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Baicalein as a potential bioactive flavonoid: a concise overview

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ABSTRACT: Baicalein (the aglycone of baicalin) is a trihydroxyflavone isolated from *Scutellaria* species, mainly *Scutellaria baicalensis* Georgi, which is used in Traditional Chinese Medicine to treat cold, hepatic and pulmonary diseases, insomnia, inflammation, hypertension, atherosclerosis, hyperlipidemia, and dysentery. In scientific literature, baicalein has been extensively reported to exert in vitro and in vivo antioxidant and anti-inflammatory effects, as well as possessing anti-cancer, anti-microbial, immune-modulatory, metabolic, and cardiovascular protection properties. It may modulate a wide array of signaling pathways such as AMPK (5' adenosine monophosphate-activated protein kinase), PPAR-γ (Peroxisome proliferator-activated receptor gamma), Bcl-2 (B-cell lymphoma 2) and Bax (Bcl-2-associated X) proteins, CDKs (Cyclin-dependent kinases), MMP (metalloproteinases), SIRT1, NF-kB (nuclear factor kappa-light-chain-enhancer), EMT (epithelial–mesenchymal transition), TLRs (Toll-like receptors), CPT1 (carnitine palmitoyl transferase-1), and SREBP-1c (sterol regulation element binding response protein-1c). The present review is designed to focus on the potential bioactive activities of baicalein and/or baicalin. tests.

Keywords: baicalein; baicalin; *Scutellaria baicalensis* Georgi; biological properties

1. Introduction

A growing body of evidence suggests that an adequate intake of dietary flavonoids may reduce the markers for systemic inflammation, the ultimate result of which is to reduce the risk of chronic pathologies such as diabetes mellitus, cardiovascular and neurodegenerative pathologies, asthmatic diseases, inflammatory

bowel disease (IBD), arthritic diseases, and cancer (Tao et al. 2023). The researching of new anti-inflammatory, antioxidant and immunomodulatory molecules, isolated from plant extracts, could provide a road-map for the discovery and design of new semi-synthetic drugs useful in targeting signalling pathways, an example is given by the NF-κB pathway, which works as a transcription factor with a key role in the immune response and whose dysfunction is directly related to cancer (Bharti and Aggarwal 2002; Galliera et al. 2008). In addition, flavonoids exert antibacterial and antibiofilm activities. Due to the increasing volume of cases of antibiotic resistance, the scientific community is continuously searching for new antimicrobial agents with improved antimicrobial spectra. A variety of studies sustain the flavonoid inhibition of biofilm formation, reduction of bacterial resistance, disruption of bacterial structure, inhibition of bacterial toxins and enzymes and synergistic effects with antibiotics (Golkar et al. 2014; Memar et al. 2017).

Baicalein (5,6,7-trihydroxy-2-phenyl-4H-chromen-4-one) is a trihydroxyflavone isolated the roots of *Scutellaria baicalensis* Georgi, used widely in Traditional Chinese Medicine to treat colds, hepatic and pulmonary ailments, insomnia, inflammation, hypertension, atherosclerosis, hyperlipidemia, and dysentery (Gong et al. 2018; Weber 2010; Zhu and Woerdenbag 1995). Baicalein shows antimicrobial activity against many microorganisms including bacteria, viruses and fungi. Furthermore, baicalein exerts interesting activity in the prevention and treatment of metabolic dysregulation, including insulin resistance, obesity, diabetes mellitus, hypertension, and hypercholesterolemia. Indeed, Baicalein activates and upregulates signaling pathways associated with lipid metabolism and glucose homeostasis, such as AMPK (5' adenosine monophosphate-activated protein kinase) and PPAR-γ (Peroxisome proliferator-activated receptor gamma). suggesting the potential of baicalein in the prevention and treatment of cardio-metabolic disorders and associated complications (Heidenreich et al. 2011; Zhao et al. 2019; Chen et al. 2015; He et al. 2016; Dai et al. 2017).

The present study consists of an up-to-date review of literature, aimed to summarize the various biological properties of baicalein, in addition to its chemistry and pharmacokinetic aspects. Electronic databases including PubMed, Scopus, and Web of Science were systematically searched, for articles published in the English language. The following terms were used in the literature search in all possible combinations: "baicalin" or "baicalein" and "chemical extraction" or "pharmacokinetics" or "biological properties" or "antioxidant" or "anti-inflammatory" or "anti-microbial" or "anti-carcinogenic" or "immune modulatory action" or "metabolic disorder" or "cardiovascular protection".

2. Chemistry and Extraction of Baicalein

Baicalein ($C_{15}H_{10}O_5$ chemically known as 5,6,7-trihydroxyflavone; Figure 1) is aglycone of baicalin or 5,6,7-trihydroxy-2-phenylchromen-4-one, predominantly isolated from the roots of certain *Scutellaria* species, including *S. baicalensis, S. rivularis, S. rehderiana, S. violacea* and *S. lateriflora* (Li-Weber 2009). *Alseodaphne semecarpifolia, Oroxylum indicum* (Indian trumpet flower) and *Thymus* have also been found to contain baicalein (Chethankumara et al. 2021; Nik Salleh et al. 2020). Multiple extraction techniques, such as dynamic microwave-assisted extraction (MAE), high-speed counter-current chromatography (HSCCC) and on-line continuous flow ultrasonic extraction, have been used to extract and isolate baicalein from the respective botanical sources. Currently, traditional extraction procedures (i.e., with 70% hydroethanolic solution) and supercritical fluid extraction (SFE) are the most frequently employed techniques for the extraction of baicalein from its botanical sources, though the method of extraction most appropriate for medicinal purposes is yet to be determined (Li C et al. 2011; Lin et al. 2013), where SFE seems more effective extraction technique, due to its efficiency and high yield (Li C et al. 2011).

Figure 1. Chemical structure of 5,6,7-trihydroxyflavone (baicalein).

A study focusing on using ultrasound irradiation and exogenous enzymes to increase the overall extraction yield of baicalein (known as ultrasonic-assisted enzymatic pretreatment (UAEP) technique), showed almost double the productive efficiency, as compared to the reference method. These findings demonstrate that the modified UAEP technique has the potential to be utilized in the pharmaceutical and food industries for the simple and convenient extraction of baicalein (Yun et al. 2022). The traditional separation extraction techniques, such HPLC and thin layer chromatography (TLC) are inefficient in extracting baicalein due to their low selectivity and affinity. Thus, more recently molecularly imprinted polymers (MIP) were used to create specific recognition sites for this target molecule. These polymers are easy to use, cheap, and very stable, and may be synthesized through polymerization of monomers and crosslinkers in the presence of baicalein. Following polymerization, the templates are removed using a chemical extraction or reaction and the cavities will have the same shape, position, and size as the target molecules. For all the reasons cited above, MIPs are used across various fields, for drug delivery, sensors, catalysis, solid-phase extraction (SPE), and chromatographic separation. Baicalein may be used to synthesize MIP through the polymerization process, with computer simulations generally being used to predict suitable solvents for use. The comparison between non-imprinted polymers (NIP) and MIP demonstrated, faster kinetics, and greater adsorbing capacity for baicalein, suggesting that the isolation and knockdown of essential phytoconstituents may be achieved with this innovative technique (Li et al. 2016).

3. Pharmacokinetics

Baicalein shows a good lipophilicity and permeability in the gastrointestinal tract, as compared to its glycoside counterpart (Kalapos-Kovács et al. 2015). The oral administration of these two molecules in rats confirms the higher absorption of baicalein compared to baicalin, even if the former is present at very low concentrations in the bloodstream (Li et al. 2014). Human studies assessed the low levels of baicalein present in blood after a single dose administration, with a maximum concentration (Cmax) being 10 times higher in comparison with baicalin. The intervention of β-glucuronidase from intestinal bacteria promotes the hydrolyzation from baicalin to baicalein in the intestinal tract, while UDP-glucuronosyltransferase restores the level of baicalin in the circulatory system (Zhang et al. 2017).

Rats free of intestinal bacteria have been used to underline the critical role played by the microbiota in metabolizing baicalin into baicalein following oral intake (Akao et al. 2010). Multiple studies have underlined the multiple peaks or bimodal absorption of this molecule, with possible explanations for this phenomenon involving enterohepatic circulation or/and gastric emptying (Lu et al. 2007; Shaw et al. 2012; Tong et al. 2012; Song et al. 2017). The affinity of baicalin and baicalein for human serum albumin (HSA) is moderate and high, respectively (Tang et al. 2006). The intervention of MRP (multidrug-resistant protein) and BCRP (breast cancer resistance protein) are essential for baicalin distribution through transportation (BCRP> MRP3> MRP2> MRP1). Intravenous administration has revealed that the highest concentration of baicalin is found in the kidneys, but alternate forms of administration, such as liposomal injection, promoted distribution throughout the lungs, more than the liver or the kidney routes (Wei et al. 2016).

Different formulations resulted in vary distributions, the passage of baicalin and baicalein through the blood-brain barrier interestingly occurs thanks to the intervention of the anion-transporting polypeptide (OATP) 2B1 and OATP1A2. Baicalin seems to be distributed differently across different parts of the brain (hippocampus, thalamus, or striatum) and its absorbance into cerebrospinal fluid is very fast (Huang et al. 2008).

The excretion of baicalin occurs through the bile, thanks to the intervention of MRP2 (Kalapos-Kovács et al. 2015; Xing et al. 2005), as confirmed by studies performed in MRP2 deficient rats. An alternative route may be through urine, but this seems to be a limited fraction compared to that of the liver route (7.2 % of the dose was found to be discarded through the urinary tract) (Xing et al. 2005). Baicalin excreted through the kidney route is found in the form of sulfated or hydroxylated compounds (Lai et al. 2003).

4. Biological Properties of Baicalein

4.1. Antioxidant and anti-inflammatory activities

Baicalin and baicalein are both utilized extensively in traditional Chinese herbal therapy for numerous ailments, including inflammatory diseases. Because of their potent anti-oxidant and anti-inflammatory capabilities, baicalin and baicalein have been shown to provide a diversity of functional activities (Medzhitov 2008). Baicalein has been demonstrated to have ROS scavenging properties via direct scavenging of superoxide and hydroxyl radicals (Cho et al. 2011). The intrinsic antioxidant activity of baicalein is provided by its catechol moieties in the A-ring **(Figure 2)**, which confers an inherent antioxidant ability through donation of electrons, is a good structural characteristic for an efficient radical quencher (Shao et al. 2002). Baicalein activates Nrf2 transcription to promote the action of superoxide dismutase (SOD), as a result of which mitochondria may withstand oxidative stress **(Figure 2)** (Lee et al. 2011). Baicalein was also shown to reduce the assertion of the phosphorylated form of the H2A.X protein, as well as the tail length of DNA in the comet test, when H_2O_2 was applied. According to these findings, baicalein shielded cellular DNA from oxidative stress damage (Palierse et al. 2021). Kang et al. (2012) investigated the preventive properties of baicalein against oxidative stress-induced harm, focusing on DNA, lipids, and proteins. The scavenging activity of baicalein observed at 10 mg/mL was 80%, as compared to 87 % antioxidant activity of N-acetyl cysteine. The schematic representation of ROS scavenging by baicalein is illustrated in Figure 2.

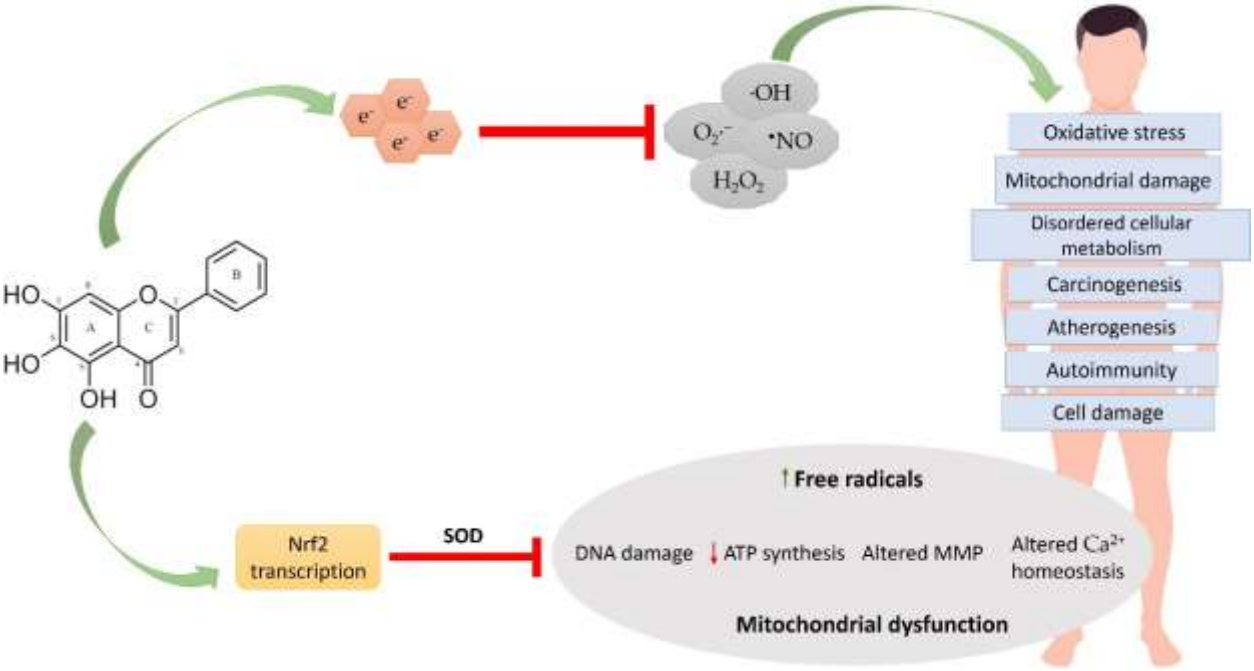

Figure 2. Schematic illustration of the ROS-scavenging properties of baicalein. Catechol moieties in the A-ring of baicalein donate electrons, responsible for the direct scavenging of free radicals. In addition, baicalein promotes the activity of SOD via Nrf2 transcription, which results in the attenuation of mitochondrial stress.

Baicalin has been found to be effective in reducing ligature-induced alveolar bone destruction in rodent models of experimental periodontitis, which might be reflect its pro-osteogenic impact on cultures of PDLCs (human periodontal ligament cells) (Fan et al. 2013). A recent study reported the proliferation of calcified nodules in PDLCs with baicalein, while baicalin did not show the same results (Lin and Shieh 1996). Furthermore, unlike baicalin, nano-

encapsulated baicalein possesses a strong anti-inflammatory impact on gingival epithelial cells in an inflammatory environment. The different effects of baicalin and baicalein may be explained by differences in their bioavailability (Butenko et al. 1993; Dinda et al. 2017). Ren et al. (2021) demonstrated the anti-inflammatory effect of baicalein, which promoted stem cell contrast, resulting in reduction of inflammation in LPS-treated PDLCs. Similarly, Kim et al. (2018) conducted a study on baicalein's anti-inflammatory effects in a mouse macrophage cell line (RAW 264.7), induced by polyinosinic-polycytidylic acid. The pre-treatment with baicalein (≈100 μM) significantly suppressed the synthesis of pro-inflammatory mediators, including nitric oxide (NO) and interleukins (IL-1 and IL-6). In poly I:C-induced RAW 264.7 cells, baicalein considerably reduced mRNA coding for some transcription factors (i.e., STAT1, STAT3, CHOP, and Fas) at doses ≈ 50 μM.

4.2. Anti-microbial effects

In two different studies, *S. baicalensis* extract showed considerable antimicrobial effects against *Escherichia coli, Staphylococcus aureus, Bacillus cereus, Salmonella anatum, Listeria monocytogenes, Candida albicans, Aspergillus fumigatus, Rhodotorula rubra*, and *Geotrichum candidum* (Shan et al. 2007; Blaszczyk et al. 2000). *S. baicalensis* extracts and isolated baicalein may also boost the antimicrobial effects of numerous antibiotics against *S. aureus* (Yang et al. 2005). A study conducted by Chan et al. (2011) demonstrated significant antibacterial actions by baicalein against resistant Methicillin-resistant *Staphylococcus aureus* (MRSA) strains via in vitro inhibition of the NorA efflux pump. Additionally, the inhibition of MRSA-specific pyruvate kinase further contributed to the anti-MRSA actions exerted by baicalein. Baicalin also possesses potent antiviral activities, and it has become a common lead molecule for natural products used for the treatment of HIV infections, possibly through non-nucleoside reverse transcriptase inhibition (De Clercq 2000; Kitamura et al. 1998).

Additionally, through the alteration of the interaction between HIV-1 co-receptors on the cell surface and HIV-1 Env, it may prevent the entry of HIV-1 into animal cells (Li et al. 2000). While studying the differential effects of baicalein and baicalin, Zhao et al. (1998) reported baicalein as having four times stronger inhibitory potential against HIV-1 reverse transcriptase. A study by Ono et al. (1989) demonstrated that baicalein (2 μg/mL) provides 90% inhibition of HIV reverse transcriptase activity. Baicalein was also shown to inhibit HIV-1 integrase, one of the essential enzymes in the viral life cycle, inducing a conformational change by binding to the hydrophobic region of the HIV-1 integrase catalytic core domain (Ahn et al. 2001).

4.3. Anti-carcinogenic potential

Baicalin has interesting anti-cancer potential, as it can affect various types of cancer cells. The development of new formulations and the publication of several studies on the metabolism and pharmacokinetics of baicalein have highlighted the potential capacity of baicalein to promote apoptosis, angiogenesis inhibition, metastasis suppression, autophagy, and modulation of molecular targets. This molecule modulates Bcl-2 (B-cell lymphoma 2) and Bax (Bcl-2-associated X) proteins, which are responsible for the apoptosis process (Gross et al. 1999; Gao and Ai-Ying 2009). Baicalin showed potent anti-cancer activity against osteosarcoma and colorectal cell lines at concentration of 25 – 100 μM and 25 – 100 μg/mL, respectively (Yang et al. 2020; Liu et al. 2019). Baicalin also showed to improve caspase-3 expression in epithelial cells isolated from spleen at concentrations of 80, 120, and 160 μmol/L, the ultimate result of which was enhanced apoptosis (Huang et al. 2019). Baicalin enhanced p53 expression in SW1990 epithelial cells (pancreatic adenocarcinoma) at 40 and 160 μmol/L concentrations (Huang et al. 2019) and in HCT116 and RKO cell lines (colon cancer cells) at 50 μg/mL and 100 μg/mL concentrations (Wang et al. 2008). Baicalin promoted apoptosis through FasL and Fas in met-ret cells at 2000 μg/mL concentration and in cervical carcinoma (HeLa) cells at 50 – 250 μg/mL concentration (Liu et al. 1998). Baicalin also inhibit cell proliferation and arrest the cell cycle via downregulation of the Cyclin-dependent kinases (CDKs), as alternation of p15, CDK2 and cyclin E1 expression was observed in SW1990 (pancreatic cancer cells) at 40 – 160 μM concentration (Huang et al. 2019). An arrest in the G2/M phase was reported in SMMC-7721 and HepG2 cells via downregulation of Cyclin A, CDK2, Cyclin D1 following treatment with

baicalin at 10 – 40 μM concentration (Yu et al. 2015).

Baicalin also has the ability to suppress cancer metastasis, reducing its invasion and migration, as seen in A2780 cells at 20 – 40 μM concentration (Gao et al. 2017) and in SW1990 cells at 40 μM – 160 μM concentration (Huang et al. 2012) via downregulation of metalloproteinase (MMP) expression. Similarly, H1299 and A549 cell migrations were inhibited through AMPK (AMP-activated protein kinase) and SIRT1 (histone/protein deacetylase) at 20 and 80 μM concentration (Wan and Ouyang 2017). The epithelial to mesenchymal transition (EMT) was inhibited with bacalein at 50 – 100 μg/mL concentration through the downregulation of Cadherins (i.e., E-cadherin and N-cadherin), and transcription factors (i.e., Snail, Slug, and Twist) (Liu et al. 2019). Even at lower concentrations i.e., 2 μM, baicalin was able to arrest the migration and invasion of breast carcinoma following the downregulation of EMT and NF-κB signaling (Fei et al. 2015).

4.4. Immune modulatory properties

Carcinoma cells can evade the immune system due to an unusual expression of programmed cell death (PD1), which is responsible for the interaction between immune cells and the target (Ke et al. 2019). The immune surveillance of hepatoma carcinoma cells was promoted by baicalin at 40 μM concentration, leading to STAT3 inhibition with the consequent activation of programmed death-ligand 1 (PD-L1). At the same concentration, T cell sensitivity was restored, in addition to CD8+ T and IL-2 T cell levels, for hepatoma cells. IL-6 levels were reduced in THP-1 cells due to the activity of Src tyrosine kinase (Zheng et al. 2012). Baicalin at 10 μM increased the activity of adriamycin in HL-60 cells, inducing apoptosis through the PI3K/Akt pathway (Zheng et al. 2017). Another important activity exerted by baicalin is the regulation of TLRs (Toll-like receptors), which are involved in the immune system for the recognition of pathogen associated molecular patterns (PAMPs), where these receptors are involved in number of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and experimental autoimmune encephalomyelitis (Takeda et al. 2003; Wang et al. 2013; Hosseini et al. 2015). Baicalin protected against murine keratinocytes against UVB-induced oxidative/inflammatory stresses and DNA damage via inhibition of TLR4 and downstream regulation of its signaling molecules such as TRIF, TRAF6, and MyD88 (Min et al. 2015). A study showed mitigation of neuroinflammation by baicalin via downregulation of MAPK and TLR4/MyD88/NF-κB pathways in LPS-stimulated BV-2 microglia. The treatment with baicalin also resulted in significant attenuation of inflammatory mediators (i.e., NO, iNOS, COX-2, PGE2, and IL-1β,), with suppressed miR-155 expression (Li B et al. 2022). Another study showed inhibition of LPS-induced inflammation in RAW264.7 cells via suppressing the expression of inflammatory mediators (i.e., iNOS, COX-2, IL-1β, IL-6, and TNF-α) and decreasing the activity of HMGB1/TLR4)/NF-κB) pathway along with upregulated miR-181b expression, where miR-181b is proved to negatively regulate High Mobility Group Box 1 (HMGB1) activity (Yan et al. 2021). Baicalein attenuated activation-induced cell death of microglia via inhibition of NO and iNOS, and downregulation of NF-κB signaling (Suk et al. 2003).

4.5. Metabolic disorders

Baicalin seems to have a positive effect on adipogenesis, NAFLD (non-alcoholic fatty liver disease), obesity, and diabetes mellitus type 2. With regards to adipogenesis, treatment with baicalin (500 mg/day for 12 weeks) reduced CRP (C-reactive protein) levels, apolipoproteins, triglycerides, total cholesterol, and low-density lipoprotein in 374 patients, aged 45 years or older, with arterial disease (Hang et al. 2018). Various studies conducted on obese mice confirmed the ability of baicalin, after oral administration, to reduce steatosis, hyperlipidemia and liver weight and fat mass (Yang et al. 2017; Xi et al. 2015; Wu et al. 2018). A reduction in cholesterol free fatty acids (FFAs) and TNF-α was registered after intraperitoneal administration of baicalin in obese mice or rats (Guo et al. 2009; Waisundara et al. 2011; Zhu et al. 2016). This type of administration suppressed food intake and consequently fat mass and body weight, Treatment of 3T3-L1 cells with a concentration ranging from 5 to 10 mM/L of baicalin for 24 hours confirmed the reduction of triglyceride and cholesterol accumulation with the formation of lipid droplet in HepG2 cells in high glucose condition after the AMPK activation (Xi et al. 2015; Lee et al. 2009; Min et al. 2012).

Baicalin seems to be able to interact with CPT1 (carnitine palmitoyl transferase-1) in liver promoting fatty acid oxidation and hepatic steatosis (Min et al. 2018), but there are several studies which also support hepatoprotective effects exerted through SREBP-1c (sterol regulation element binding response protein-1c), fatty acid synthase, PPARγ and the Ca2+/calmodulin-dependent protein kinase kinase β (CaMKKβ)/AMPKα/acetyl-CoA carboxylase pathway (Yang et al. 2017; Waisundara et al. 2011; Zhu et al. 2016). Baicalin also enhanced CPT1, nuclear respiratory factor 2 and AMPK and suppressed SREBP-1c, fatty acid synthase, ACC and staroyl-CoA desaturase (Li P et al. 2022).

Hyperglycemia is reduced in rodent model after intraperitoneal administration of baicalin (50 or 100 mg/kg) in streptozotocin - nicotinamide induced diabetic rats (Li HT et al. 2011). At higher dose, baicalin also reduced the serum TNF-α and significantly increased the hepatic glycogen content. The oral glucose tolerance test showed a decreased postprandial blood glucose level with baicalin administration, through the inhibition of intestinal disaccharidases, while promoting the plasma insulin levels in STZ-induced diabetic rats (Liu et al. 2013). Recent studies also indicated that baicalein may activate AMPK pathway and downregulate SIRT1/STAT3 signaling pathway to inhibit the expression of hepatic glucose-6-phosphatase (G6PC) and phosphoenolpyruvate carboxykinase (PEPCK), the rate limiting enzymes in gluconeogenesis (Fang et al. 2020).

4.6. Cardiovascular protection

Scutellaria treatment at 200 mg/kg/day for 12-weeks suppressed p-ERK, MMP-9 and 12-lipoxygenase in rats with heart fibrosis and intraventricular septum thickness (Kong et al. 2011). The use of 5 and 10 mM of baicalin in HUVECs (Primary Human Umbilical Vein Endothelial Cells) up-regulated NF-κB and suppressed endothelial barrier disruption (Ku and Bae 2015). Rats treated with increasing doses (20 mM, 40 mM and 60 mM) of baicalin reduced migration in VSMCs (vascular smooth muscle cells) through the reduction of Cyclin E-CDK2 and the up-regulation of p27 protein. The dose of 70 mg/kg/d in rats ameliorated left carotid thickness after the upregulation of p27 and the downregulation of protein cyclin E (PCNA) (Dong et al. 2010). The administration of 20 mg/kg of baicalin promoted the NF-κB pathway with the production of iNOS, NO, superoxide anions and TNF-α, with a consequent improvement in the blood pressure of rats treated with LPS (Cheng et al. 2007). However, differing studies also sustain suppression of NF-κB, with the inhibition of thiorexin reductase (TrxR) and the activation of lymphocytes (Patwardhan et al. 2016), in fact, septic rats treated with 10 mg/kg demonstrated reduced LPS-induced myocardial inflammation. A study reported attenuation of hypoxia-induced pulmonary artery hypertension (PAH) in rats by pretreatment with baicalin (30 mg/kg), via upregulated p38 MAPK and downregulated MMP-9 expression in lung tissues (Yan et al. 2016).

5. Conclusions/future directions

Baicalein is a polyphenolic compound, widely distributed across *Scutellaria* species, with interesting biological effects. It resulted to beneficial properties against general pathogenic mechanisms in a variety of preclinical experimental models, where its main biological effects are prompted by its antioxidant and anti-inflammatory activities. Thus, baicalein may halt the progression of chronic degenerative disorders, such as cardiometabolic, neurological, bone and oncological disorders. Unlike other flavonoids, baicalein is liposoluble, with considerable permeability and absorption through the gastrointestinal tract, and fast distribution to the cerebrospinal fluid. Thus, it could be considered as a possible alternative to conventional therapies, especially in the treatment and prevention of neurodegenerative disorders. However, the efficacy and tolerability of baicalein in humans is still lacking, and its in-depth analysis in robust randomized clinical trials should be highly encouraged before any solid conclusions are drawn, so as to obtain information on its bioactive doses and routes of administration.

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References

Ahn, H.C., Lee, S.Y., Kim, J.W., Son, W.S., Shin, C.G., Lee, B.J., 2001. Binding aspects of baicalein to HIV-1 integrase. Mol. Cells. 12, 127-130.

Akao, T., Kawabata, K., Yanagisawa, E., Ishihara, K., Mizuhara, Y., Wakui, Y., Sakashita, Y., Kobashi, K., 2010. Balicalin, the predominant flavone glucuronide of *Scutellariae* Radix, is absorbed from the rat gastrointestinal tract as the aglycone and restored to its original form. J. Pharm. Pharmacol. 52, 1563–1568.

Alam, S., Khan, F., 2018. Virtual screening, docking, ADMET and system pharmacology studies on *Garcinia* caged xanthone derivatives for anticancer activity. Sci. Rep. 8, 5524.

Bharti, A.C., Aggarwal, B.B., 2002. Nuclear factor-kappa B and cancer: Its role in prevention and therapy. Biochem. Pharmacol. 64, 883–888.

Blaszczyk, T., Krzyzanowska, J., Lamer-Zarawska, E., 2000. Screening for antimycotic properties of 56 traditional Chinese drugs. Phytother. Res. 14, 210-212.

Butenko, I.G., Gladtchenko, S.V., Galushko, S.V., 1993. Anti-inflammatory properties and inhibition of leukotriene C4 biosynthesisin vitro by flavonoid baicalein from *Scutellaria baicalensis* Georgy roots. Agents Actions 39, C49-51.

Chan, B.C., Ip, M., Lau, C.B., Lui, S.L., Jolivalt, C., Ganem-Elbaz, C., Litaudon, M., Reiner, N.E., Gong, H., See, R.H., Fung, K.P., 2011. Synergistic effects of baicalein with ciprofloxacin against NorA over-expressed methicillin-resistant *Staphylococcus aureus* (MRSA) and inhibition of MRSA pyruvate kinase. J. Ethnopharmacol. 137, 767-773.

Chen, H., Xu, Y., Wang, J., Zhao, W., Ruan, H., 2015. Baicalin ameliorates isoproterenol-induced acute myocardial infarction through iNOS, inflammation and oxidative stress in rat. Int. J. Clin. Exp. Pathol. 8, 10139–10147.

Cheng, P.Y., Lee, Y.M., Wu, Y.S., Chang, T.W., Jin, J.S., Yen, M.H., 2007. Protective effect of baicalein against endotoxic shock in rats in vivo and in vitro. Biochem. Pharmacol. 73, 793-804.

Chethankumara, G.P., Nagaraj, K., Krishna, V., Krishnaswamy, G., 2021. Isolation, characterization and in vitro cytotoxicity studies of bioactive compounds from *Alseodaphne semecarpifolia* Nees. Heliyon 7, e07325.

Cho, Y.A., Choi, J.S., Burm, J.P., 2011. Effects of the antioxidant baicalein on the pharmacokinetics of nimodipine in rats: a possible role of P-glycoprotein and CYP3A4 inhibition by baicalein. Pharmacol. Rep. 63, 1066-73.

Dai, H., Zhang, X., Yang, Z., Li, J., Zheng, J., 2017. Effects of baicalin on blood pressure and left ventricular remodeling in rats with renovascular hypertension. Med. Sci. Monit. 23, 2939–2948.

De Clercq, E., 2000. Current lead natural products for the chemotherapy of human immunodeficiency virus (HIV) infection. Med. Res. Rev. 20, 323-349.

Dinda, B., Dinda, S., DasSharma, S., Banik, R., Chakraborty, A., Dinda, M., 2017. Therapeutic potentials of baicalin and its aglycone, baicalein against inflammatory disorders. Eur. J. Med. Chem. 131, 68-80.

Dong, L.H., Wen, J.K., Miao, S.B., Jia, Z., Hu, H.J., Sun, R.H., Wu, Y., Han, M., 2010. Baicalin inhibits PDGF-BB-stimulated vascular smooth muscle cell proliferation through suppressing PDGFRβ-ERK signaling and increase in p27 accumulation and prevents injury-induced neointimal hyperplasia. Cell Res. 20, 1252-1262.

Fan, G.W., Zhang, Y., Jiang, X., Zhu, Y., Wang, B., Su, L., Cao, W., Zhang, H., Gao, X., 2013. Anti-inflammatory activity of baicalein in LPS-stimulated RAW264. 7 macrophages via

estrogen receptor and NF-κB-dependent pathways. Inflammation 36, 1584-91.

Fang, P., Yu, M., Shi, M., Bo, P., Gu, X., Zhang, Z., 2020. Baicalin and its aglycone: a novel approach for treatment of metabolic disorders. Pharmacol. Rep. 72, 13-23.

Fei, F., Zhang, D., Yang, Z., Wang, S., Wang, X., Wu, Z., Wu, Q., Zhang, S., 2015. The number of polyploid giant cancer cells and epithelial-mesenchymal transition-related proteins are associated with invasion and metastasis in human breast cancer. J. Exp. Clin. Cancer Res. 34, 158.

Galliera, E., Corsi, M.M., Bonecchi, R., Locati, M., Mantovani, A., 2008. Chemokines as pharmacological targets. Mini Rev. Med. Chem. 8, 638–646.

Gao, C., Ai-Ying, W., 2009. Significance of increased apoptosis and Bax expression in human small intestinal adenocarcinoma. J. Histochem. Cytochem. 57, 1139–1148.

Gao, C., Zhou, Y., Li, H., Cong, X., Jiang, Z., Wang, X., Cao, R., Tian, W., 2017. Antitumor effects of baicalin on ovarian cancer cells through induction of cell apoptosis and inhibition of cell migration in vitro. Mol. Med. Rep. 16, 8729–8734.

Golkar, Z., Bagasra, O., Pace, D.G., 2014. Bacteriophage therapy: A potential solution for the antibiotic resistance crisis. J. Infect. Dev. Ctries. 8, 129–136.

Gong, G., Wang, H., Kong, X., Duan, R., Dong, T.T., Tsim, K.W., 2018. Flavonoids are identified from the extract of *Scutellariae* radix to suppress inflammatory-induced angiogenic responses in cultured raw 264.7 macrophages. Sci. Rep. 8, 17412.

Gross, A., McDonnell, J.M., Korsmeyer, S.J., 1999. BCL-2 family members and the mitochondria in apoptosis. Genes Dev. 13, 1899–1911.

Guo, H.X., Liu, D.H., Ma, Y., Liu, J.F., Wang, Y., Du, Z.Y., Wang, X., Shen, J.K., Peng, H.L., 2009. Long-term baicalin administration ameliorates metabolic disorders and hepatic steatosis in rats given a high-fat diet. Acta Pharmacol. Sin. 30, 1505–1512.

Hang, Y., Qin, X., Ren, T., Cao, J., 2018. Baicalin reduces blood lipids and inflammation in patients with coronary artery disease and rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. Lipids Health Dis. 17, 146.

He, X.W., Yu, D., Li, W.L., Zheng, Z., Lv, C.L., Li, C., Liu, P., Xu, C.Q., Hu, X.F., Jin, X.P., 2016. Anti-atherosclerotic potential of baicalin mediated by promoting cholesterol efflux from macrophages via the PPARγ-LXRα-ABCA1/ABCG1 pathway. Biomed. Pharmacother. 83, 257–264.

Heidenreich, P.A., Trogdon, J.G., Khavjou, O.A., Butler, J., Dracup, K., Ezekowitz, M.D., Finkelstein, E.A., Hong, Y., Johnston, S.C., Khera, A., Lloyd-Jones, D.M., 2011. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 123, 933–944.

Hosseini, A.M., Majidi, J., Baradaran, B., Yousefi, M., 2015. Toll-like receptors in the pathogenesis of autoimmune diseases. Adv. Pharm. Bull. 5, 605-614.

Huang, H., Zhang, Y., Yang, R., Tang, X., 2008. Determination of baicalin in rat cerebrospinal fluid and blood using microdialysis coupled with ultra-performance liquid chromatography-tandem mass spectrometry. J. Chromatogr. B. 874, 77–83.

Huang, Q., Zhang, J., Peng, J., Zhang, Y., Wang, L., Wu, J., Ye, L., Fang, C., 2019. Effect of baicalin on proliferation and apoptosis in pancreatic cancer cells. Am. J. Transl. Res. 11, 5645–5654.

Huang, Y., Hu, J., Zheng, J., Li, J., Wei, T., Zheng, Z., Chen, Y., 2012. Down-regulation of the PI3K/Akt signaling pathway and induction of apoptosis in CA46 Burkitt lymphoma cells by baicalin. J. Exp. Clin. Cancer Res. 31, 48.

Kalapos-Kovács, B., Magda, B., Jani, M., Fekete, Z., Szabó, P.T., Antal, I., Krajcsi, P., Klebovich, I., 2015. Multiple ABC transporters efflux baicalin. Phytother. Res. 29, 1987–1990.

Kang, K.A., Zhang, R., Piao, M.J., Chae, S., Kim, H.S., Park, J.H., Jung, K.S., Hyun, J.W., 2012. Baicalein inhibits oxidative stress-induced cellular damage via antioxidant effects. Toxicol. Ind. Health. 28, 412-21.

Ke, M., Zhang, Z., Xu, B., Zhao, S., Ding, Y., Wu, X., Wu, R., Lv, Y., Dong, J., 2019. Baicalein and baicalin promote antitumor immunity by suppressing PD-L1 expression in

hepatocellular carcinoma cells. Int. Immunopharmacol. 75, 105824.

Kim, Y.J., Kim, H.J., Lee, J.Y., Kim, D.H., Kang, M.S., Park, W., 2018. Anti-inflammatory effect of baicalein on polyinosinic–polycytidylic acid-induced RAW 264.7 mouse macrophages. Viruses 10, 224.

Kitamura, K., Honda, M., Yoshizaki, H., Yamamoto, S., Nakane, H., Fukushima, M., Ono, K., Tokunaga, T., 1998. Baicalin, an inhibitor of HIV-1 production in vitro. Antivir. Res. 37, 131-140.

Kong, E.K., Yu, S., Sanderson, J.E., Chen, K.B., Huang, Y., Yu, C.M., 2011. A novel anti-fibrotic agent, baicalein, for the treatment of myocardial fibrosis in spontaneously hypertensive rats. Eur. J. Pharmacol. 658, 175-181.

Ku, S.K., Bae, J.S., 2015. Baicalin, baicalein and wogonin inhibits high glucose-induced vascular inflammation in vitro and in vivo. BMB Rep. 48, 519.

Lai, M.Y., Hsiu, S.L., Chen, C.C., Hou, Y.C., Chao, P.D.L., 2003. Urinary pharmacokinetics of baicalein, wogonin and their glycosides after oral administration of *Scutellariae* Radix in humans. Biol. Pharm. Bull. 26, 79–83.

Lambert, J.D., Elias, R.J., 2010. The antioxidant and pro-oxidant activities of green tea polyphenols: A role in cancer prevention. Arch. Biochem. Biophys. 501, 65–72.

Lee, H., Kang, R., Hahn, Y., Yang, Y., Kim, S.S., Cho, S.H., Chung, S.I., Yoon, Y., 2009. Antiobesity effect of baicalin involves the modulations of proadipogenic and antiadipogenic regulators of the adipogenesis pathway: antiobesity mechanism of baicalin. Phytother. Res. 23, 1615–1623.

Lee, I.K., Kang, K.A., Zhang, R., Kim, B.J., Kang, S.S., Hyun, J.W., 2011. Mitochondria protection of baicalein against oxidative damage via induction of manganese superoxide dismutase. Environ. Toxicol. Pharmacol. 31, 233-241.

Li, B., Wang, M., Chen, S., Li, M., Zeng, J., Wu, S., Tu, Y., Li, Y., Zhang, R., Huang, F., Tong, X., 2022. Baicalin mitigates the neuroinflammation through the TLR4/MyD88/NF-κB and MAPK pathways in LPS-stimulated BV-2 microglia. Biomed. Res. Int. 2022, 3263446.

Li, B.Q., Fu, T., Dongyan, Y., Mikovits, J.A., Ruscetti, F.W., Wang, J.M., 2000. Flavonoid baicalin inhibits HIV-1 infection at the level of viral entry. Biochem. Biophys. Res. Commun. 276, 534-538.

Li, C., Lin, G., Zuo, Z., 2011. Pharmacological effects and pharmacokinetics properties of Radix *Scutellariae* and its bioactive flavones. Biopharm. Drug Dispos. 32, 427–445.

Li, H., He, H., Huang, J., Wang, C.Z., Gu, X., Gao, Y., Zhang, H., Du, S., Chen, L., Yuan, C.S., 2016. A novel molecularly imprinted method with computational simulation for the affinity isolation and knockout of baicalein from *Scutellaria baicalensis*. Biomed. Chromatogr. 30, 117–125.

Li, H.T., Wu, X.D., Davey, A.K., Wang, J., 2011. Antihyperglycemic effects of baicalin on streptozotocin–nicotinamide induced diabetic rats. Phytother. Res. 25, 189-194.

Li, M., Shi, A., Pang, H., Xue, W., Li, Y., Cao, G., Yan, B., Dong, F., Li, K., Xiao, W., He, G., 2014. Safety, tolerability, and pharmacokinetics of a single ascending dose of baicalein chewable tablets in healthy subjects. J. Ethnopharmacol. 156, 210–215.

Li, P., Zhang, R., Wang, M., Chen, Y., Chen, Z., Ke, X., Zuo, L., Wang, J., 2022. Baicalein prevents fructose-induced hepatic steatosis in rats: In the regulation of fatty acid de Novo synthesis, fatty acid elongation and fatty acid oxidation. Front. Pharmacol. 13, 917329.

Lin, C.C., Shieh, D.E., 1996. The anti-inflammatory activity of *Scutellaria rivularis* extracts and its active components, baicalin, baicalein and wogonin. Am. J. Chinese Med. 24, 31-6.

Lin, M.G., Liu, L.P., Li, C.Y., Zhang, M., Chen, Y., Qin, J., Gu, Y.Y., Li, Z., Wu, X.L., Mo, S.L., 2013. *Scutellaria* extract decreases the proportion of side population cells in a myeloma cell line by down-regulating the expression of ABCG2 protein. Asian Pac. J. Cancer Prev. 14, 7179–7186.

Liu, S.Z., Deng, Y.X., Chen, B., Zhang, X.J., Shi, Q.Z., Qiu, X.M., 2013. Antihyperglycemic effect of the traditional Chinese *Scutellaria-Coptis* herb couple and its main components in streptozotocin-induced diabetic rats. J. Ethnopharmacol. 145, 490–8.

Liu, W., Kato, M., Akhand, A.A., Hayakawa, A., Takemura, M., Yoshida, S., Suzuki, H., Nakashima, I., 1998. The herbal medicine sho-saiko-to inhibits the growth of malignant melanoma cells by upregulating Fas-mediated apoptosis and arresting cell cycle through downregulation of cyclin dependent kinases. Int. J. Oncol. 12, 1321–1326.

Liu, Y., Hong, Z., Chen, P., Wang, J., Zhou, Y., Huang, J., 2019. Baicalin inhibits growth and induces apoptosis of human osteosarcoma cells by suppressing the AKT pathway. Oncol. Lett. 18, 3188–3194.

Li-Weber, M., 2009. New therapeutic aspects of flavones: the anticancer properties of *Scutellaria* and its main active constituents wogonin, baicalein and baicalin. Cancer Treat. Rev. 35, 57-68.

Lu, T., Song, J., Huang, F., Deng, Y., Xie, L., Wang, G., Liu, X., 2007. Comparative pharmacokinetics of baicalin after oral administration of pure baicalin, Radix *Scutellariae* extract and Huang-Lian-Jie-Du-Tang to rats. J. Ethnopharmacol. 110, 412–418.

Medzhitov, R., 2008. Origin and physiological roles of inflammation. Nature 454, 428-35.

Memar, M.Y., Raei, P., Alizadeh, N., Aghdam, M.A., Kafil, H.S., 2017. Carvacrol and thymol: strong antimicrobial agents against resistant isolates. Rev. Med. Microbiol. 28, 63–68.

Min, H.K., Kapoor, A., Fuchs, M., Mirshahi, F., Zhou, H., Maher, J., Kellum, J., Warnick, R., Contos, M.J., Sanyal, A.J., 2012. Increased hepatic synthesis and dysregulation of cholesterol metabolism is associated with the severity of nonalcoholic fatty liver disease. Cell Metab. 15, 665–674.

Min, W., Ahmad, I., Chang, M.E., Burns, E.M., Qian, Q., Yusuf, N., 2015. Baicalin protects keratinocytes from Toll-like receptor-4 mediated DNA damage and inflammation following ultraviolet irradiation. Photochem. Photobiol. 91, 1435-1443.

Min, W., Wu, M., Fang, P., Yu, M., Shi, M., Zhang, Z., Bo, P., 2018. Effect of baicalein on GLUT4 translocation in adipocytes of diet-induced obese mice. Cell. Physiol. Biochem. 50, 426–436.

Nik Salleh, N.N.H., Othman, F.A., Kamarudin, N.A., Tan, S.C., 2020. The biological activities and therapeutic potentials of baicalein extracted from *Oroxylum indicum*: a systematic review. Molecules 25, 5677.

Ono, K., Nakane, H., Fukushima, M., Chermann, J.C., Barré-Sinoussi, F., 1989. Inhibition of reverse transcriptase activity by a flavonoid compound, 5, 6, 7-trihydroxyflavone. Biochem. Biophys. Res. Commun. 160, 982-987.

Palierse, E., Hélary, C., Krafft, J.M., Génois, I., Masse, S., Laurent, G., Echazu, M.I., Selmane, M., Casale, S., Valentin, L., Miche, A., 2021. Baicalein-modified hydroxyapatite nanoparticles and coatings with antibacterial and antioxidant properties. Mater. Sci. Eng. C. 118, 111537.

Patwardhan, R.S., Sharma, D., Thoh, M., Checker, R., Sandur, S.K., 2016. Baicalein exhibits anti-inflammatory effects via inhibition of NF-κB transactivation. Biochem. Pharmacol. 108, 75-89.

Ren, M., Zhao, Y., He, Z., Lin, J., Xu, C., Liu, F., Hu, R., Deng, H., Wang, Y., 2021. Baicalein inhibits inflammatory response and promotes osteogenic activity in periodontal ligament cells challenged with lipopolysaccharides. BMC Complement. Med. Ther. 21, 43.

Shan, B., Cai, Y.Z., Brooks, J.D., Corke, H., 2007. The in vitro antibacterial activity of dietary spice and medicinal herb extracts. Int. J. Food Microbiol. 117, 112-119.

Shao, Z.H., Vanden Hoek, T.L., Qin, Y., Becker, L.B., Schumacker, P.T., Li, C.Q., Dey, L., Barth, E., Halpern, H., Rosen, G.M., Yuan, C.S., 2002. Baicalein attenuates oxidant stress in cardiomyocytes. Am. J. Physiol. Heart Circ. Physiol. 282, H999-1006.

Shaw, L.H., Lin, L.C., Tsai, T.H., 2012. HPLC–MS/MS Analysis of a traditional Chinese medical formulation of Bu-Yang-Huan-Wu-Tang and its pharmacokinetics after oral administration to rats. PLoS One 7, e43848.

Song, J.Z., Li, L.J., Ji, L., Shun, L., Rui, Y., 2017. The pharmacokinetics of Tiangou antihypertensive capsule in rat in vivo. Biomed. Rep. 6, 113–119.

Suk, K., Lee, H., Kang, S.S., Cho, G.J., Choi, W.S., 2003. Flavonoid baicalein attenuates activation-induced cell death of brain microglia. J. Pharmacol. Exp. Ther. 305, 638-645.

Takeda, K., Kaisho, T., Akira, S., 2003. Toll-like receptors. Annu. Rev. Immunol. 21, 335–376.

Tang, Y., Zhu, H., Zhang, Y., Huang, C., 2006. Determination of human plasma protein binding of baicalin by ultrafiltration and high-performance liquid chromatography. Biomed. Chromatogr. 20, 1116–1119.

Tao, H., Zhao, Y., Li, L., He, Y., Zhang, X., Zhu, Y., Hong, G., 2023. Comparative metabolomics of flavonoids in twenty vegetables reveal their nutritional diversity and potential health benefits. Food Res. Int. 164, 112384.

Tong, L., Wan, M., Zhang, L., Zhu, Y., Sun, H., Bi, K., 2012. Simultaneous determination of baicalin, wogonoside, baicalein, wogonin, oroxylin A and chrysin of Radix *Scutellariae* extract in rat plasma by liquid chromatography tandem mass spectrometry. J. Pharm. Biomed. Anal. 70, 6–12.

Waisundara, V.Y., Siu, S.Y., Hsu, A., Huang, D., Tan, B.K.H., 2011. Baicalin upregulates the genetic expression of antioxidant enzymes in type-2 diabetic Goto-Kakizaki rats. Life Sci. 88, 1016–1025.

Wan, D., Ouyang, H., 2017. Baicalin induces apoptosis in human osteosarcoma cell through ROS-mediated mitochondrial pathway. Nat. Prod. Res. 32, 1996–2000.

Wang, N., Tang, L.J., Zhu, G.Q., Peng, D.Y., Wang, L., Sun, F.N., Li, Q.L., 2008. Apoptosis induced by baicalin involving up-regulation of P53 and bax in MCF-7 cells. J. Asian Nat. Prod. Res. 10, 1129–1135.

Wang, T., Jiang, H., Cao, S., Chen, Q., Cui, M., Wang, Z., Li, D., Zhou, J., Qiu, F., Kang, N., 2017. Baicalin and its metabolites suppresses gluconeogenesis through activation of AMPK or AKT in insulin resistant HepG-2 cells. Eur. J. Med. Chem. 141, 92-100.

Wang, X., Smith, C., Yin, H., 2013. Targeting Toll-like receptors with small molecule agents. Chem. Soc. Rev. 42, 4859.

Weber D. 2010. Inflammation and cancer: tumor initiation, progression and metastasis, and Chinese botanical medicines. Chin. J. Integr. Med. 8, 1006–1013.

Wei, Y., Pi, C., Yang, G., Xiong, X., Lan, Y., Yang, H., Zhou, Y., Ye, Y., Zou, Y., Zheng, W., Zhao, L., 2016. LC-UV determination of baicalin in rabbit plasma and tissues for application in pharmacokinetics and tissue distribution studies of baicalin after intravenous administration of liposomal and injectable formulations. Molecules 21, 444.

Wu, Y., Wang, F., Fan, L., Zhang, W., Wang, T., Du, Y., Bai, X., 2018. Baicalin alleviates atherosclerosis by relieving oxidative stress and inflammatory responses via inactivating the NF-κB and p38 MAPK signaling pathways. Biomed. Pharmacother. 97, 1673–1679.

Xi, Y., Wu, M., Li, H., Dong, S., Luo, E., Gu, M., Shen, X., Jiang, Y., Liu, Y., Liu, H., 2015. Baicalin attenuates high fat diet-induced obesity and liver dysfunction: dose-response and potential role of CaMKKβ/AMPK/ACC pathway. Cell. Physiol. Biochem. 35, 2349–2359.

Xing, J., Chen, X., Zhong, D., 2005. Absorption and enterohepatic circulation of baicalin in rats. Life Sci. 78, 140–146.

Yan G, Chen L, Wang H, Wu S, Li S, Wang X. 2021. Baicalin inhibits LPS-induced inflammation in RAW264. 7 cells through miR-181b/HMGB1/TRL4/NF-κB pathway. Am. J. Transl. Res. 13, 10127.

Yan, S., Wang, Y., Liu, P., Chen, A., Chen, M., Yao, D., Xu, X., Wang, L., Huang, X., 2016. Baicalin attenuates hypoxia-induced pulmonary arterial hypertension to improve hypoxic cor pulmonale by reducing the activity of the p38 MAPK signaling pathway and MMP-9. Evid. Based Complement. Alternat. Med. 2016, 2546402.

Yang, B., Bai, H., Sa, Y., Zhu, P., Liu, P., 2020. Inhibiting EMT, stemness and cell cycle involved in baicalin-induced growth inhibition and apoptosis in colorectal cancer cells. J. Cancer. 11, 2303–2317.

Yang, L.L., Xiao, N., Liu, J., Liu, K., Liu, B., Li, P., Qi, L.W., 2017. Differential regulation of baicalin and scutellarin on AMPK and Akt in promoting adipose cell glucose disposal. Biochim. Biophys. Acta Mol. Basis Dis. 1863, 598–606.

Yang, Z.C., Wang, B.C., Yang, X.S., Wang, Q., Ran, L., 2005. The synergistic activity of antibiotics combined with eight traditional Chinese medicines against two different strains of *Staphylococcus aureus*. Colloids Surf. B: Biointerfaces 41, 79-81.

Yu, Y., Pei, M., Li, L., 2015. Baicalin induces apoptosis in hepatic cancer cells in vitro and suppresses tumor growth in vivo. Int. J. Clin. Exp. Med. 8, 8958–8967.

Yun, C., Wang, S., Gao, Y., Zhao, Z., Miao, N., Shi, Y., Ri, I., Wang, W., Wang, H., 2022. Optimization of ultrasound-assisted enzymatic pretreatment for enhanced extraction of baicalein and wogonin from *Scutellaria baicalensis* roots. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 1188, 123077.

Zhang, R., Cui, Y., Wang, Y., Tian, X., Zheng, L., Cong, H., Wu, B., Huo, X., Wang, C., Zhang, B., Wang, X., 2017. Catechol-O-methyltransferase and UDP-glucuronosyltransferases in the metabolism of baicalein in different species. Eur. J. Drug Metab. Pharmacokinet. 42, 981–992.

Zhao, D., Liu, J., Wang, M., Zhang, X., Zhou, M., 2019. Epidemiology of cardiovascular disease in China: current features and implications. Nat. Rev. Cardiol. 16, 203–212.

Zhao, J., Zhang, Z., Chen, H., Zhang, X., Chen, X., 1998. Synthesis of baicalin derivatives and evaluation of their anti-human immunodeficiency virus (HIV-1) activity. Yao Xue Xue Bao 33, 22-27.

Zheng, J., Asakawa, T., Chen, Y., Zheng, Z., Chen, B., Lin, M., Liu, T., Hu, J., 2017. Synergistic effect of baicalin and adriamycin in resistant HL-60/ADM leukaemia cells. Cell. Physiol. Biochem. 43, 419–430.

Zheng, J., Hu, J.D., Huang, Y., Chen, Y.Y., Li, J., Chen, B.Y., 2012. Effects of baicalin on HL-60 cell xenografts in nude mice and its mechanism. Zhongguo Shi Yan Xue Ye Xue Za Zhi 20, 1066–1071.

Zhu, D., Wang, S., Lawless, J., He, J., Zheng, Z., 2016. Dose dependent dual effect of baicalin and herb Huang Qin extract on angiogenesis. PLoS One 11, e0167125.

Zhu, Y.P., Woerdenbag, H.J., 1995. Traditional Chinese herbal medicine. Pharm. World Sci. 17, 103–112.