone, follicle stimulating hormone and testosterone, and inhibited apoptosis of ovarian granulosa cells [79]. In addition, an aqueous extract of *S. baicalensis* enhanced the effect of metformin in reducing the cholesterol level *via* the excretion of bile acid through faeces in Otsuka Long Evans Tokushima Fatty rats. The mechanism was associated with farnesoid X receptor signalling pathway which increased glycogen synthesis, decreased glycolysis and protected beta cell function [80]. Interestingly, the positive interaction of metformin and *S. baicalensis* involves both pharmacodynamic and pharmacokinetic mechanism, of which the pharmacokinetic interaction will be discussed in Section 4.1.

3.2.2. Interactions with rosiglitazone

Two *in vivo* studies showed that baicalin combined with rosiglitazone significantly reduced the blood glucose level in alloxan-induced diabetic mice. The activity of superoxide dismutase was enhanced and the level of malondialdehyde was reduced, indicating that baicalin may assist rosiglitazone in preventing and treating peripheral neuropathy in diabetic mice by lowering intracellular oxidative stress [81,82].

3.3. Anti-microbial drugs

The wide use of antibiotics against bacterial infections has led to the emergence of multi-drug resistant pathogens such as tuberculosis and methicillin-resistant *Staphylococcus aureus* (MRSA). The main challenge in combating the evolution of drug resistance is to develop new therapies or improve current therapies. The screening and identification of novel anti-microbial agents from natural compounds are of a significant research interest. Presently, it is debatable whether or not the adoption of synergistic combination therapy with an increased selectivity and efficacy would overcome multi-drug resistance [83]. There have been numerous studies, most preclinical, on the anti-microbial activity of *S. baicalensis* and its bioactives, although the clinical efficacy of these bioactives is still to be determined. Nevertheless, the knowledge regarding the mechanistic actions of these bioactives against microorganisms can help predicate potential interactions when they are used in combination with conventional anti-microbial drugs [84].

3.3.1. Interactions with antibiotics

Studies have found that *S. baicalensis* and its bioactives positively interacted with a variety of antibiotics by enhancing the overall anti-bacterial effects and reducing drug resistance. The main contributing bioactive compounds were baicalein and baicalin.

A biofilm is a thick layer of prokaryotic organisms that helps build the resistance against antibiotics and immune system [85]. Although an aqueous extract of *S. baicalensis* alone did not exhibit any anti-bacterial effect, its combination with levofloxacin significantly reduced bacterial survival in the biofilm of *Pseudomonas aeruginosa* compared with levofloxacin alone [86]. Thus, *S. baicalensis* extract could be potentially useful in improving the efficacy of antibiotics to prevent drug resistance and chronic bacterial infection.

Numerous studies have identified baicalein and baicalin as the key compounds that contribute mostly to the anti-bacterial effect of *S. baicalensis*. Qiu et al. (2016) investigated five flavones from *S. baicalensis* including baicalein, baicalin, wogonin, wogonoside and oroxylin A in combination with cefazolin against methicillin-resistant *S. aureus,* and found that baicalein and baicalin significantly increased the anti-bacterial effect of cefazolin compared to other flavones, with baicalein-cefazolin having the lowest minimum inhibitory concentration (MIC), followed by baicalin-cefazolin [87].

The beneficial synergistic effects of baicalein have been studied with many other antibiotics against oral bacteria, (methicillin-resistant) *S. aureus* (MRSA) strains and vancomycin-resistant *Enterococcus*. For instance, baicalein synergistically enhanced the antibacterial effect of ampicillin, gentamicin [88], ciprofloxacin [89], penicillins [90] and gentamicin [91] as determined by MIC and fractional inhibitory concentration (FIC) values. The mechanisms behind the synergy against various bacterial appear to be versatile. In particular, *S. aureus* SA-1199B developed resistance to ciprofloxacin by overexpressing the NorA efflux pump. Baicalein restored the antibacterial action of

Table 1
Interaction of *S. baicalensis* bioactives with other chemotherapy drugs and its associated molecular mechanisms.

Bioactive compounds	Chemotherapy drugs	Study type	Cancer type	Key results	Molecular mechanisms	References
S. baicalensis aqueous extract	Cyclophosphamide	*In vivo*	Lewis lung carcinoma	The combined therapy showed a significant suppressing effect against cancer starting from course treatment of day 22.	NA	[57]
Apigenin	Cetuximab	*In vitro* and *in vivo*	Glioblastoma	The combination produced a greater pro-apoptosis effect.	Enhanced the capacity of cetuximab to inactivate EGFR signalling pathway	[58]
Apigenin	Gemcitabine	*In vitro* and *in vivo*	Pancreatic cancer	Apigenin enhanced anti-tumour efficacy of gemcitabine.	Down-regulated NF-κB activity with the suppression of Akt activation	[59]
Apigenin	Gefitinib	*In vitro*	Non-small cell lung cancer	The combination inhibited mutation, induced G0/G1 cell cycle arrest, metastasis and apoptosis.	Damaged glucose utilisation and thus suppressed cell growth and malignant behaviour; inhibited AMPK pathway and autophagy flux, leading to augmented H1975 apoptotic cell death	[60]
Apigenin	Gemcitabine	*In vitro*	Human pancreatic cancer cells	Pre-treatment for 24 h with low concentration of apigenin (15 μM) followed by the addition of gemcitabine (10 μM) for 36 h exhibited higher inhibitory effects on cell proliferation.	NA	[61]
Apigenin	Vemurafenib (PLX4032)	*In vitro*	Thyroid carcinoma	PLX4032 augmented apigenin-induced cytotoxicity in ATC cells harbouring BRAFV600E.	Suppression of Akt pathway	[62]
Aceteoside	Temozolomide	*In vitro*	Glioblastoma	The combination exhibited synergistic effects in glioblastoma therapy.	Increased phosphorylated p53 and up-regulated MAPK induced autophagy and apoptosis	[63]
Baicalein	Dexamethasone	*In vitro*	Myeloma	The combination consistently suppressed cell growth.	The activation of peroxisome proliferator-activated receptors β which suppressed the NF-κB activity.	[64]
Baicalein	Gemcitabine	*In vitro* and *in vivo*	Pancreatic cancer	The combination inhibited the growth of the human CFPAC-1 pancreatic cancer cell line and xenografts in nude mice.	Altered expression levels of pro-apoptotic and anti-apoptotic molecules including Bcl-2, bcl-2-like protein 4 (Bax), survivin, poly-ADP ribose polymerase (PARP) and caspase-3	[65]
Baicalein	Gemcitabine and Docetaxel	*In vitro*	Pancreatic cancer	Synergism of baicalein with gemcitabine or docetaxel in inducing apoptosis of pancreatic cancer cells	Arrested pancreatic cancer cells in the S phase; associated with caspase-3/PARP signalling pathway	[66]
Baicalein	10-Hydroxy camptothecin (HCPT)	*In vitro* and *in vivo*	Gastric, breast and liver cancer	Baicalein at non-toxic doses prominently enhanced the anti-cancer activities of HCPT.	Up-regulated p53 to induce cell apoptosis and cell cycle arrest	[67]
Baicalein	Lenalidomide	*In vitro*	Myeloma	The combination synergistically induced cell apoptosis.	Up-regulated of CRBN mRNA expression and consequent cereblon protein expression, which inhibited NFκB activation and led to cell apoptosis	[68]
Baicalin	Oxaliplatin	*In vitro*	Gastric cancer	The combination exhibited an enhanced activity in the growth inhibition and apoptosis rate on human gastric cancer cell line SGC-7901.	NA	[69]
Luteolin	Gemcitabine	*In vitro*	Human pancreatic cancer cells	Pre-treatment for 24 h with 13 μM of luteolin, and gemcitabine for 36 h was optimal to inhibit cell proliferation.	Inhibition of the Glycogen synthase kinase-3β (GSK-3β)/NF-κB signalling pathway leading to apoptosis	[61]
Scutellarin	Bleomycin	*In vitro* and *in vivo*	Hepato-carcinoma	The combination prolonged the survival time of mice bearing H22 ascites tumour, alleviated bleomycin-induced pulmonary fibrosis, reduced inflammatory cytokines and increased apoptotic rate.	Increased the protein expression of p53 and gene expression of miR-29b, and decreased the expression of Transforming growth factor beta 1 (TGF-β1)	[70]
Wogonin	Doxorubicin	*In vitro* and *in vivo*	Breast cancer	Wogonin increased the doxorubicin sensitivity in breast cancer cells.	Regulation of insulin-like growth factor 1 receptor (IGF-1R)/AKT signalling pathway	[71]
Wogonin	Icotinib	*In vitro*	Lung cancer	The combination produced a more pronounced growth inhibition and significantly increased the percentage of early apoptotic cells and cleavage of caspase-3.	Up-regulated the levels of phosphorylated mammalian target of rapamycin (mTOR) which enhanced the effects on apoptosis and autophagy	[72]
Wogonin	Oxaliplatin	*In vitro* and *in vivo*	Gastric cancer	The combination resulted in strong synergistic inhibition of the cell viability in BGC-823 cells and in a zebrafish xenograft model.	Increased phosphorylation of c-Jun N-terminal kinase (JNK), induced autophagy, suppressed the phosphorylation of ULK1, loss of mitochondrial transmembrane potential, and activation of mitochondrial apoptotic pathways	[73]
Wogonin	Sorafenib	*In vitro*	Hepato-cellular carcinoma	The combination exhibited an enhanced cell death.	Effectively inhibited sorafenib-induced autophagy which enhanced apoptosis rate	[74]

ciprofloxacin against MRSA strains *via* the reduction of over-expressed NorA efflux pump which led to the synergistically enhanced anti-bacterial effect *in vitro* [89]. A similar effect was found in the synergistic interaction of baicalein-tetracycline in *Escherichia coli,* of which baicalein strongly inhibited the efflux of tetracycline with membrane vesicles, contributing to significantly lower MIC values [92]. In addition, Cai et al. (2016) suggested that the synergy of baicalein and cefotaxime against *Klebsiella pneumoniae* was associated with the inhibition of CTX-M-1 mRNA expression and the dissemination of the resistance gene, and thus reduced the drug cefotaxime resistance [93].

Baicalin has been shown to enhance the anti-bacterial effect of ceftazidime, meropenem, norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, meropenem and sulbactam-cefoperazone on *P. aeruginosa* and/or its biofilm formation as evidenced by further reduced MIC values [94–99]. In addition, baicalin enhanced the effect of amoxicillin [100], b-Lactam antibiotics [101], ciprofloxacin [102] and azithromycin [103] in reducing the bacterial colony of helicobacter pylori, benzylpenicillin against MRSA and penicillin resistant *S. aureus*, *E. coli* and *Staphylococcus saprophyticus*, respectively. However, the mechanistic action of the observed synergy is yet to be investigated.

3.3.2. Interactions with anti-fungal drugs

Amphotericin B is a gold standard anti-fungal drug albeit with some severe side effects. Fu et al. (2011) reported that the combination of baicalein and amphotericin B accelerated apoptosis accompanied with increased ROS and caspase activity *via* the corresponding increase of gene CaMCA1 in *Candida. albicans* [104]. In addition, acteoside combined with amphotericin B also resulted in further reduced minimum biofilm reduction and enhanced fungicidal effect on *C. albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus*. The potentiation was likely due to the subinhibitory concentrations of amphotericin B that facilitated the uptake of acetoside which resulted in increased of fungal cell death [105].

Other studies have investigated the synergistic interaction of baicalin and fluconazole against *C. albicans* biofilms, and found that the combination further down-regulated the RNA expression of agglutinin-like sequence (ALS) genes including ALS1, ALS3, EAP1, SUN41 and CSH1, which inhibited the adherence of *Candida* sp. to host tissues and cells [106]. The synergy was also related to the down-regulation of Ras/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signalling pathway, which inhibited the morphological transition from yeast to hyphae and thus reduced the virulence of *Candida* sp. [107].

3.3.3. Interactions with anti-viral drugs

The synergistic interaction of baicalin and ribavirin (antiviral drug) was investigated in influenza A (H9N2, H5N1, H1N1) infected MDCK cell lines. By comparing individual and combined EC_{50} values, it was found that the combined ribavirin and baicalin exhibited strong synergy in inhibiting viral replication of H9N2, but caused additive effects against H5N1 and H1N1 *in vitro*. The combination enhanced the protection of mice against lethal dose of H1N1 infection with 100% survival rate compared to 60% and 50% survival rate in ribavirin and baicalin monotherapy groups, respectively [108].

Collectively, there is a great potential for *S. baicalensis* and its bioactives to be used in combination with anti-microbials as synergistic drug therapy to reduce the undesirable side effects and multi-drug resistance of anti-microbials in human and animals. However, further studies are needed to address the stability, selectivity and bioavailability of individual bioactives to confirm the beneficial interactions with pharmacodynamic and/or pharmacokinetic evidence clinically, including if any adverse interactions. In this regards, animal models with engineered strains lacking the particular resistant genotype can be used to precisely define the pharmacokinetic and pharmacodynamic targets followed by stringent human studies to verify the optimal ratio and dosing regimens to maintain efficacy with minimal toxicological profiles [109].

3.4. Other pharmaceutical drugs

3.4.1. Levodopa (drug for Parkinson's disease)

Baicalein (10 mg/kg) improved the effect of levodopa (25 mg/kg) in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonism in old C57BL/6 mice, with significant improvements in gait function, dynamic gait function, restoration of walking speed and gait coordination in the combined treatment in comparison to that of the same dosage of baicalein and levodopa alone. However, such augmented effect was not detected in the baicalein (10 mg/kg) combined with high dose of levodopa (50 mg/kg). Tissue processing and immunohistochemistry assays revealed that the combined treatment allowed a higher number of viable dopamine neurons to survive. Such effect can be attributed to baicalein which exerted a neurotrophic effect by suppressing caspase-3 and inflammation *via* the down-regulation of tumor necrosis factor-α expression [110].

3.4.2. Labetalol hydrochloride (anti-epileptic drug)

A randomised controlled trial compared the therapeutic effect of combined baicalin capsule and labetalol hydrochloride injection to that of labetalol hydrochloride injection alone on severe preeclampsia. A total of 78 women in pregnancy at 30.86 ± 1.52 weeks were recruited, who were diagnosed with severe preeclampsia but without kidney diseases, chronic hypertension and any other haematological system diseases. After 7 days of treatments with labetalol hydrochloride (150 mg/200 mL, 1 time/day) in glucose injection (5%) with or without baicalin capsule (0.5 g/time, 3 times/day), the combined treatment showed a greater improvement in the clinical outcomes than using labetalol hydrochloride alone, with decreased systolic pressure and diastolic pressure, lowered urine protein, restored kidney function, and reduced incidence of complications [111]. However, the mechanisms involved are not clear.

3.4.3. Mefenamic acid (nonsteroidal anti-inflammatory drug)

It was reported that the co-administration of *S. baicalensis* extract (300 mg/kg, twice daily) and mefenamic acid (40 mg/kg, daily) in rats for 5 days potentiated the inhibition of prostaglandin E_2 in murine macrophage RAW264.7 cells compared to that of the individual administration. *S. baicalensis* extract also prolonged the COX-2 inhibitory effect, alleviated the gross ulcer index and sum of lesion length of mefenamic acid, suggesting the co-administration enhanced the anti-inflammatory effects while relieving the stomach adverse effects of mefenamic acid. *S. baicalensis* did not alter the pharmacokinetic parameters of mefenamic acid in Sprague-Dawley rats, and thus the combined administration may not affect the drug concentration of mefenmic acid in the body (information also shown in Table 2) [112].

3.4.4. Acetaminophen (analgesics and antipyretics drug)

Acetaminophen (APAP) is one of the most widely used anti-pyretic and analgesic drugs. However, APAP overdose can cause severe liver injury and even acute liver failure which limits its efficacy in clinics. The liver injury of APAP is mainly attributed to oxidative stress [113] and inflammation response [114,115]. Zhou et al. (2019) [116] established an APAP-induced liver injury model by giving the infusion of APAP (350 mg/kg) to mice, and liver injury was manifested as reduced body weight, and elevated serum alanine transaminase and aspartate aminotransferase levels. The pre-treatment of baicalein (100 mg/kg) significantly alleviated oxidative stress, cytokine release in serum and liver in a dose-dependent manner, and modulated autophagy-related proteins in response to APAP overdose. The mechanistic action of baicalein against APAP-induced cytotoxicity is versatile, involving MAPK, janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3), and AKT/mTOR signalling pathways [116]. A diagram depicting the mechanistic pathway of baicalein in protecting the liver from APAP overdose is depicted in Fig. 3. In addition, luteolin was found to strongly block APAP sulfation by inhibiting CYP1A2 and CYP3A4

Table 2
Pharmacokinetics herb-drug interaction of *S. baicalensis* and its bioactives.

Herb	Dose and route of compound	Drugs	Dose and route of drugs	Drug class	Subjects	Pharmacokinetics consequences of the drug	Molecular mechanisms	References
S. baicalensis	2.4 g/kg, i.g.	Tolbutamide	50 mg/kg, i.g.	Antidiabetic	Female Rats	↑AUC_{0-t}	NA	[133]
S. baicalensis	2.4 g/kg, i.g.	Tolbutamide	50 mg/kg, i.g.	Antidiabetic	Male Rats	No interaction	NA	[133]
S. baicalensis	200 mg/kg, 28 days, oral	Metformin	100 mg/kg, 28 days, oral	Antidiabetic	Rats	↓biliary excretion of metformin, ↑ metformin concentration in the liver	↓mRNA level of hepatic toxin extrusion protein 1	[141]
S. baicalensis	300 mg/kg, twice daily, 5 days, oral	Mefenamic acid	40 mg/kg, daily, 5 days, oral	Nonsteroidal anti-inflammatory drugs	Sprague-Dawley rats	No interaction on C_{max}, AUC_{0-24}, T_{max} or clearance.	NA	[112]
S. baicalensis	1.0 g/kg, oral	Methotrexate	5.0 mg/kg, oral	Chemotherapy	Rats	↑C_{max}, AUC_{0-30}, AUC_{0-280} and mean residence time (MRT)	↓BCRP and MRP2 mediated efflux transport	[131]
S. baicalensis	2.0 g/kg, oral	Methotrexate	5.0 mg/kg, oral	Chemotherapy	Rats	↑AUC_{0-2880} and MRT ↓AUC_{0-30}	↓BCRP and MRP2 mediated efflux transport	[131]
S. baicalensis	1 g/kg and 2 g/kg, i.g.	Cyclosporine	1.25 mg/kg, i.g.	Immunosuppressants	Rats	↓C_{max} and AUC_{0-540}	NA	[132]
Compounds	**Dose and route of compound**	**Drugs**	**Dose and route of drugs**	**Drug class**	**Subjects**	**Pharmacokinetics consequences of the drug**	**Molecular mechanisms**	**References**
Apigenin	250 mg/kg, i.g.	Venlafaxine	20 mg/kg, i.g.	Anti-depressant	SD rats	↑AUC_{0-t} and C_{max}	↓metabolism rate	[149]
Baicalein	1.5 and 6 mg/kg, i.g.	Doxorubicin	50 mg/kg, i.g.; 10 mg/kg, i.v.	Chemotherapy	Rats	↑AUC_{0-t} and C_{max}, ↑absolute and relative bioavailability	↓P-gp and the CYP3A subfamily in the intestine and/or liver	[124]
Baicalein	2 and 8 mg/kg	Nimodipine	orally (12 mg/kg)	Calcium channel blockers	Rats	↑AUC_{0-t} and C_{max}	↓CYP3A4 and P-gp	[143]
Baicalein	20, 40, 80 mg/kg/day for 5 consecutive days, i.g.	Ciprofloxacin	20 mg/kg, i.g.	Quinolone antibiotics	Rats	↓C_{max}, AUC_{0-480} min and relative bioavailability	↑P-gp	[125]
Baicalein	3 and 10 mg/kg, i.g.	Tamoxifen	10 mg/kg, i.g.	Chemotherapy	Rats	↑AUC, C_{max} ↑absolute bioavailability	↓metabolism ↓P-gp	[126]
Baicalein	50 mg/kg/day, 7 days, i.g.	Florfenicol	25 mg/kg, i.g.	Antibiotics	Rats	↑$AUC_{0-24\ h}$, C_{max}, $MRT_{0-24\ h}$, ↓reduced CLz and Vz	NA	[150]
Baicalein	112 μmol/kg, oral	Cyclosporine	112 μM/kg, i.g., i.g.	Immunosuppressants	Rats	↑C_{max} and AUC_{0-540}	NA	[132]
Baicalin	50 mg, 14 days, oral	Rosuvastatin	20 mg, oral	Statin	Healthy adult men who were CYP2C9*1/*1 with different OATP1B1 haplotypes	↓$AUC_{0-72\ h}$ and $AUC_{0-\infty}$	↑ organic anion transporter family member 1B1 and thus ↑ uptake into the liver	[127]
Baicalin	80 mg/kg, i.v., 7 days	Cyclosporine	80 mg/kg, i.v., 7 days	Immunosuppressants	Rats	No interaction	NA	[142]
Baicalin	80 mg/kg, 7 days, i.g.	Cyclosporine	80 mg/kg, 7 days, i.g.	Immunosuppressants	Rats	↓Cmax, AUC_{0-t} and $AUC_{0-\infty}$	↑P-gp ↓the absorption in intestine *in vitro*	[142]
Baicalin	0.6 and 0.2 g/kg, i.g.	Nifedipine	10 mg/kg	Calcium channel blockers	Rats	↑AUC_{0-t} and bioavailability ↑C_{max}, ↓CLz and Vz	↓CYP3A	[128]
Baicalin	200 mg/kg, 7 days, i.g.	Fexofenadine	30 mg/kg	Antihistamines	Rats	↑Cmax and AUC_{0-12}	↓P-gp	[129]
Baicalin	112 μM/kg, oral	Cyclosporine	112 μM/kg, i.g.	Immunosuppressants	Rats	↑C_{max} and AUC_{0-540}	NA	[132]
Baicalin	100 mg/kg, 10 days	Norfloxacin	50 mg/kg	Antibiotics	*Fenneropenaeus chinensis*	Faster clearance ↓$t_{1/2}$.	↑CYP450	[130]
Baicalin	200 mg/kg/10 mL corn oil, oral	Caffeine	1 mg/kg, oral	Psychoactive	Rats	No interaction	NA	[151]

(*continued on next page*)

Table 2 (*continued*)

Herb	Dose and route of compound	Drugs	Dose and route of drugs	Drug class	Subjects	Pharmacokinetics consequences of the drug	Molecular mechanisms	References
Chrysin	100 mg/kg/ 2 mL corn Oil, i.g.	Caffeine	5 mg/kg, i.g.	Psychoactive	Rats	No interaction on metabolism	Chrysin metabolites rapidly and almost no bioavailability No inhibitory effects on CYP enzymes responsible for caffeine metabolism	[152]
Luteolin	4 and 10 mg/ kg, iv bolus doses	γ-hydroxybutyrate	400 and 1000 mg/ kg	Psychoactive	Rats	↓plasma concentration and AUC ↑the total and renal clearances	Inhibited the monocarboxylate transporter 1 mediated transport of γ-hydroxybutyrate	[153]
Scutellarin	6.8 mg/kg, oral	Clopidogrel	11.8 mg/ kg, oral	Anti-platelet	Rats	↑$AUC_{0-\infty}$ and C_{max}	↓metabolism	[154]
Wogonin	10, 20 and 40 mg/kg, 3 days, oral	Docetaxel	10 mg/ kg, i.v.	Chemotherapy	Rats	↑C_{max} and AUC_{0-t}	NA	[155]
Compounds	**Dose and route of compound**	**Drugs**	**Dose and route of drugs**	**Drug class**	**Subjects**	**Pharmacokinetics consequences of the compound**	**Molecular mechanisms**	**References**
Baicalin	3, 10, 30 mg/ kg, i.v.	Cyclosporine	20 mg/ kg, i.v.	Immunosuppressants	Rats	↑the active transport into bile ↓ AUC	The metabolism of baicalin in the liver was extremely affected by the CYP450 inhibitor, SKF-525A, thus promoting rapid biliary excretion of baicalin, but not associated with P-gp	[145]
Baicalin	3, 10, 30 mg/ kg, i.v.	Quinidine	10 mg/ kg, i.v.	Antiarrhythmic	Rats	↑the active transport into bile ↓ AUC	As above	[145]
Baicalein	10, 30 and 60 mg/kg, i.v.	Cyclosporin A	20 mg/ kg, i.v.	immunosuppressant	Rats	No interaction in blood. ↓AUC and Cmax in the bile. ↑ blood-to-brain distribution (AUC and Cmax)	NA	[146]
Scutellarin	Breviscapine injection containing scutellarin (20 mg/kg, iv)	Valsartan	15 mg/ kg, i.g.	Anti-hypertensive	Rats	↓the plasma clearance (CL_p) and the bile clearance (CL_b)	NA	[140]
Scutellarin	Breviscapine injection containing scutellarin (50 mg/kg, i. v.)	Pravastatin	50 mg/ kg, i.g.	Statins	Mouse	↓plasma clearance (CL) ↑AUC	NA	[147]

which are the major pathways of APAP clearance. The clinical significance of these findings on APAP-induced liver toxicity is not clear due to the high IC_{50} concentration *in vitro* [117]. On the other hand, the herbal extract of *S. baicalensis* was also linked with potential hepatotoxicity as reported by clinical case studies [118,119]. The reason of this discrepancy warrants further investigations.

3.4.5. Alpha-interferon (immunomodulator)

Two clinical studies compared the combination and individual drug therapies of oral baicalin capsule and alpha-interferon (intramuscular or subcutaneous injection) to treat chronic hepatitis B induced liver fibrosis. After a 6-month treatment regime, the combined treatment showed a higher effectiveness in restoring liver function (manifested by reduced levels of alanine transaminase, aspartate transaminase, gamma-glutamyl transferase, and total bilirubin) and lower hepatitis B virus (HBV) DNA levels compared to that of alpha-interferon monotherapy [120]. In addition, the combined treatment significantly alleviated the fibrosis level as evidenced by significantly lowered levels of type III procollagen, type IV collagen, laminin and hyaluronidase. Moreover, Lv et al. (2018) showed reduced side effects of alpha-interferon-baicalin in treating hepatitis [121]. In addition, baicalin used together with adefovir or lamivudine yielded more desired clinical outcomes, not only inhibiting HBV replication, but also restoring liver function and enhancing cellular immunity [122,123]. The reduction by baicalin of oxidative stress and inflammation complement induced by adefovir or lamivudine may explain the observed synergistic action of the combined treatment.

4. Pharmacokinetic drug-herb interaction

4.1. Modulation of efflux and uptake transporters for absorption, distribution and elimination

Despite the large number of pharmacokinetic studies on *S. baicalensis*-drug interaction, the results are quite conflicting, with most studies tested on animals only. Notably, most of the interactions were attributable to the modulation of efflux and uptake transporters which then affected the absorption, distribution and elimination of

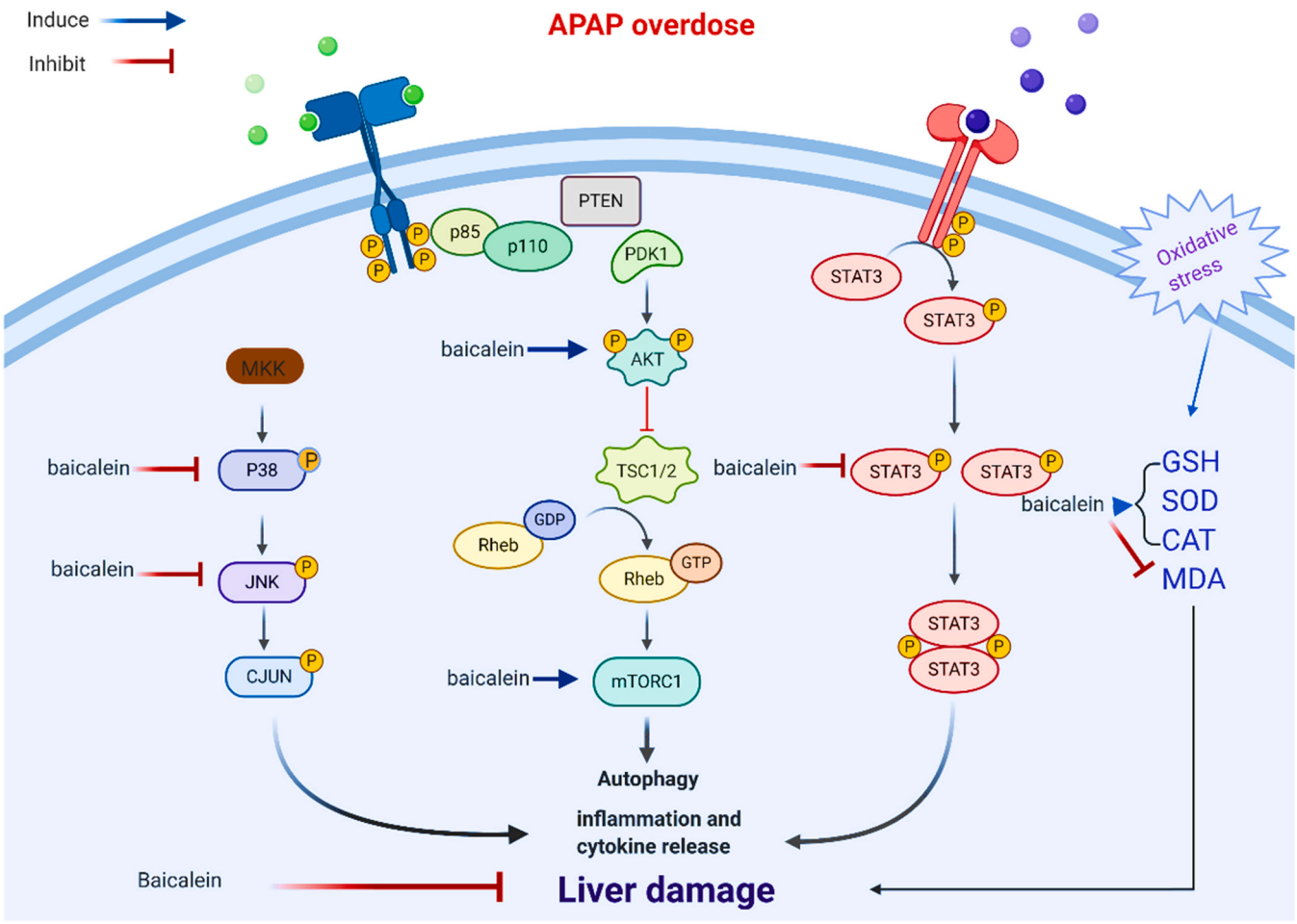

Fig. 3. Diagram of baicalein in protecting liver from the APAP overdose by inhibiting oxidative stress, regulating autophagy and suppressing inflammation pathways.

various drugs, such as P-gp and multidrug resistance-associated protein 2 (MRP2). P-gp is also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1), whereas MRP2 is also known as canalicular multispecific organic anion transporter 1 (cMOAT) or ATP-binding cassette sub-family C member 2 (ABCC2). They are both ATP-binding cassette transporter members that affect the uptake and efflux of many important drugs [124–130]. A summary of the pharmacokinetics studies that are associated with these transporters is listed in Table 2 and these studies can be classified into three categories: (1) the effect of *S. baicalensis* extract altering the pharmacokinetics of a drug (2) the effects of *S. baicalensis* bioactive(s) altering the pharmacokinetics of a drug (3) the effects of a drug on the pharmacokinetics of *S. baicalensis* bioactive(s). The current findings on each of the category include.

1) The administration of a single oral dose of *S. baicalensis* aqueous decoction in rats increased the blood level of methotrexate and liver concentration of metformin [131], lowered the bioavailability of cyclosporine [132], showed no interaction with mefenamic acid [112], and exhibited conflicting results with tolbutamide [133]. The increased absorption of methotrexate was associated with the inhibition of breast cancer resistance protein (BCRP) and MRP-2 efflux transports by serum metabolites of *S. baicalensis*, resulting in restricted transport of their substrates from the extracellular space into cells [134,135]. Thus it increased the distribution and overall exposure of methotrexate in the body [136,137]. Similar mechanism was suggested for baicalein, baicalin and scutellarin [136–140]. Another animal study suggested that a 28-day metformin treatment with *S. baicalensis* aqueous extract increased the liver concentration of metformin through the reduction of mRNA level of hepatic toxin extrusion protein 1-mediated metformin uptake, leading to sequentially decreased metformin efflux from the liver to bile, and higher hepatic distribution of metformin in rats. Although the extract did not affect the overall pharmacokinetics of metformin, it led to an increased plasma lactate and glucose tolerance distribution in liver without causing hypoglycemia in rats compared to rats with 28-day metformin only [141].
2) A number of studies have demonstrated the pharmacokinetics interaction of *S. baicalensis* bioactives including apigenin, baicalein, baicalin, chrysin, scutellarin, luteolin and wogonin and different classes of pharmaceutical drugs including anti-depressant, chemotherapy, cardiac, antibiotic and psychoactive drugs. However, it is difficult to draw a concrete conclusion for each interaction due to limited amount of studies and varied results. For example, three studies investigated the interaction between baicalin and cyclosporin, and obtained different results: no interaction if both were injected intravenously [142], decreased absorption (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) with oral administration of high dose (80 mg/kg) of baicalin [142], and increased absorption (C_{max} and AUC_{0-540}) with oral administration of low dose (112 μM/kg) of baicalin [132]. Most studies have linked the mechanism of dual regulation of the CYP3A subfamily and P-gp. Several studies have revealed that baicalein interacted with P-gp in the small intestine, and thus affected the oral bioavailability of their substrates including doxorubicin, tamoxifen and ciprofloxacin. However, whether baicalein acted as P-gp inducer or inhibitor seems to be dependent on the treatment duration. For

instance, Cho et al. (2011) suggested that 3 h of baicalein treatment inhibited P-gp in MCF-7/ADR cells that overexpressed P-gp [143], whereas a 72 h treatment upregulated the gene expression of P-gp on S174T and HepH2 cells [144]. The role of baicalin in regulating P-gp is also unclear. Tsai et al. (2004) suggested that baicalin was not the substrate of P-gp, as they found that the effect of ciclosporin on baicalein was similar to the interaction with SKF-525A (a non-specific CYPs inhibitor) without crossing with P-gp function in rats [145]. In agreement with this finding, Fan et al. (2008) showed that baicalin had no impact on the induction of P-gp. They observed that baicalin decreased the systemic plasma exposure of rosuvastatin substantially, and it was mainly relevant to OATP1B1 (an hepatic drug uptake transporter) which promoted the hepatic uptake of this drug from blood [127]. However, Tian et al. (2019) showed that multiple doses of baicalin decreased the oral bioavailability of ciclosporin which may be attributable to the induction of P-gp [142]. Overall, more studies warrant further investigation, especially clinical trials, to determine the clear interaction of baicalin associated with P-gp.

3) Several studies explored the pharmacokinetics profile of *S. baicalensis* compound(s) that were altered by drugs to understand the actions of these compounds in the body and brain. Cyclosporin A significantly increased the distribution of unbound baicalein in the brain and reduced excretion into the bile, suggesting that there was a rapid exchange and equilibration of baicalin between the peripheral compartment and the central nervous system, which was facilitated by cyclosporin A [146]. Moreover, it was suggested that the disposition of baicalein was regulated by P-gp which was reputedly expressed in blood-brain barrier and hepatobiliary membrane. Interestingly, the blood circulation of baicalein was not affected by cyclosporin A. Further study is warranted to investigate if this process is associated with the involvement of P-pg. In contrast, baicalin was not detected in the brain striatum either treated alone or with cyclosporin, suggesting that baicalin might not be able to pass through the blood-brain barrier [145]. Another two studies investigated the pharmacokinetics of scutellarin, and suggested that MRP2 played an essential role in the uptake and elimination of scutellarin [140,147]. It was observed that the plasma clearance (CL_p) and the bile clearance (CL_b) of scutellarin was significantly reduced in the presence of valsartan (MRP2 substrate), and the action may be attributed to the active transportation of scutellarin by MRP2 [140]. Interestingly, the pharmacokinetic parameters of valsartan were not affected by the coadministration of scutellarin. Thus it was considered to be clinically safe if valsartan was co-administered with scutellarin for the therapeutic use of valsartan against diabetic nephropathy [148].

It is worth mentioning that the inhibitory effect of *S. baicalensis* and bioactives on drug transporters may be useful to enhance the bioavailability or the therapeutic index of certain drugs and P-gp/MRP2 substrates. However, there is still a gap between findings of preclinical studies and clinical applications.

4.2. Inhibition or induction of CYP-450 activities for metabolism

CYP450 enzymes play a pivotal role in the metabolism of various drugs in the body. Drug interactions *via* CYP450 enzyme(s) have been well studied using various *in vitro* and *in vivo* methods including substrate cocktail assays [156]. Generally speaking, the inhibition of CYP450 enzymes may reduce drug/substrate's metabolism, which often leads to increased drug effects or even toxicities, while induction of CYP450 enzymes may result in reduced drug effects *via* increased drug metabolisms [157].

Table 3 summarises the studies regarding the effects of *S. baicalensis* and its bioactives on CYP enzymes *in vitro* or *in vivo*. There are significant variations in findings, which may be related to experimental conditions, species difference, and concentrations/doses used.

For instance, Yi et al. (2009) investigated the aqueous extract of *S. baicalensis* on a series of CYP450 enzymes in healthy human volunteers, and found that the extract strongly inhibited CYP2C9 and increased CYP2E1 activity manifested by altered plasma metabolic ratios of their probe drugs. No significant change was observed for CYP3A4 [158]. In contrast, the total flavonoids of *S. baicalensis* had no effect on CYP2E1 in human liver microsomes. Baicalein was found to down-regulate CYP3A4 in human baculovirus-infected insect cells [143] and liver microsomes [159], whereas it induced CYP3A4 in LS174T cells [144] (see Table 3). The reason for this discrepancy is not clear. It may be related to complex interactions among *S. baicalensis* constituents, such as baicalein, baicalin, wogonin, scutellarin and 2′,5,6′,7-tetrahydroxyflavone which showed different effects on metabolic enzymes (induction or inhibition). It was also noted that effects of baicalein and baicalin on certain CYP enzymes were time and dose dependent. For instance, the treatment of baicalin (0.01–1 μM) for 24–36 h increased the expression of CYP3A4, CYP2C9 and CYP2C19, but decreased the expressions of CYP3A4, CYP2C9 at 48 h in HeLa cells [160]. It is assumed that a lower dosage and a certain time frame with the co-incubation of baicalin would lead to an induction of enzymes, whereas persistent induction and high dose would lead to cytotoxicity and/or mRNA degradation which would then result in decreased expressions of CYPs. Further studies are needed to elucidate the mechanism of these interactions.

In addition, it is notable that some *S. baicalensis* bioactives showed pronounced effects *in vitro* but not *in vivo*. For example, chrysin inhibited CYP1A and 1A activities, with IC_{50} values of 28.5 and 2.9 μM respectively in rat liver microsomes *in vitro*. However, it did not alter the pharmacokinetic parameters of caffeine (CYP1A substrate) and its metabolites in rats *in vivo* [152]. This may be related to a rapid metabolism of chrysin *in vivo* which could not be replicated in the cultured cells [152]. Overall, the current evidence of CYP-mediated drug interactions by *S. baicalensis* and its bioactives is still limited. Further studies on other clinical relevant CYPs such as 2D6, CYP2C9, CYP2C19, CYP2D6 and CYP3A should also be explored [156,161].

5. Conclusion and future perspectives

The present review highlights potential interactions of *S. baicalensis* and its bioactives with various drugs *via* pharmacodynamic and pharmacokinetic mechanisms. Most research on the pharmacodynamic interactions centres around the synergistic actions to enhance drug's efficacy or reduce drug resistance. Such synergistic interactions have been demonstrated for *S. baicalensis* extract and its bioactives (*i.e.* baicalein, baicalin, apigenin and oroxylin A) in combination with various drugs used for cancer, diabetes, microorganism infection, Parkinson's disease, epilepsy and inflammatory diseases. However, there is lack of studies, especially in clinical trials, that evaluate the adverse reactions induced by *S. baicalensis* drug interaction. The pharmacokinetic interactions of *S. baicalensis* and various drugs have also been demonstrated mainly *via* the regulation of P-gp and CYP enzymes. However, it is important to note that most of these studies were conducted in cultured cells or animals. There are still gaps in correlating *in vitro* and *in vivo* data and translating preclinical findings into clinical implications.

There are also challenges in studying interactions mediated by complex multi-herb formulae and metabolites of *S. baicalensis*. The future studies in these areas may help verify or predict important drug-herb interactions which may be used for developing complementary or adjunct therapies to improve clinical outcomes or minimising the potential risks or adverse reactions of conventional therapies.

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Table 3
The effect of *S. baicalensis* and its bioactives on cytochrome P450 isoenzyme in *in vitro*, *in vivo* and human.

Compounds	Subjects	CYP	Key results	References
Aqueous extract of *S. baicalensis*	Healthy human male volunteers	↓CYP2C9, ↑CYP2E1 No effect on CYP1A2, 2C19, 2D6 and 3A4.	After repeated doses, the metabolic ratios of losartan (CYP2C9) were decreased to 71% of baseline value, and the metabolic ratio of chlorzoxazone (CYP2E1) was increased significantly. No significant change was found for CYP1A2, 2C19, 2D6 and 3A4.	[158]
Flavonoids isolated from *S. baicalensis*	Human liver microsomes	No effect on CYP2B1, CYP2C19, CYP2D6 and CYP2E1	All flavonoids did not substantially inhibit pentoxyresorufin O-deethylation (CYP2B1), mephenytoin 4-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), and chlorzoxazone 6-hydroxylation (CYP2E1): $IC_{50} > 50$ μM.	[159]
Apigenin	Human liver and kidney microsomes	↓CYP4F2 No effect on CYP4A11	Apigenin inhibited CYP4F2 with an IC_{50} value of 4.6 μM.	[163]
Baicalein	Human baculovirus-infected insect cells	↓CYP3A4	Baicalein inhibited CYP3A4 with an $IC_{50} = 9.2$ μM. Baicalein significantly enhanced the bioavailability of nimodipine in rats possible due to its inhibition of CYP3A4.	[143]
Baicalein	Human LS174T cells	↑CYP3A4	Baicalein induced the expression of CYP3A4 and MDR1 mRNA by activating pregnane X receptor and constitutive androstane receptor.	[144]
Baicalein	Human baculovirus infected insect cells	↓CYP3A4	Baicalein inhibited CYP3A4 with an $IC_{50} = 9.2$ mM. Baicalein enhanced the oral bioavailability of tamoxifen, which may be mainly attributable to the inhibition of the CYP3A4-mediated metabolism of tamoxifen in the small intestine and/or in the liver.	[126]
Baicalein	Rat liver microsomes	↓CYP1A, ↓CYP2B, No effect on CYP2E1, CYP3A	Baicalin inhibited CYP1A (EROD), CYP1A (MROD) and CYP2B (BROD) with IC_{50} values of 6.4, 0.5 and 35.9 μM, respectively.	[151]
Baicalein	Human liver microsomes	↓CYP3A4	Baicalein inhibited hepatic testosterone 6β-hydroxylation (CYP3A4) activity with an IC_{50} of 17.4 μM.	[159]
Baicalin	Human LS174T cells	No effect on CYP3A4	Baicalin had no effect on either CYP3A4 or MDR1 gene expression.	[144]
Baicalin	Rat liver microsomes (RLMs)	↓CYP3A2	Multiple doses of baicalin decreased the expression of hepatic CYP3A2 by approximately 58% ($p < 0.01$), and it competitively inhibited midazolam metabolism in rat liver microsomes in a concentration-dependent manner.	[164]
Baicalin	Rat liver microsomes	↓CYP3A	*In vitro*: Baicalin competitively inhibited CYP3A activity in rat liver microsomes in a concentration-dependent manner and thus increased bioavailability of nifedipine in rats.	[165]
Baicalin	HeLa [Chang Liver] cells	CYP3A4, CYP2C9 and CYP2C19	Treatment of baicalin (0.01–1 μM) for 24–36 h increased the expression of CYP3A4, CYP2C9 and CYP2C19. However, decreased expressions were seen for CYP3A4, CYP2C9 at 48 h.	[160]
Baicalin	Rat Primary Cultured Hepatocytes	↑CYP3A1	The expression of CYP3A1 in rat hepatocytes increased gradually with the treatment of low concentration baicalin (<10 mol/L).	[166]
Baicalin	Rat and human liver microsomes	CYP1A2 , CYP2B6 , CYP2C9 , CYP2C19 , CYP2D6 , CYP2E1 and CYP3A4	In rat liver microsomes: baicalin showed no inhibition on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. In human liver microsomes: CYP1A2, CYP2C19 and CYP2E1 were inhibited weakly by baicalin, IC_{50} were 39.72, 40. 91 and 32. 83 μmol/L, respectively.	[167]
Baicalin	On *Paralichthys olivaceus* liver	↑CYP1A	Treatment of baicalin (50, 100, and 100 mg/kg/d) for 3, 6 and 9 days upregulated gene and enzyme expressions of CYP1A.	[168]
Baicalin	Healthy male volunteers	↑CYP2B6	Baicalin significantly induced CYP2B6-catalysed bupropion hydroxylation.	[169]
Baicalin	Rats liver microsome	↓CYP3A	Baicalin with concentrations of 30 and 90 μg/mL reduced amounts of oxidised nifedipine in incubation solution, and inhibited the activities of CYP3A.	[170]
Baicalin	Rat liver microsomes	↓CYP1A, ↓CYP2B, No effect on CYP2E1, CYP3A	Baicalin inhibited CYP1A (7-ethoxy-resorufin *O*-deethylation), CYP1A (7-methoxyresorufin *O*-demethylation) and CYP2B (7-benzyloxyresorufin oxidation) with IC_{50} values of 24.2, 9.3 and 22.9 μM, respectively. However, it did not alter the pharmacokinetic parameters of oral caffeine and its three metabolites between control and baicalin-treated rats.	[151]
Chrysin	Rat liver microsomes	↓CYP1A	Chrysin inhibited CYP1A (7-ethoxy-resorufin *O*-deethylation) and 1A (7-methoxyresorufin *O*-demethylation) with IC_{50} values of 28.5 and 2.9 μM, respectively. However, the treatment of chrysin in rats did not alter the pharmacokinetic parameters of caffeine and its three metabolites.	[152]
Luteolin	Human liver microsomes	↓CYP3A	Luteolin partially inhibited both 1′-OH-MDZ and 4-OH-MDZ formation with mixed competitive–non-competitive type.	[171]
Luteolin	Human liver microsomes	↓CYP1A2, CYP3A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1	The IC_{50} values ranged from 0.61-103.4 μM.	[117]
Wogonin	Human microsomal	CYP1A2	Wogonin had a strong biological activity against CYP1A2, with an IC_{50} value of 248 nM.	[172]
Oroxylin A	Human microsomal	CYP1A2	Oroxylin A had a strong biological activity against CYP1A2, with an IC_{50} value of 579 nM.	[172]
Scutellarin	Human liver microsomes; rat liver microsome	↓CYP2C19, Weak inhibitory of CYP1A2, CYP2C8, CYP2C9, CYP2D6 and CYP3A4	Scutellarin showed negligible inhibitory effects on the six tested CYPs except for a weak inhibition in CYP2C19. Scutellarin had no inhibitory effect on six tested CYPs using rat liver microsome, except for weak inhibitions in CYP2C7 and CYP2C79.	[173]

(*continued on next page*)

Table 3 (*continued*)

Compounds	Subjects	CYP	Key results	References
Scutellarin	Rat liver microsomes	↓CYP1A2	The inhibitory effect of CYP1A2 with an IC_{50} value of scutellarin was 108.20 ± 0.657 μM and it was not time and NADPH-dependent. Scutellarin inhibited CYP1A2 directlyin whole animal studies.	[174]
Scutellarin	Rat microsomes	↓CYP3A1, CYP2C11	The results showed that the inhibition concentrations of scutellarin on CYP3A1 and CYP2C11 were not greater than 1 μM, suggesting that scutellarin was a strong inhibitor of CYP3A1 and CYP2C11.	[175]
Wogonin	Human liver microsomes	↓CYP1A2, CYP2C19 No effect on CYP2C9, CYP2D6, CYP2E1 and CYP3A4	Wogonin was a potent and competitive inhibitor of CYP1A2 (Ki = 0.24 μM), and a weak inhibitor of CYP2C19 (IC_{50} = 101.10 μM). Wogonin was not able to inhibit CYP2C9, CYP2D6, CYP2E1 and CYP3A4 (IC_{50} >200 μM).	[176]
2′,5,6′,7-tetrahydroxyflavone	Human liver microsomes	↓CYP3A4	2′,5,6′,7-tetrahydroxyflavone inhibited CYP3A4 (hepatic testosterone 6β-hydroxylation) activity with an IC_{50} of 7.8 μM.	[159]

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Conflict of interest statement

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Appendix A. Chemical compounds identified from *S. baicalensis* Georgi (*Huang Qin*) and analysis methods

Analysis method	Identified compounds	References
Capillary electrophoresis	Baicalein, baicalin, wogonin, wogonin 7-*O*-glucuronide	[177]
HPLC	Baicalin, wogonin-7-O-glucuronide, wogonin, baicalein	[18]
Micellar electrokinetic chromatography	baicalin, baicalein and wogonin, phenylethanoid glycoside	[178]
RP-HPLC	Baicalin, baicalein, wogonin glucuronide, wogonin, oroxylin A	[179]
HPLC	Baicalin, wogonin 7-O-glucuronide, oroxylin A 7-O-glucuronide, baicalein, wogonin, oroxylin A, wogonoside	[21]
HPLC	Baicalein, wogonin, oroxylin A	[180]
HPLC	Baicalein, wogonin, neobaicalein, skullcapflavone	[20]
HPLC	baicalein, wogonin, neobaicalein, and skullcapflavone	[20]
High-speed counter-current chromatography	Baicalin, wogonoside	[19]
HPLC-DAD and LC-MS-MS	2′,3,5,6′,7-Pentahydroxyflavanonol, 6-C-arabinose-8-C-glucose-chrysin, cynaroside, 6-C-glucose-8-C-arabinose-chrysin, viscidulin III-2′-O-D–glucoside, viscidulin I, chrysin 8-C-β-D-glucoside, 5,7,2′,6′-tetrahydroxyflavone, baicalin, dihydrobaicalin, apigenin-7-O-β-D-glucuronide, oroxylin A 7-O-β-D-glucuronide, chrysin-7-O-β-D-glucuronide, wogonoside, norwogonin, baicalein, 8,8′′- baicalein, wogonin, chrysin, oroxylin A	[22]
HPLC	Baicalin, baicalein, wogonin	[19]
LC-DAD	Scutellarin, scutellarein, baicalin, wogonoside, apigenin, baicalein, wogonin, chrysin, oroxylin A, acteoside	[17]
HPLC	Baicalin, wogonoside, baicalein, wogonin	[181]
HPLC	Baicalin and baicalein	[182]
HPLC and LC-MS	Baicalin, wogonoside, baicalein, wogonin, oroxylin A	[183]
UHPLC/orbitrap-MS	More than 100 compounds Isoschaftoside, schaftoside, 5,7,2,6-tetrahydroxyflavone 2-O-d-glucoside, (2R,3R)-3,5,7,2,6-pentahydroxyflavanone, (2S)-5,7,2,6-tetrahydroxy flavanone 2-O-d-glucoside, 3,5,7,2,6-pentahydroxyflavone, scutellarin, viscidulin III 6-O-d-glucoside, chrysin 6-C-α-l-arabinopyranoside-8-C-β-d-glucoside, acteoside, chrysin 6-C-β-l-arabinopyranoside-8-C-β-d-glucoside, 5,2,6-trihydroxy-7,8-dimethoxyflavone 2-O-β-d-glucoside, chrysin 6-C-β-dglucoside-8-C-α-l-arabinopyranoside, chrysin 6-C-β-d-glucoside-8-C-β-l-arabinopyranoside, chrysin 8-C-β-d-glucoside, (2S)-5,7,2,6-tetrahydroxyflavanone, viscidulin III, 5,7,2-trihydroxy-6-methoxyflavone 7-O-β-d-glucuronide, baicalin, baicalein 7-O-β-d-glucoside, norwogonin 7-O-β-d-glucuronide, wogonin 5-O-β-d-glucoside, cistanoside D, chrysin 7-O-β-d-glucuronide, oroxylin A 7-O-β-d-glucuronide, oroxylin A 7-O-β-d-glucoside, (2S)-5,7-dihydroxy-6-methoxyflavanone 7-O-β-d-glucuronide, wogonoside, 5,7,6-trihydroxy-8,2-dimethoxyflavone, baicalein, wogonin, chrysin, 5,6-dihydroxy-6,7,8,2-tetramethoxyflavone, and oroxylin A	[23]
Near-infrared spectroscopy	Baicalein, baicalin, wogonin	[184]
HPLC-DAD	Scutellarin, apigenin-7-*O*-β-*D*-glucopyranoside, baicalin, luteolin, wogonoside, alpinetin, apigenin, baicalein, wogonin, chrysin, and oroxylin A	[185]
UPLC-Q-TOF-MS	Apigenin-6-C-glucosyl-8-C-arabinoside, 6-C-arabinopyranosyl-8-C-glucopyranosyl-5,7-dihydroxyflavone, 3,5,7,20,60-pentaydroxyflavanone, carthamidin, dihydroscutellarin, scutellarin, 7,2′,6′-trihydroxy-5-methoxyldihydroflavone, viscidulin I, hispidulin-7-O-glucuronide, 5,7,2′-trihydroxy-6-methoxyflavone, 6-methoxynaringenin, 5,7-dihydroxy-8,2′-dimethoxydihydroflavone-7-O-glucuronide, baicalin, norwogonin, baicalein-7-O-glucoside, scutellarein, viscidulin III, dihydrobaicalin, naringenin, 5,8-dihydroxy-6,7-dimethoxyflavone, apigenin-7-glucoside, acacetin, apigenin, apigenin-7-O-glucuronide, 5,8,2′-trihydroxy-7-methoxyflavone, scutevulin-7-O-glucuronide, oroxylin A-7-O-glucuronide, eriodyctiol, chrysin-7-O-glucuronide, kaempferol 5-rhamnoside, negletein, wogonoside, dihydrooroxylin A, 5,7-dihydroxy-8,2′-dimethoxylflavone7-O-glucuronide, 5,7-dihydroxy-8,2′-dimethoxyflavone, skullcapflavone, 4′-hydroxywogonin, 5,2′,5′-trihydroxy-6,7,8- trimethoxyflavone, apigenin-7-O-glucuronide-6-ethyl ester, hispidulin, baicalein, viscidulin II, 5,2′,4′-trihydroxy-6,7,5′- trimethoxyflavone, 5,2′-dihydroxy-6,7,8- trimethoxyflavone, wogonin, chrysin, skullcapflavon I, skullcapflavon II, oroxylin A, 5,2′-dihydroxy-6′,7,8- trimethoxyflavone, dibutyl phthalate, linoleic acid	[186]

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