

Research progress on pharmacological effects and new dosage forms of baicalin

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Abstract

Background: As a kind of flavonoid, baicalin (C₂₁H₁₈O₁₁) is extracted from *Scutellaria baicalensis* Georgi, the extract of which can be added to animal feed in China.

Objectives: The present review will describe the current understanding of the pharmacological effects of baicalin in the regulation of inflammation, oxidative stress anti-virus and anti-tumour responses.

Methods: We highlight emerging literature that the application in livestock health and performance, the biological activities, the molecular mechanisms and the dosage forms of baicalin by analysing and summarising the main points of the cited literatures.

Results: It is found that baicalin can improve the functions of multiple physiological systems. Baicalin has a strong anti-inflammatory effect by regulating TLR4-NFκB-MAPK signalling pathway; it also can reduce oxidative stress by regulating Nrf2-Keap1 pathway; it can inhabit many kinds of virus such as influenza virus, respiratory virus, hepatitis virus and others; it can also inhibit the growth of tumour cells by blocking the cell cycle or inducing apoptosis; and new dosage forms such as cationic solid lipid nanoparticles, cyclodextrin inclusion complexes or nanocrystalline can be applied to improve the deficiency of baicalin.

Conclusions: In summary, these studies have elucidated a comprehensive report on the anti-inflammatory, anti-oxidant, anti-virus and anti-tumour of baicalin, these findings thus indicated that baicalin can be used effectively to the field of animal production in future when the appropriate dosage form is determined.

KEYWORDS

anti-inflammatory, anti-oxidant, anti-tumour, anti-viral, baicalin

Baicalin (C₂₁H₁₈O₁₁) is a flavonoid extracted from the dried roots of *Scutellaria baicalensis* Georgi. The species can be planted and produced in most provinces of northern China with relatively sufficient resources. Baicalin is the main active component of *Scutellaria*

baicalensis, and it possesses several biological effects, such as anti-inflammatory (Yanqiu et al., 2019), anti-oxidant (Yutao et al., 2017), anti-viral (Jia et al., 2016) and anti-tumour (Yuan et al., 2015) activity. Other pharmacological actions of the compound include anti-bacterial

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activity, heat clearing, and detoxification (Bin et al., 2019). In this paper, the molecular mechanisms of the anti-inflammatory, anti-oxidant and anti-tumour effects of baicalin, as well as the relationships among inflammation, oxidative stress, and cancer metastasis, are summarised to clarify the targets of baicalin and facilitate its clinical use.

1 | APPLICATION OF BAICALIN IN LIVESTOCK HEALTH AND PERFORMANCE

Baicalin is a natural compound with multiple biological functions, such as anti-inflammatory, anti-oxidant, anti-viral and so on. Though the effects and mechanisms of baicalin playing biological functions have been explicated successfully, there were few review about the application of baicalin for animal husbandry production. At present, it has been proved that baicalin can improve the functions of multiple physiological systems (respiratory system, digestive system, cardiovascular system, etc.) by the ways of anti-inflammatory, anti-oxidant or anti-viral to protect pigs, cattle, birds, fish and others. Moreover, according to regulations of Ministry of Agriculture and Rural Development of the People's Republic of China, the extract of *Scutellaria baicalensis Georgi* (the content of baicalin is more than 85%) plays the role of anti-inflammatory, bacteriostatic and growth promotion, which can be added to animal feed as a medicine to improve the growth performance of broilers and weaned piglets. So, it can be anticipated that baicalin would be used effectively to the field of animal production in future. The therapeutic effects of baicalin on animal husbandry production are shown below (Table 1).

2 | ANTI-INFLAMMATORY EFFECTS OF BAICALIN AND ITS MOLECULAR MECHANISMS

Inflammation is a process by which the body resists foreign pathogens. However, excessive inflammation can lead to tissue damage. Inflammatory reactions have roles in several diseases in organisms. Acute inflammatory reaction is generally the attack period of the course of disease. This process involves the release of a large number of inflammatory mediators, causing symptoms such as swelling and pain (Zeng et al., 2020). The acute aggravation of allergic respiratory tract inflammation caused by particulate matter results in extensive inflammatory factor secretion, which leads to respiratory oedema (Dai et al., 2020). Chronic low-grade inflammation may occur in various aging tissues (Franceschi & Campisi, 2014). The types of tissue damage associated with excessive inflammation include intestinal immune cell damage following excessive tumour necrosis factor alpha (TNF- α) release, which leads to intestinal barrier dysfunction (Soderholm, 2002).

Baicalin has a strong anti-inflammatory effect. In mice, baicalin can protect the intestinal epithelium of rats by inhibiting the secretion of inflammatory factors (Jian et al., 2015). Baicalin can suppress the inflammatory response in the liver and reduce cell death (Huilian et al., 2020). Baicalin can also effectively suppress lipopolysaccharide (LPS)-induced liver inflammation in poultry (Cheng et al., 2017). At the

cellular level, baicalin can enhance the cytotoxic effect of neutrophils on *Staphylococcus aureus* and effectively suppress the inflammatory response in bovine mammary epithelial cells (Jia et al., 2020). Baicalin can protect the intestinal mucosal barrier by blocking the adhesion of pathogenic *Escherichia coli* to porcine small intestinal epithelial cells, and reducing the inflammatory response in cells (Liu et al., 2019). Baicalin can exert inhibitory effects on *E. coli* by inhibiting the biological activity of ATP synthase of *E. coli*. This function is important for maintaining the integrity of the intestinal mucosal barrier (Chinnam et al., 2010). Baicalin improved cell viability, suppress apoptosis (Guo et al., 2014), and inhibit the production of the inflammatory factors TNF- α , interleukin (IL-6 and IL-8) in a mouse mammary epithelial cell mastitis model (Yang et al., 2018). These studies illustrated that baicalin, as a natural plant extract, has a good therapeutic effect on inflammation induced by inflammatory diseases or in vitro treatments.

The Toll-like receptor 4 (TLR4) NF- κ B signalling pathway plays an extremely important role in the regulation of inflammation in the body. TLR4, a member of the TLR family that is expressed on the surface of cell membranes, can recognise cascades of extracellular stimuli that ultimately lead to inflammation (Wada & Makino, 2016). NF- κ B is a pleiotropic regulator of a variety of damage response genes. In normal cells, NF- κ B binds to inhibitor of kappa B (I κ B) and exists in the cytoplasm. Following stimulation, I κ B is phosphorylated and degraded, which leads to NF- κ B activation. Activated NF- κ B binds to p65/p50 proteins and enters the nucleus in the form of heterodimers to bind to corresponding target sites on DNA, thereby regulating downstream pro-inflammatory factors (TNF- α , IL-1 β , chemokines and adhesion factors) (Sumner et al., 2014).

In vivo, baicalin can reduce the mRNA and protein expression of TLR2/4 and reduce the expression of NF- κ B, p65, cyclooxygenase-2, TNF- α and IL-6 in serum (Tu et al., 2011). Baicalin (Yan et al., 2019) can inhibit the protein expression of p-p65 and p-extracellular signal-related kinase (ERK) and promote the expression of p-AKT and p-endothelial nitric oxide synthase in rats. Baicalin can inhibit the TLR-NF- κ B signalling pathway to alleviate experimental colitis and hepatic inflammation in chicken (Heng Zhai, 2019; Zhang et al., 2013). Baicalin can improve chronic gastritis and cerebral ischaemic inflammation in rats (Wanli et al., 2019). In vitro, baicalin can suppress the inflammatory injury of porcine intestinal epithelial cells by inhibiting the NF- κ B signalling pathway (Zhongqing et al., 2019). Baicalin has obvious therapeutic effect on the inflammatory response induced by LPS in human cardiomyocytes. Baicalin significantly downregulated TLR4, p-NF- κ B p65, p-p38 MAPK and p-I κ B protein expression in prior research (Xiangyu et al., 2020). Cui et al. (2014) found that baicalin can block TLR4-NF- κ B pathway activation and inhibit the inflammatory response to LPS in RAW264.7 cells. Baicalin can significantly inhibit inflammatory responses in vivo and at the cellular level in animals. Baicalin can inhibit the upregulation of TLR4 signalling on the cell surface and thus block the production of inflammatory mediators. From these findings, it can be stated that the main target of baicalin as an anti-inflammatory agent is TLR4, and inhibition of p38 phosphorylation (Liu et al., 2020) might have a key anti-inflammatory role.

TABLE 1 Therapeutic effect of baicalin on livestock and poultry diseases

Species	Pathogen infections	Pathological system	Action mechanism	Treatment dose and time
Pig	<i>G. parasuis</i>	Cardiovascular system	Anti-inflammation Anti-apoptotic (Fu et al., 2020)	50–100 mg/kg for 7 days
		Peritoneal system	Protect the integrity of peritoneal tight junction protein (Liu et al., 2021)	50–100 mg/kg for 8 days
	Deoxyrivinalenol	Intestinal system	Anti-oxidative stress Anti-inflammation Protect the structural integrity of Intestinal mucosa (Liao et al., 2020)	1% of basic diet for 14 days
Chicken	<i>Mycoplasma gallisepticum</i>	Respiratory system (lung and tracheal)	Anti-inflammatory Restoring energy or phenylalanine metabolism regulating the intestinal microbiota (Wang et al., 2021; Zou et al., 2021; Ishfaq et al., 2019; Ishfaq et al., 2021)	450 mg/kg for 5–7 days
		Immune system (bursa of fabricius, thymus, spleen etc.)	Anti-inflammation Anti-oxidative stress Anti-autophagy Anti-apoptosis (Li et al., 2019; Ishfaq et al., 2019; Zhang et al., 2020)	450 mg/kg for 5–7 days
	Zearalenone	Metabolic system (liver and kidney)	Anti-inflammation Anti-oxidative stress (Xu et al., 2021)	20–80 mg/kg for 7 days
	Avian pathogenic <i>Escherichia coli</i>	Respiratory system (lung and tracheal)	Anti-inflammation Regulating microorganism (Cheng et al., 2022, Peng et al., 2021)	50–200 mg/kg for 7 days
		Liver system	Anti-inflammation	50–200 mg/kg for 7 days
		Digestive system (intestine)	Anti-inflammation Improve intestinal barrier function (Peng et al., 2019; Peng et al., 2019)	10–20 mg/kg for 15 days
	H ₉ N ₂	Respiratory system (lung and tracheal)	Anti-bacterial Anti-inflammation (Wu et al., 2019)	0.05% of basic diet for 12 days
Cow	Milk quality	Lactation system	Anti-inflammation Reduce the number of Somatic cells Increase lactation (Olagaray et al., 2019)	3.3 g/day for 120 days
Duck	Duck virus hepatitis	Liver system	Anti-inflammation Anti-oxidative stress Inhibit virus replication (Su et al., 2021; Chen et al., 2019; Chen et al., 2018; Chen et al., 2018)	3 mg/kg for 3 days
Fish	H ₂ O ₂	Tilapia liver system	Anti-oxidative stress Promote growth (Jia et al., 2021)	0.8–1.6 mg/kg for 60 days
	Thioacetamide	Zebrafish liver system	Anti-inflammation Anti-oxidative stress Anti-apoptotic Promote liver growth and development (Zhang et al., 2020)	10 mg/kg for 2 days

The MAPK signalling pathway is a key signalling pathway that promotes inflammation, and p38 is one of the main effectors of this pathway (Gu et al., 2017). Phosphorylated p38 activates Janus kinase (JNK) and NF- κ B (Wang et al., 2018); thus, p38 phosphorylation can be an important indicator of inflammation. Baicalin exerts anti-inflammatory effects by inhibiting the phosphorylation of p38 and thereby inhibiting

the expression of related inflammatory factors (Winkler et al., 2017). For example, baicalin can reduce chronic inflammation in atherosclerosis by inhibiting p38 expression (Wu et al., 2018). Therefore, baicalin can regulate downstream signalling factors to exert anti-inflammatory effects through the TLR4–NF- κ B and p38 MAPK signalling pathways, and its possible target sites are TLR4 and p38.

Baicalin has been proven to have anti-microbial effects in particular. Some studies illustrated that baicalin can alleviate the pulmonary symptoms caused by *S. aureus* in mice (Luo et al., 2017). Baicalin can significantly inhibit the biological activity of *E. coli* cultured in vitro (Luo et al., 2017). Baicalin also has a significant inhibitory effect on drug-resistant *S. aureus* (Zhang et al., 2020) and *Helicobacter pylori* (Wu et al., 2013). For drug-resistant bacteria, baicalin can be used as an SOS inhibitor, which can significantly reduce the resistance mutation rate of *Staphylococcus aureus* to rifampicin induced by ciprofloxacin (Peng et al., 2011). For fungi, baicalin has a good inhibitory effect on *Candida albicans* (Dai et al., 2009). The invasion of bacterial pathogens into the body has been proved to be one of the important factors leading to inflammatory response (Ikuse et al., 2019). The antibacterial activity of baicalin is an important factor for baicalin to play a role in the treatment of inflammatory response.

3 | ANTI-OXIDANT EFFECTS OF BAICALIN AND ITS MOLECULAR MECHANISMS

Oxidative stress can cause tissue damage, and it occurs when free radicals attack tissue or cells (Kattoor et al., 2017). Oxidative stress is significantly associated with tumorigenesis (Chikara et al., 2018), aging (Zhang et al., 2018), pulmonary fibrosis (Gross & Hunninghake, 2001), Alzheimer's disease (Kamat et al., 2016), diabetes (McCracken et al., 2018), depression (Sumiao & Xingbing, 2019) and other diseases. Under normal conditions, the levels of free radicals and anti-oxidants are in a dynamic state of balance. When this balance is destroyed by some cause (e.g., acute hypoxia, drug toxicity, acute inflammatory reaction), the increased content of oxygen-rich active factors can lead to damage in the internal environment, including damage to DNA mitochondrial organelles (Fandy et al., 2014). Baicalin can scavenge free radicals and reactive oxygen species (ROS), inhibit oxidase activity, and enhance the expression of anti-oxidant and detoxification enzymes (Shi et al., 2018). Baicalin can reduce oxidative stress injury in trabecular meshwork cells in vitro by reducing oxidative stress, suppressing the activity of senescence-associated beta-galactosidase, and down-regulating carboxylated proteins (Gong & Zhu, 2018). Baicalin can improve oxidative stress induced by acute lung injury in mice through Nrf2-mediated haeme oxidase (HO-1) signalling (Meng et al., 2019).

The nuclear factor erythroid 2-related factor 2 (Nrf2)-Kelch like-ECH-associated protein (Keap1) pathway, a key signalling pathway in oxidative stress responses, has a significant anti-oxidant effect that is critical for cellular protection and cell survival. Under normal conditions, the Nrf2-Keap1 complex binds to actin in the cytoplasm. Nrf2-Keap1 is dissociated when oxidative stress occurs, and Nrf2 translocates to the nucleus, in which it binds anti-oxidative response elements and induces the synthesis of corresponding detoxification and anti-oxidant enzymes (Li et al., 2014; Tong et al., 2006). Baicalin has strong anti-oxidant effects, and it induces the nuclear translocation of Nrf2 (Draheim et al., 2016; Xue et al., 2017). Baicalin has a good effect against diseases caused by oxidative stress in animals. For example, baicalin can improve liver fibrosis in mice by regulating

oxidative stress and Nrf2 (Cui et al., 2014). The compound can inhibit oxidative stress through Nrf2-mediated HO-1 signalling, thereby alleviating acute lung injury induced by LPS in mice. The primary effect of baicalin on lung injury involves its direct activation of Nrf2, which regulates downstream anti-oxidant factors (Meng et al., 2019). Baicalin can improve insulin resistance in the livers of obese mice by increasing Nrf2 expression and reducing oxidative stress (Cui et al., 2014). Baicalin can improve oxidative damage in the oviduct in mice under heat stress (Xue et al., 2017). Therefore, these studies indicated that baicalin can reduce damage associated with diseases caused by oxidative stress by improving the oxidative stress response.

p38 MAPK phosphorylates I κ B (Shen et al., 2019). There are important relationships between oxidative stress and inflammatory responses. The in vitro stimulation of inflammatory responses, such as those induced by LPS through TLRs, leads to NF- κ B activation. Activated NF- κ B forms a complex with p65 and p50 in the nucleus to regulate the secretion of anti-inflammatory factors. In the presence of oxidative stress, the increased production of ROS promotes the activation of p38 MAPK and its downstream factors in the nucleus, which regulate the secretion of related signalling factors and form a negative feedback regulation to reduce intracellular ROS levels (Zhangzhao, 2019). Therefore, the p38 MAPK signalling pathway may be an important cascade for the interaction between inflammatory responses and oxidative stress. As a member of the MAPK family, p38 MAPK regulates a variety of intracellular signalling factors. The protein levels of the phosphorylated forms of NF- κ B, p38 MAPK, and I κ B are significantly increased and those of I κ B are decreased during the inflammatory response. Therefore, the inflammatory response is considered important in the regulation of MAPK signalling molecules.

Baicalin reduces inflammatory and oxidative stress responses through the p38 MAPK signalling pathway, thereby improving insulin resistance in the livers of obese mice (Fang et al., 2019). As a therapeutic agent, baicalin can reduce both inflammatory responses and oxidative stress. Baicalin can treat liver fibrosis in mice by regulating inflammatory responses, oxidative stress and Nrf2 (Cui et al., 2014). Baicalin can inhibit oxidative stress and inflammation through the Nrf2-mediated HO-1 signalling pathway, which leads to improvements of acute lung injury induced by LPS in mice (Meng et al., 2019). Baicalin can improve insulin resistance in the livers of obese mice by increasing Nrf2 expression and reducing oxidative stress and inflammatory responses (Cui et al., 2014). In summary, the pharmacological action of baicalin involves the combination of multiple pathways targeting both inflammatory responses and oxidative stress. Its molecular pathways interact with each other through MAPK, NF- κ B and other signalling factors (Figure 1).

Baicalin can play a therapeutic role on cardiovascular diseases through antioxidant biological function. Baicalin can ameliorate acute myocardial infarction in rats induced by isoproterenol by inhibiting nitric oxide synthase, oxidative stress, and inflammation (Sun et al., 2015). Baicalin can reduce myocardial ischaemic injury in rats by reversing the inflammatory response through inducing the inactivation of aryl hydrocarbon receptor (Xue et al., 2015). In a rabbit

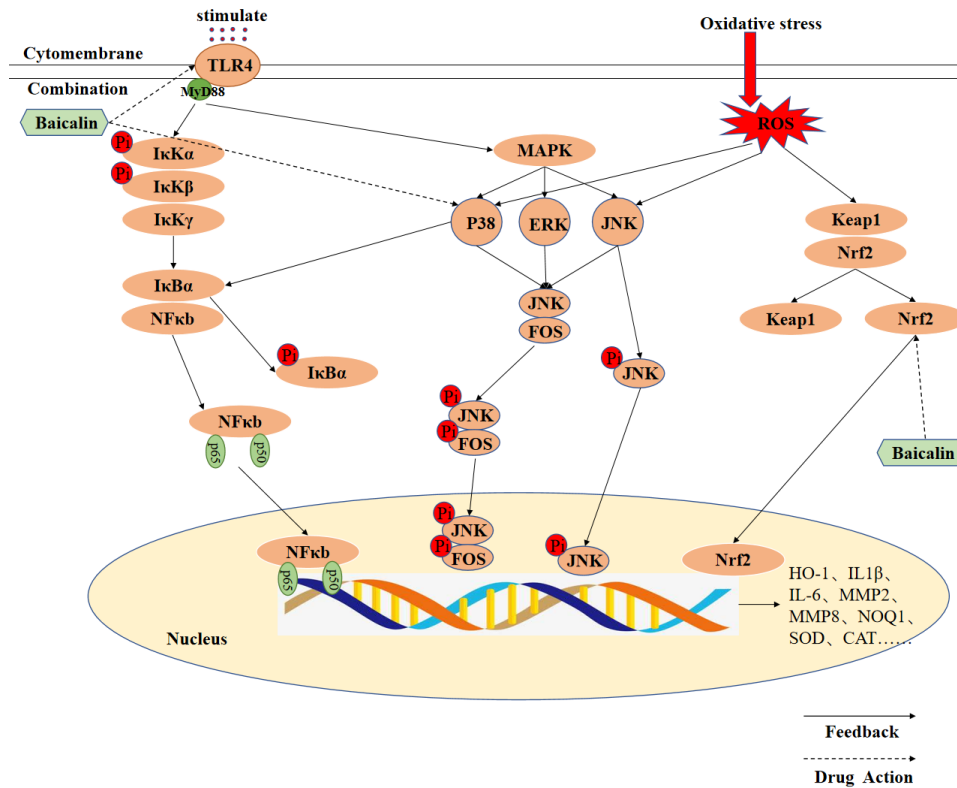


FIGURE 1 Molecular mechanism of the effects of baicalin on inflammation and oxidation

atherosclerosis model, baicalin reduced lesion size and improved arterial elasticity (He et al., 2016). At present, the effects of baicalin on cardiovascular disease are being increasingly studied, but little research has clarified its mechanism of action.

4 | ANTI-VIRAL EFFECTS OF BAICALIN

Baicalin has been proven to have anti-viral effects (Xuexue et al., 2020). In particular, baicalin can effectively inhibit the growth of human herpes virus type 6 (Chen & Zhang, 2012). Baicalin has obvious therapeutic effects on viral myocarditis in humans, and its therapeutic mechanism may be related to miR21 (Liu et al., 2020). Baicalin can inhibit the activity of H₁N₁/H₃N₂ influenza viruses in mice at the cellular level and in vivo (Ding et al., 2014) and its mechanism may involve the suppression of neuraminidase activity (Jin et al., 2018). In terms of anti-microbial activity for hepatitis virus, the combination of baicalin and ETV exhibited significant efficacy in HepG2 cells infected with anti Na HBV^{rtM204V/rtLI180M}, which blocked the transcription of HBV-RNAs by inhibiting the transcription and expression of HNF1α and HNF4α, which are required for HBV replication, thereby inhibiting the synthesis of HBV RNAs, viral protein templates and HBV-DNA (Huang et al., 2017). For coxsackievirus, in the CVB3 constructed mouse myocarditis model, baicalin could exert biological functions of inhibiting the replication of CVB3 by inhibiting the activation of Akt and p38 (Fu et al., 2019). Baicalin could significantly inhibit the formation of autophagosomes and increase lipid content in HeLa cells induced by CVB3 infection

(Wang et al., 2020). For respiratory synthetic virus (RSV), in a mouse model of RSV infection, baicalin can reduce T lymphocyte infiltration and pro-inflammatory factor gene expression caused by RSV infection, inhibiting RSV through anti-inflammatory and antiviral effects (Shi et al., 2016).

Studies have shown that baicalin can inhibit neuraminidase activity, so it has obvious anti influenza virus activity in cells and mouse models and shows dose-dependent tolerance (Ding et al., 2014). Baicalin can promote the production of IFN-γ. Thus it showed anti influenza virus activity in mice (Hai-Yan et al., 2015). For human immunodeficiency virus 1 (HIV 1), baicalin can inhibit the replication of HIV-1 virus by inhibiting the expression of HIV-1 specific core antigen p24 and the activity of reverse transcriptase (Li et al., 1993; Zhang et al., 1991). Baicalin can stimulate the body to produce nonspecific antibodies to vascular stomatitis virus (VSV) by regulating the release of cytokines and innate immune translation (Orzechowska et al., 2014). In addition, baicalin has inhibitory effects on human cytomegalovirus (Evers et al., 2006), Zika virus (Oo et al., 2019), chikungunya virus (Oo et al., 2017), tick borne encephalitis virus (Leonova et al., 2020) and respiratory syncytial (Shi et al., 2016) virus in vitro.

Baicalin can effectively protect against viruses through direct virucidal, inhibition of viral replication, regulation of functional protein expression in host cells, and anti-inflammatory mechanisms. At present, there are few studies about baicalin as a clinical anti-viral treatment, and the specific mechanism of its biological function has not been extensively studied. Therefore, further research is needed to clarify the anti-viral properties of baicalin.

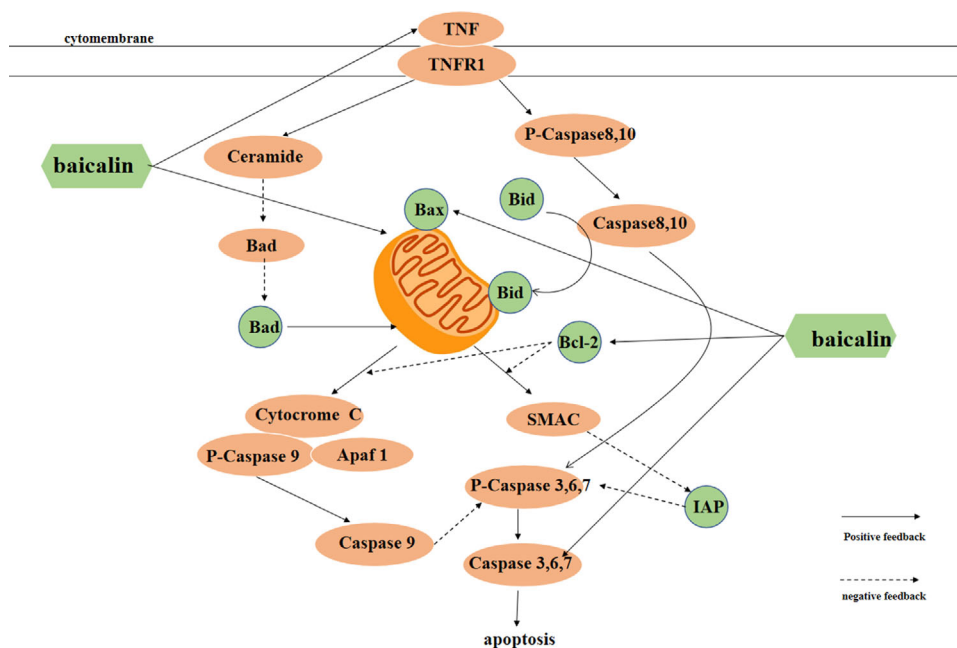


FIGURE 2 Molecular mechanism of the effects of baicalin on the mitochondrial apoptosis pathway

5 | ANTI-TUMOUR EFFECTS OF BAICALIN

Tumours are masses of abnormal cells in the body that grow in large numbers, and they can be benign or malignant. Malignant tumours cause serious damage, and they are the second leading cause of death globally (Siegel et al., 2019). Increasing attention has been paid to the anti-tumour effects of baicalin (Kim & Lee, 2012). The anti-tumour effects of baicalin mainly include inhibiting the proliferation of tumour cells by blocking the cell cycle, inducing apoptosis in tumour cells by producing cytotoxicity (Chao et al., 2007; Qinfeng, 2016), and suppressing the erosion and metastasis of tumour cells (Wang et al., 2017).

The cell cycle refers to the process of eukaryotic cells from the end of one round of mitosis to the next, and it is generally divided into G1, S, G2, M and other stages. Cancerous cells usually have abnormal cell division cycles (Champeris Tsaniras et al., 2014). Cell cycle proteins (cyclins) are important in the normal regulation of the cell cycle. Reports indicated that baicalin can block cell cycle progression in S phase by suppressing cyclin A, whereas in SK-LU1, SK-MES-1 and DU145 cells, baicalin suppresses the expression of cyclin D1, which leads to cell cycle arrest in G1 phase (Gao et al., 2011; Narushima et al., 2016). Cyclin-dependent kinase 2 (CDK2) is an important protein regulating cell cycle progression. It has been demonstrated that CDK2 can inhibit the phosphorylation of apoptotic proteins, thereby promoting the apoptosis of tumour cells (Wall et al., 2003). Meanwhile, baicalin inhibited the proliferation of T-GH8301 and BFTC905 bladder cancer cells by suppressing the activity of the CDK2–cyclin B1 complex (Chao et al., 2007) (Figure 2).

The JAK–signal transducer and activator of transcription (STAT) signalling pathway plays an important role in cell growth and apoptosis by promoting cell cycle progression and inhibiting cell apoptosis (Booz

et al., 2002). Abnormal activation of the signalling pathway occurs in a variety of tumour cells, and it is believed that the JAK–STAT signalling pathway may be related to the abnormal cell cycle regulation of tumour cells (Wang et al., 2019). Baicalin can also participate in the regulation of the cell cycle in tumours through a variety of other regulatory signalling pathways. For example, baicalin can inhibit tumour growth through the phosphoinositide 3-kinase (PI3K)–AKT signalling pathway (Zhaoqin et al., 2017) and the JAK–STAT signalling pathway (Guoli & Jinfeng, 2011). Baicalin inhibits the activity of P13K (Kong et al., 2011), thereby suppressing the phosphorylation of AKT in tumour cells (Xu et al., 2017). Activation of the P13K–AKT signalling pathway might lead to cell cycle dysregulation or inhibition of apoptosis, and this signalling pathway is abnormally activated in a variety of tumour cells (Kong et al., 2011). Baicalin can significantly inhibit the activation of STAT signalling factors in human liver cancer cells SMMC-7721 (Guoli & Jinfeng, 2011); therefore, it is believed that baicalin may inhibit the growth of tumour cells through the JAK–STAT signalling pathway.

Apoptosis is a complex physiological process that is influenced and regulated by many factors, including the death receptor-mediated exogenous and mitochondria-mediated endogenous pathways. The exogenous pathway mainly induces apoptosis by through the death acceptor Fas and TNF. Mitochondrial pathways are regulated by multiple factors. For example, pro-apoptotic factors such as Bad (Xiao-Ping et al., 2016) and cytochrome c (Li et al., 2000) can induce a series of cascade reactions of cysteine proteases (caspases) leading to apoptosis, and caspases are generally the ultimate inducers of cell apoptosis. The two pathways of apoptosis are not independent of each other, and they can both influence each other and eventually induce caspase-3 as the final factor that induces apoptosis (Choudhary et al., 2015). It has been reported that baicalin can downregulate the expression of the anti-apoptotic protein Bcl-2 in various cancer cells (Shasha et al., 2019) and

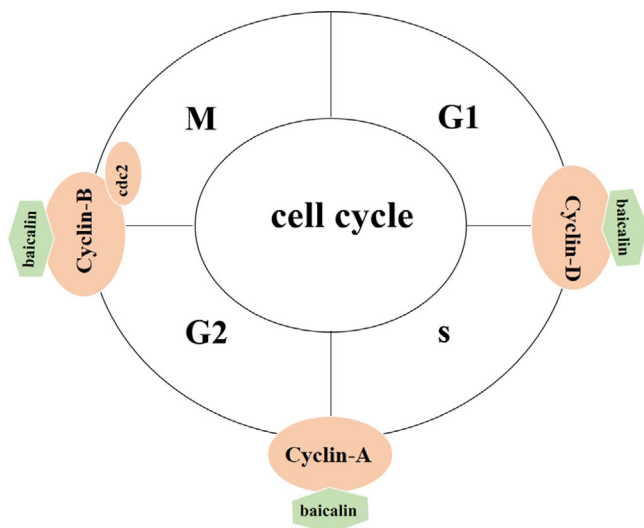


FIGURE 3 Molecular mechanism of the effects of baicalin on cell cycle pathways

upregulate Bad expression and promote the release of cytochrome c in mitochondria to promote apoptosis in cancer cells (Zheng et al., 2012). The expression of caspase-3 is significantly increased in gastric cancer cells treated with baicalin, which significantly elevates the apoptosis rate (Qinfeng, 2016). Baicalin can inhibit QBC939 cell growth by regulating the expression of caspase-3 (Yang, 2020). These findings suggest that baicalin can synergistically increase the expression of caspase-3 as an apoptotic factor through exogenous and mitochondrial pathways, thereby promoting apoptosis in tumour cells (Figure 3).

The invasion and metastasis of tumour cells to other normal tissues are important processes in tumour development. Matrix metalloproteinases (MMPs) and their inhibitors metalloproteinase tissue inhibitors (TIMPs) play important roles in these processes. Abnormal expression of MMPs and TIMPs may lead to the metastasis of cancer cells and poor prognoses (Huang et al., 2019; Kosaka et al., 2016). It has been reported that baicalin inhibits the metastasis of HeLa cervical cancer cells by downregulating the expression of MMP-2/MMP-9 through the p38 MAPK signalling pathway (Yue et al., 2016).

NF- κ B has been revealed to inhibit tumour cell metastasis and prevent immune avoidance (Dolcet et al., 2005; Hoesel & Schmid, 2013). Baicalin has a significant activating effect on NF- κ B, and dose-dependent reductions of NF- κ B p65 phosphorylation induced by baicalin significantly inhibit breast cancer progression (Zhao et al., 2019). There is evidence that NF- κ B has an important influence on the formation of tumour cells. At the same time, NF- κ B influences cell cycle progression and apoptosis in tumour cells (Greten, 2004). Baicalin can inhibit the effects of TLR4-NF- κ B pathway activation (Jin et al., 2019) thereby affecting tumour cells. However, research on the effects of baicalin on tumour cells through the NF- κ B pathway is relatively sparse.

As a phytochemical extract, baicalin can influence the tumour cell cycle through the JAK-STAT and P13K-AKT signalling pathways, activate caspase-3 to promote the apoptosis of tumour cells, and inhibit

the migration and invasion of tumour cells through MMP-2, MMP-9 and other factors. These findings indicate that baicalin has great applicability as an anti-cancer agent.

6 | NEW DOSAGE FORM OF BAICALIN

Flavonoids have the characteristics of poor water solubility and low bioavailability (Badshah et al., 2021). Baicalin, as a flavonoid, also has the characteristics of poor water solubility and low bioavailability (Li et al., 2019) (Ikuse et al., 2019); therefore, the modification or coating of baicalin has important application value. Baicalin has a good neuroprotective effect, but it is eliminated quickly in the body and does not easily reach the brain (Cao et al., 2011). The research shows that cationic baicalin solid lipid nanoparticles modified with OX26 antibody and polyethylene glycol (PEG) can significantly increase the content of Baicalin in mouse spine. The principle is that the binding of antibody, surface PEGylation and the reduction of drug loaded particle size are conducive to improve the bioavailability of baicalin, and the cationic polymer is used as the carrier to make the surface of SLN positively charged, which can promote drug uptake by cells. In addition, because there are many transferrin receptors at the top of the blood-brain barrier, SLN binding OX26 has more advantages in the ability to pass through BBB (Liu et al., 2015). Borneol-Baicalin-liposomes can significantly improve the pharmacokinetic parameters and half-life time of baicalin compared with baicalin alone, and can significantly promote the drug effect (Zhang et al., 2020). Baicalin's cyclodextrin inclusion complexes have the characteristics of improving its water solubility and bioavailability and also have research prospects (Jakab et al., 2019). The inclusion process of baicalin and cyclodextrin only has physical changes without changing its chemical properties. In the process of forming the inclusion, the hydrophobic benzene ring of baicalin is embedded into the cavity of cyclodextrin, which greatly improves the water solubility of baicalin (Jing et al., 2017). Nanocrystalline treatment of baicalin can significantly improve the bioavailability and water solubility of oral baicalin (Xie et al., 2019). Baicalin through a novel mesoporous carbon nanopowder drug carrier has better water solubility and bioavailability than baicalin monomer in rats (Li et al., 2016). Baicalin phospholipid complex has better cell transfer performance and can significantly improve its bioavailability (Li et al., 2012). At the same time, studies have shown that baicalin phospholipid complex has good antiviral performance for duck hepatitis A virus type 1 (Chen et al., 2018). Baicalin gel delivery system triggered by pH can be used to improve the bioavailability of ophthalmic drug because of its slow release effect. After topical injection of the drug delivery system, the local pH environment (35°C, pH 6.8) will change the liquid from the liquid to the viscous gel to prolong the contact time, thereby improving the pharmacokinetic parameters such as AUC, Cmax and t1/2 of baicalin (Wu et al., 2012).

Researchers have prepared it into new drug-delivery systems such as solid lipid nanoparticles, nanocrystals, solid dispersions and phospholipid complexes. β -Cyclodextrin inclusion complex has attracted extensive attention in improving the water solubility, bioavailability

and stability of insoluble drugs. Its liposomes have the advantages of controlling drug release, prolonging drug half-life and improving drug bioavailability. However, there are few studies on how to combine the new drug delivery system with various inclusion complexes to further improve the bioavailability of baicalin, which may be the focus of the next research.

7 | CONCLUSION

This review offers a comprehensive report on the anti-inflammatory, anti-oxidant, anti-virus and anti-tumour of baicalin. Baicalin has a strong anti-inflammatory effect, and it may regulate the inflammation reaction through TLR4/NF- κ B signalling pathway. Baicalin has a strong anti-oxidative effect, while the Nrf2- HO1 signalling pathway maybe an important target. In the process of inflammation and oxidative stress, MAPKs may function as an crosstalk target to mediate NF- κ B and Nrf2-HO-1 signalling pathways. Baicalin can also inhibit the growth of tumour cells, suppress tumour metastasis, play anti-viral and anti-bacterial effects and so on. The water solubility and bioavailability of baicalin can be significantly improved after preparation treatment or coating treatment, so as to give better play to its biological activity in organisms. It can be expected that baicalin would be an effective medicine for clinical application.

AUTHOR CONTRIBUTIONS

M-LB: Conceptualisation, writing original draft and writing review & editing. M-YF: Writing review & editing. LM and S-XY: Investigation. J-XH and Y-YH: Project administration and supervision. L-XX: Conceptualisation, writing original draft, writing review & editing, funding acquisition and resources.

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CONFLICT OF INTEREST

All of the authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated, or the article describes entirely theoretical research.

ETHICAL STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journals author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

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PEER REVIEW

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