ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

Baicalin and Baicalein as Dual Modulators of Tumor Microenvironment: Unveiling New Horizons in Cancer Therapy

D.Dhachinamoorthi[1], K Balaram Kumar[2,] L. Ramachandra Reddy[3],Mr. M.Rajan[4]

1.Professor , Department of pharmaceutics , QIS College of pharmacy , Ongole, A.P

2.Professor , Department of pharmacognosy , QIS College of pharmacy , Ongole, A.P

3.Associate Professor , Department of pharmacognosy, QIS College of pharmacy , Ongole , A.P

4. Professor , Department of pharmacognosy, QIS College of pharmacy , Ongole , A.P

A B S T R A C T

One of the main causes of mortality in the globe is cancer. The incidence and mortality burden of cancer is rising quickly. There is an urgent need for innovative methods of cancer prevention and therapy. Natural products are dependable and effective resources for the development of anticancer medications. Two important flavones that were separated from Scu- tellaria baicalensis Georgi, a multipurpose traditional Chinese medicinal herb, are baicalin and baicalein. These flavones have anticancer properties against a variety of malignancies. Notably, the toxicity of these phytochemicals to healthy cells is quite minimal. Recent research has shown that baicalin and baicalein modulate a variety of tumor stromal cells and extracellular matrix (ECM) in the tumor microenvironment (TME), which is crucial for tumorigenesis, cancer progression, and metastasis, in addition to their cytotoxic and cytostatic activities toward various tumor cells. In this review, we provide an overview of the therapeutic potential and mechanism of action of baicalin and baicalein in the regulation of endothelial cells, fibroblasts, tumor microenvironmental immune cells, and extracellular matrix (ECM). These cells reshape the TME and cancer signaling, which hinders the growth, metastasis, and angiogenesis of tumors. We also go into baicalin and baicalein's biotransformation routes, associated therapeutic issues, and potential future research avenues to increase their bioavailability and clinical anticancer uses. Recent developments in baicalin and baicalein justify further research into these crucial natural approaches to cancer prevention and treatment.

- Corresponding Author

Dachinamoorthi

ddmoorthi@gmail.com

1. Introduction

Uncontrolled cell proliferation in almost every organ or tissue in the body, along with the capacity to spread to other organs, are characteristics of cancer, a broad category of disorders. As one of the world's top causes of mortality, cancer is becoming more and more common, putting a great deal of physical, psychological, and financial pressure on people, families, communities, and healthcare systems [1,2]. A complex tumor ecology known as the tumor microenvironment (TME) is created as a consequence of the clear range of dynamic changes in host tissues brought about by cancer genesis, progression, and metastasis [3]. Natural substances have been crucial to the development and manufacturing of antitumor medications ever since chemotherapy was first used to treat cancer. In folk medicine, including the traditional medicine widely utilized in China, Japan, India, and other countries, several phytochemicals have been extracted and created from herbal medicine [4–6]. Since ancient times, traditional medicine has been practiced extensively and is becoming more and more significant in today's society. The Global Centre for Traditional Medicine (GCTM) of the World Health Organization (WHO) estimates that around 80% of the world's population and 177 member nations utilize and benefit from traditional medicine. Natural ingredients make up more than 40% of pharmaceutical formulations, and Traditional medicine was the source of important medications like aspirin and artemisinin [7]. The Lamiaceae flowering plant Scutellaria baicalensis Georgi, also called Huang-qin in China, is found throughout

ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

Russia, East Asia, and North America [6]. For over 2000 years, its dried roots have been used as a herbal remedy for fever and pulmonary and hepatic ailments. This use was first documented in Shennong Bencaojing, a Chinese ancient medicine textbook written between 200 and 300 AD [8]. It is regarded as a multipurpose medicinal herb that was extensively used in traditional Chinese medicine's old classical prescriptions. Scutellaria, for instance, is a necessary component of Xiaochaihu Decoction, which helps to treat spleen shortage and liver stagnation [9]. Numerous conditions, including hyperlipidemia, hypertension, atherosclerosis, dysentery, respiratory infections, inflammation, and tumors, have been shown to benefit from Scutellaria baica-lensis [10]. Flavonoids, which are abundantly found in plant blooms and cause anthocyanin pigments to become blue, are rich in Scutelaria baicalensis, according to an increasing number of phytochemical investigations conducted over the last several decades [11]. Baicalin (7-glucuronic acid-5, 6-dihydroxyflavone), baicalein (5,6,7-trihydroxyfavone), wogonoside, wogonin, scutellarin, and scutellarein are the common flavones that are isolated from Scutellaria (Fig. 1) [12]. Depending on the extraction techniques and plant development circumstances, the components and their ratios change [13,14]. Baicalin and baicalein, two of the bioactive flavones extracted with 60% ethanol, show around 10.11 and 5.41 percent of the dry substances, respectively (Fig. 1) [13]. Their favorable biological qualities, such as their low toxicity, anti-inflammatory, antioxidant, anticarcinogenic, antithrombotic, and antiviral qualities, have been drawing more and more attention [15–17]. The tumor interacts closely with the TME, which is created by tumor development and proliferation. The extracellular matrix (ECM), blood vessels, immune cells, cancer-associated fibroblasts (CAFs), signaling molecules, and other elements make up the tumor microenvironment (TME) [18,19]. TME has a key role in coordinating cancer and carcinogenesis. The primary bioactive compounds extracted from the dry roots of Scutellaria Radix have been shown in numerous recent studies to have a strong impact on all aspects of TME, including fibrosis, angiogenesis, matrix metalloproteinases (MMPs), inflammation-associated cytokines, and immune cells' anticancer immunity [17,20]. As a result, using Scutellaria's bioactive components to prevent and cure cancer via modifying TME shows promise. We provide an overview of the latest findings about the positive effects of baicalein and baicalin on the TME in this review. We clarify the different signaling pathways and the processes that underlie their therapeutic advantages. We also provide some suggestions for the future to enhance their clinical use in the treatment of cancer.

2. Biotransformation and bioavailability of baicalin and baicalein

2.1. Biotransformation

With an apparent permeability (Papp) of 0.037 × 10—6 cm/s, baicalin is extremely permeable yet has a low water solubility (aqueous solubility 52 μg/mL) [21]. Baicalein has a greater lipophilicity (Papp 1.7 × 10—5 cm/s) and a lower hydrophilicity (aqueous solubility 16.82 μg/mL), which is consistent with their structural characteristics [22, 23]. Baicalein's low molecular mass and high lipophilicity, despite the lack of its transporters, allow it to pass readily through the epithelium from the gut lumen to the blood below. On the other hand, baicalin's greater hydrophilicity and bigger molecular mass contribute to its restricted permeability [24]. Baicalin and baicalein's poor bioavailability is partly caused by their generally low water solubility. Furthermore, baicalin's absorption is restricted by its low lipophilicity [25, 26]. According to a recent research, rats given baicalein orally had very little baicalein in their plasma, but its sulfate or glucuronide conjugates showed up very well. In that research, the relative absorption of baicalin to baicalein is 65%, whereas the absolute absorption of baicalein is 40% [27, 28]. 76% of baicalein was converted to its glucuronide/sulfate conjugates upon intravenous delivery [28]. The dosages, animals, and computation techniques used all affect the relative absorption and bioavailability of baicalin and baicalein [25, 29–31]. Following

ISSN:0976-0172
Journal of Bioscience And Technology
www.jbstonline.com

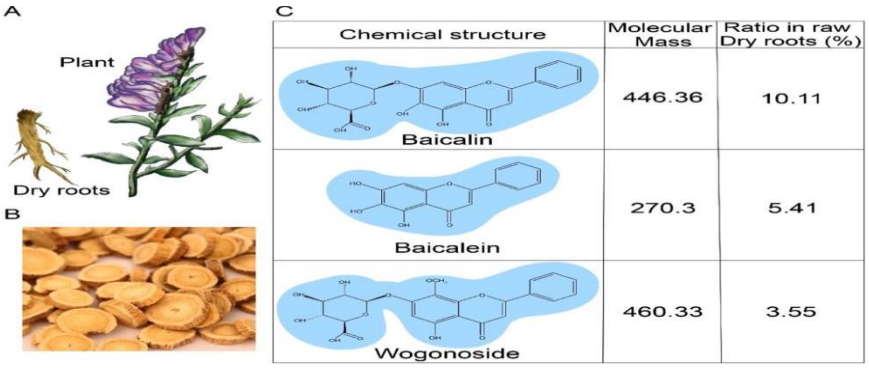


Fig. 1. Structures of Scutellaria baicalensis-derived wogonoside, baicalin, and baicalein Georgi. A. The dried roots of the shrub Scutellaria baicalensis. B. Traditional Chinese medicine uses the dried roots of Scutellaria baicalensis. C. The molecular mass and chemical structures of the primary components that were separated from Scutellaria baicalensis, together with the weight-to-dry raw material ratio.

Following intestinal absorption, baicalin passes through a number of conjugative modifications in the ileum and jejunum [32]. Although both are poorly absorbed in the colon, baicalein is well absorbed in the stomach and small intestine whereas baicalin is poorly absorbed there [33]. Several investigations shown that intestinal microbiota (IM) degraded the majority of baicalin into baicalein and that baicalin was poorly absorbed directly in the colon [25]. β-glucuronidase's deglycosylation of flavonoids is a crucial first step in their absorption, metabolism, and biological actions. After coming into contact with gut bacteria, bacterial β-glucosidase hydrolyzes baicalin to baicalein. Baicalein is subsequently taken up by the colon and circulated throughout the body, where it undergoes a variety of metabolizations, including glucuronidated, sulfated, methylated, and dehydroxylated forms [14]. In the liver, where the majority of the metabolites enter the bloodstream via the hepatic veins, UDP-glucuronyltransferases (UGTs) and other conjugated metabolites change the absorbed baicalein into baicalin through Phase II biotransformation events. About 35% of phase II metabolisms are attributed to UGTs, which are members of a superfamily that catalyzes the conjugation of glucuronic acid (GA) to xenobiotics with polar groups to aid in their clearance as well as endogenous compounds including hormones and bile acids [34, 35]. Consequently, their glucuronidated forms, such as wogonoside and baicalin, are the main metabolites in the blood [14]. The efflux transporter multidrug resistance-associated protein 2 (MRP2) primarily excretes baicalin into the bile duct in the liver. It then passes through the intestine for reabsorption into the enterohepatic circulation or excretion in the methylated and dehydroxylated forms, as well as the form of baicalein catalyzed by IM (Fig. 2) [23,36]. Certain metabolites, such glycosided and glucuronidated baicalin metabolites, have therapeutic effects and are crucial in the treatment of intestinal disorders [37–39]. Long-term accumulation of high concentrations of baicalein metabolites catalyzed by UGT occurs in the gut [23, 40]. On the other hand, very little baicalin and its byproducts are eliminated in the urine [27, 36]. The functions of each metabolite, both alone and in combination, should be described in each illness state in addition to the functions of their parent medications, taking into account the biotransformation of baicalein and baicalin as well as IM. Above all, identifying their objectives should significantly enhance our

ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

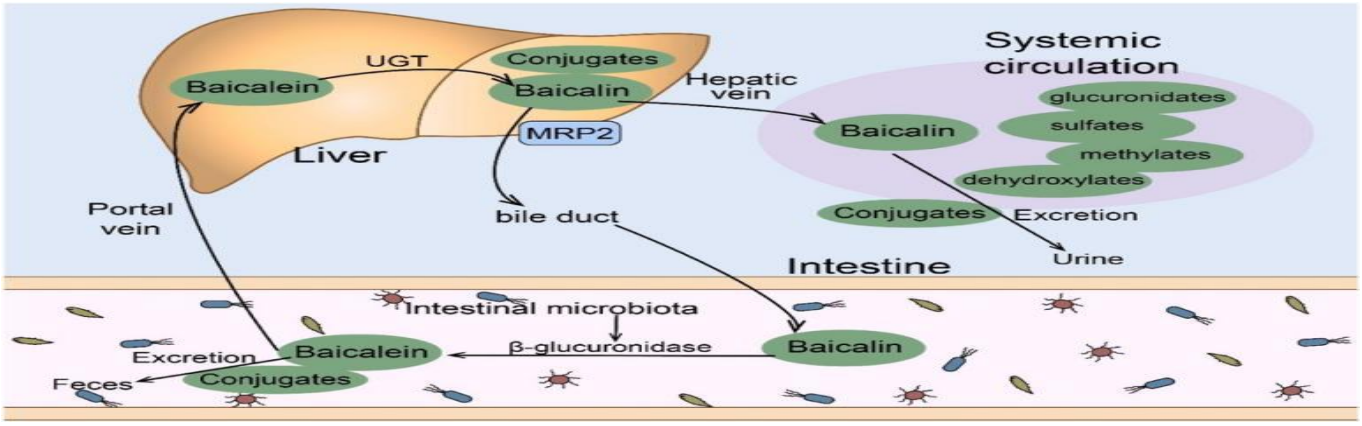


Fig. 2. Baicalin and baicalein undergo biotransformation.

β-glucuronidase from the gut microbiota mostly hydrolyzes oral absorption of baicalin to baicalein. Following intestinal absorption, baicalein enters the bloodstream and undergoes further metabolism to become glucuronidated, sulfated, methylated, and dehydroxylated. Through the portal vein, intestinal baicalin and baicalein enter the liver, where UGT and other conjugates convert the former to the latter. Hepatic veins allow baicalin and other liver-produced metabolites to reach the bloodstream. MRP2 excretes some baicalin and other conjugates into the liver's bile duct, where they either enter the enterohepatic circulation or are eliminated in feces in their different conjugated forms. A little portion of the blood's baicalin conjugates are eliminated in the urine. understanding of their mechanisms of action.

*2.2. **Bioavailability***

Both baicalin and baicalein have several medicinal uses for a range of illnesses. However, their low contents in Scutellaria bai- calensis and poor water solubility and oral bioavailability limit their medicinal potential, resulting in a low effective concentration and restricted absorption in the gastrointestinal tract [20,41,42]. In addition to its high lipophilicity and low aqueous solubility, baicalin is also rather unstable in biological fluids and at basic pH [43]. Consequently, a lot of effort was devoted to enhancing flavones' bioavailability for therapeutic usage. Because of their vast surface area and tiny particle sizes (often less than 100 nm in diameter), nanoparticles offer various benefits, including improving the solubility and rate of dissolution of poorly soluble medicines. In order to avoid drug aggregation and guarantee the physical stability of drug suspensions, nanoparticles usually incorporate nanosized drug particles, water-soluble biocompatible polymers, and/or surfactants [44]. Another kind of nanoparticle is a nanoemulsion, which is often made up of water, oil, and cosurfactant and surfactant. An interfacial layer of surfactant and cosurfactant stabilizes nanoemulsions, which are thermodynamically stable and isotropically transparent dispersion systems [45]. Like nanoparticles, nanoemulsions enhance medication solubility and dissolution rates by having tiny droplets with a greater surface area [46]. Methods mediated by nanoparticles show promise and effectively increase flavone bioavailability. Baicalin's solubility and oral bioavailability were improved, for instance, by new redispersible nanosuspensions made with co-processed nanocrystalline cellulose and sodium carboxymethyl starch as a synergistic stabilizer [47]. To target tumor-associated macrophages, baicalin-loaded co-polymers of lactide and glycolide (PLGA) nanoparticles with an antigenic peptide and cytidine phosphate guanosine (CpG) oligodinucleotides, an agonist of toll-like receptor (TLR) 9, were developed [48]. The pattern recognition receptor TLR9 is primarily expressed by immune cells, including macrophages and dendritic cells. By promoting the absorption and destruction of microorganisms and cancer cells, as well as by inducing an inflammatory response, CpG stimulates macrophages [49]. PLGA nanoparticles have garnered a lot of attention because of their superior biocompatibility and biodegradability. Furthermore, it has been shown

ISSN:0976-0172
Journal of Bioscience And Technology
www.jbstonline.com

that the absorption of these weakly water-soluble extracts may be enhanced by the use of mucus-penetrative nanoparticles and nanoemulsion [46,50]. The gastrointestinal (GI) tract lumen expresses ABC efflux transporters, such as P-glycoprotein, and drug-metabolizing enzymes, such as CYP450, which restrict the oral absorption and effectiveness of anticancer medications. By preventing P-glycoprotein and CYP450-mediated elimination, a lecithin-based self-nanoemulsifying nanoemulsion preconcentrate (LBSNENP) containing baicalein and iri-notecan (also referred to as CPT11), a derivative of DNA topoisomerase I inhibitor camptothecin, enhanced their oral bioavailability and therapeutic efficacy against pancreatic adenocarcinomas [51]. The surfactant combination lecithin/Tween 80/Cremophor EL, oil Capryol 90, and cosurfactant propylene glycol make up LBSNENP, which may be created with the ideal proportion of each ingredient for the various applications. To improve intestinal absorption, Capryol 90 has the ability to self-microemulsify into nano-range oil droplets that carry medication molecules. Pluronic F127-modified mucus-penetrative nanoparticles and chitosan-modified mucoadhesive nanoparticles based on phospholipid complex have been shown to improve oral bioavailability of baicalein by increasing the diffusion and penetration rate in the mucus layer [52]. The mucoadhesive feature of chitosan, a biocompatible and biodegradable positively charged polymer, allows it to interact with negatively charged mucus and extend its stay in the respiratory system [53]. By reducing the sticky interactions between nanoparticles and mucus components, the nonionic polymer pluronic F-127 helps nanoparticles pass through very viscoelastic mucus [52]. Overall, the diffusion rate of these altered nanoparticles was greater in mucus, improved local distribution and bioavailability, enhanced trans-epithelial transport and medication distribution in airways, and deeper penetration into the mucus layer. To get the intended therapeutic response, various multifunctional nanoparticles or their mimics, such as extracellular vesicles, should be produced in the future. These should include many medicines and alterations with tissue- or cell-specific targeting characteristics and prolonged release.

3. TME regulates tumorigenesis and malignancy

The characteristics of cancer malignancy include metastasis, invasiveness, and anaplasia. A change in differentiation is called anaplasia. Anaplastic cells provide malignancies their very unexpected characteristics, such as resistance to chemotherapy and radiation treatment, and are usually poorly differentiated with advanced pleomorphism [54]. Malignant cells and tumor stromal cells, including fibroblasts, endothelial cells, and infiltrating immune cells, interact to control these cancer malignant characteristics (Fig. 3). Tumor start, development, and progression depend on the interaction between tumor cells and their surroundings [55–57]. TME changes to aid in the development of cancer as the tumor grows [18,58]. Through abnormal immune responses, stromal cell signaling, and tumor vasculature creation, TME impacts all stages of cancer development, including initiation, progression, metastasis, and recurrence [59,60].

Prolonged inflammation promotes carcinogenesis and growth and predisposes the tumor to advance. A complex program, inflammation involves many interactions between different immune cells and non-immune cells, such as parenchymal cells and non-immune mesenchymal cells [61]. The characteristic of carcinoma is the constant renewal and proliferation of neoplastic cells, which causes chronic inflammatory responses in contrast to normal tissues [62]. Through proliferation and autocrine and paracrine cytokines, tumor cells engage with TME.

ISSN:0976-0172

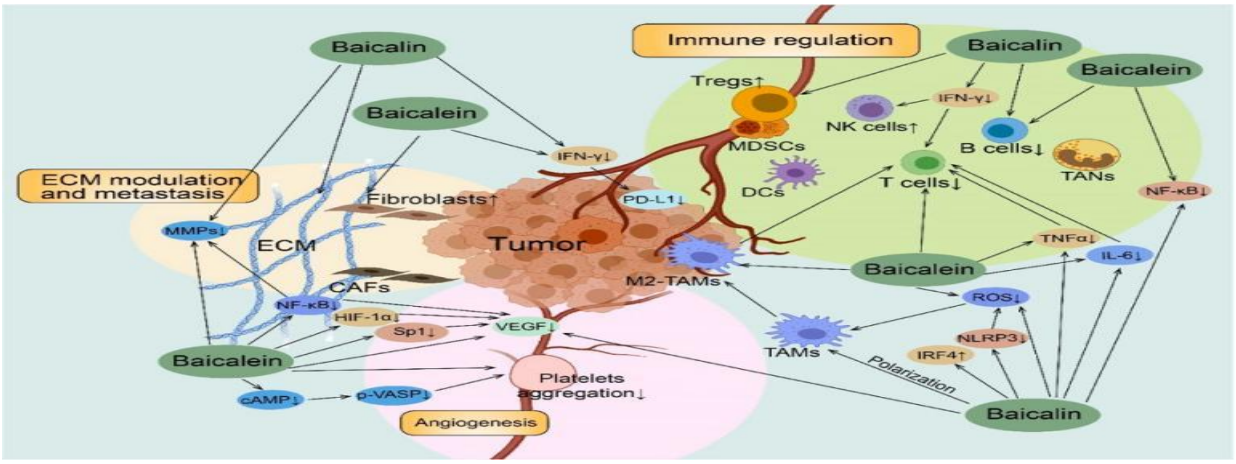


Fig. 3.

the ways in which baicalin and baicalein affect the TME. Immunosuppressive cells, such as Tregs and myeloid-derived suppressor cells (MDSCs), are drawn from the circulatory system to the TME as the tumor grows. They obstruct immune surveillance by preventing DCs from presenting antigens, T and B cells from activating and proliferating, and NK cells from cytotoxically attacking. By controlling the activity of immune cells, angiogenesis, and ECM-associated cells, baicalin and baicalein control TME. NK cells, T cells, Tregs, B cells, tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), tumor-associated neutrophils (TANs), tumor endothelial cells, and platelets are all regulated in terms of activation and proliferation by baicalin and baicalein. TAMs secrete cytokines, proteases, and tumorigenic growth factors that control tumor development, angiogenesis, and metastasis. CAFs aid in the development of the extracellular matrix and basement membrane. Angiogenesis and metastasis are caused by tumor endothelial cells and platelets. By inhibiting VEGF and platelet aggregation, baicalin and baicalein inhibit angiogenesis. By preventing the expression of MMPs, baicalin and baicalein stop the degradation of ECM.

factors or communication mediated by direct cell-cell contact, which leads to changes in gene expression and the development of an inflammatory malignant environment that promotes tumor growth [63–65].

4. Modulation of tumor-associated immune cells by baicalin and baicalein

One of the primary sites of interaction between tumor cells and host immune cells is the TME. Different immune-related cells, such as T cells, regulatory T cells (Tregs), B cells, dendritic cells (DCs), macrophages, natural killer (NK) cells, and myeloid-derived suppressor cells (MDSCs), induce different modulations in primary and metastatic malignancies (Fig. 3) [66,67]. The host immune system encounters neoplastic cells throughout the metastatic cascade and is able to recognize them and stop their proliferation [68]. Numerous studies have shown that immunosuppressive cells aid tumor cells in avoiding cytotoxic killer cell destruction. Additionally, by preventing the effects of immunotherapy, immunosuppressive cells cause tumor metastases and tumor progression [56,69]. We examined the impact of baicalin and baicalein on the regulation of immune cells in the contexts of inflammation and cancer as inflammation controls immune cell immunity and is strongly linked to the development of cancer.

4.1. Macrophages

The progression of neoplasms to malignancy is facilitated by tumor-associated macrophages (TAMs). Macrophages cause tumor angiogenesis, cancer cell invasion, and intravasation at the main location. TAM's repolarization toward the M1 phenotype creates an immune-competent milieu that promotes tumor regression. Baicalin and baicalein limit the growth and spread of tumors and control the polarization of TAMs (Table 1). Additionally, by suppressing the antitumor immune response, macrophages encourage the cir-culation and extravasation of cancer cells as well as the development of a pre-metastasized niche [70]. Baicalin inhibits lipopolysaccharide (LPS)-induced M1 macrophage polarization in acute inflammation, as seen by reduced expression of interleukin (IL)—23, tumor necrosis factor α (TNFα), and interferon regulatory factor (IRF) 5 [71]. Experimental models of colitis have often used dextran sulfate sodium (DSS), a water-soluble sulfated polysaccharide that directly damages intestinal epithelial cells [72]. By promoting IRF4 expression and regulating macrophage polarization to the M2 phenotype, baicalin reduced DSS-induced colitis [71]. Baicalin was crucial in reducing the inflammatory response and preventing the activation of the NLRP3 inflammasome in murine macrophages. Baicalin improved peritonitis brought on by monosodium urate crystal (MSU) and inhibited NLRP3 inflammasome activation by boosting the PKA signaling pathway [73,74]. Furthermore, by upregulating autophagy and the TLR2-NFκB pathway, baicalin shielded macrophages against ROS generation and NLRP3 inflammasome activation caused by Mycoplasma gallisepticum (MG) [75]. Consequently, baicalin inhibits the NLRP3 inflammasome. When it comes to hepatocellular carcinoma (HCC), TAM plasticity is crucial. Baicalin suppressed HCC by promoting TAM reprogramming to M1-like macrophages and inducing the production

of pro-inflammatory cytokines through autophagy-mediated activation of RelB/p52 [76]. By preventing apoptosis, the creation of ROS, and the production of Nitric Oxide (NO), baicalin improved the dysfunction of endothelium and vascular smooth muscle cells brought on by microparticles [77]. By controlling NRF2 and MAPK signaling, baicalin also prevented ROS and prevented the invasion of macrophages [78,79]. For the oxidative stress response, NRF2 is a master transcription factor [19, 80]. Baicalin therefore activates the NRF2 antioxidant pathway to provide potent antioxidant activity. Proangiogenic factors secreted by M2 macrophages have the potential to trigger the development of tumor vasculature. According to reports, baicalin stimulates the production of vascular endothelial growth factor (VEGF) and its receptors (VEGFRs), which upregulates M2 macrophage polarization.

Table 1
The effects of baicalin and baicalein on the modulation of cells in TME.

	Baicalein	mechanism	type	
Macrophages	Baicalin	increases IRF4 protein expression and regulates macrophages polarization to the M2 phenotype;	CRC-related	[71]
		inhibits activation of NLRP3 inflammasome by augmenting PKA signaling pathway;		[73]
		inhibits the PERK/TXNIP/ NLRP3 pathway to repress MAPKs activation and suppressing the activity of NFκB.	LC-related	[132]
Fibroblasts	Baicalin	reduces the production of UVB-generated DNA photoproducts CPDs	SKC-related	[128]
	Baicalein	reduces UVB-induced cell apoptosis;	SKC-related	[129]
		downregulates ERK and PI3K-AKT signaling by suppressing LOX	ET	[130]

type
and inhibits TGF-β1 secretion; attenuates DRP1 expression and ROS production;
downregulates JAK/STATs signaling and inhibits ROS production. NLRP3 Inflammasome- induced pyroptosis; induces autophagy- associated activation of RelB/p52;inhibits ROS production and MMP-9 expression; induces M2 macrophages polarization with the upregulation ofVEGF and its receptors; represses NFκB/CCL2/ CCR2 pathway activation; downregulates RhoA/ ROCK signaling and modulates macrophages polarization and efferocytosis; Baicaleinregulates M2 polarization
inhibits expression and phosphorylation of AKT; induces M1 polarization via PI3Kγ/NFκB pathway;

B-ALL stands for acute B-lymphoblastic leukemia; TLL for T-lymphoblastic lymphoma; SKC for skin cancer; ET for epidermoid tumors; CRC for colorectal cancer; LC for lung cancer; HCC for hepatocellular carcinoma; BC for breast cancer; M for melanoma. Autocrine VEGF signaling in M2 macrophages inhibits PD-L1 production, which in turn inhibits T cell anticancer immunity [81]. M2 macrophage transplantation into allogeneic mice resulted in increased bone marrow CD4+ CD25+ Tregs and decreased peripheral blood CD4+ T and CD8+ T cells [81,82]. This finding implies that baicalin may have the potential to accelerate tumor growth in the particular instance by adversely affecting TME, which is dose-, context-, and cell or cancer type-dependent. To determine the prerequisites for baicalin's unique activity and any
hazards, further research is required. Remarkably, baicalein has been shown to reduce TGF-β1 expression in THP-1 generated M2 macrophages and change M2-like TAMs into M1-like phenotypes [83]. Consequently, when breast cancer cells were co-cultured with THP-1 generated M2 macrophages, baicalein decreased lung

ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

metastatic lesions and neoplasm size [83]. This suggests that baicalein's regulation of TAMs may be used as a therapy for breast cancer metastases. But in other situations, baicalein causes an M2-like phenotype in various cancer or inflammation settings, much as baicalin does. An elevated risk of pancreatic ductal adenocarcinoma (PDAC) is linked to acinar-to-ductal metaplasia (ADM), which is brought on by chronic pancreatitis. The team led by Li-Kang Sun discovered that baicalein The lymphocytes Baicalin induces Foxp3 expression, which promotes Treg differentiation and maintains the Treg/Th17 balance;CRC-related ameliorated the inflammatory microenvironment and inhibited the

ADM of AR42J cells by suppressing TNFα-NFκB signaling [84]. In addition, they found that baicalein inhibited the production of NO, TNFα, and inflammatory response in LPS-stimulated macrophages,

Induces cell cycle arrest at the G0/G1 and inhibits GSK3β activity;

Baicalein promotes T cells immune response by suppressing IFNγ-induced PD-L1 expression in the tumor cells;

upregulates the activity of ASK1 and caspase-3; reduces Wnt/β-catenin signaling pathway to suppress proliferation; activates ASK1/JNK pathway and decreases the level of NFκB.

Neutrophils Regulates neutrophils by improving NRF2-induced HO-1 signaling;

-ALL
HCC
TLL
TLL
BLL

This significantly reduced AR42J cells' ADM [84]. Baicalein may thereby prevent PDAC by reducing pancreatitis. By regulating dynamin-related protein 1 (DRP1)-mediated mitochondrial fission in macrophages, baicalein may reduce the generation of inflammatory mediators brought on by LPS [85]. Baicalein reduced LPS-induced JAK1/2-STAT1/3 signaling and iNOS expression in RAW264.7 macrophages, which in turn reduced the production of NO and inflammatory cytokines such IL-1β, IL-6, NF-κB, CCL2, and TNFα [86–89]. These findings imply that baicalein prevents tumor development and spread via reducing ROS and inflammation. To comprehend acute and chronic inflammation in a particular cancer environment and their possible cancer consequences in vivo, further research is required to fully grasp the unique functions of baicalein in macrophage polarization. When using baicalin and baicalein to prevent inflammation and carcinogenesis, one should exercise caution since both ROS and inflammation are double-edged swords for the development of cancer. The results depend on how much suppresses the NFκB pathway; [120] and duration of ROS and inflammation and the specific disease activates NRF2 and inhibits MAPK pathway; ameliorates neutrophils via suppressing TLR4 signaling cascade;

Baicalein reduces the neutrophil infiltration by inhibiting

Lymphocytes

5. T cells, T helper 1 (Th1) cells, Tregs, B cells, and NK cells are among the many types of lymphocytes seen in the TME. These cells may be found in primary and metastatic locations, as well as peripheral tissues [66]. Lymphocytes are crucial in controlling metastasis and the mesenchymal-epithelial transition (MET) of tumors [90–92]. Bioactives from Scutellaria baicalensis have been shown in several trials to have beneficial effects on controlling lymphocyte secretion (Table 1) [93–95]. Through the release of inflammatory cytokines and cytotoxic molecules, T cells—which have their origins in bone marrow, grow from the thymus, and become activated in the lymph nodes and spleen—drive the tumor immune response and decide whether the malignancy is eliminated or promoted. The cytotoxic T cells and NK cells carry out their cancer cell killing activities during tumor metastasis in order to regulate the growth of the metastases [96]. T cells may be targeted by baicalein and baicalin in a variety of cancers connected to immune cells. Bai-calein decreased the expression of thioredoxin reductase and thioredoxin-1 in murine T cell lymphoma, which increased the activities of ASK1 and caspase-3 and caused cell death. [97]. Cutaneous T-cell

ISSN:0976-0172
Journal of Bioscience And Technology
www.jbstonline.com

lymphomas (CTCLs), a rare kind of non-Hodgkin lymphoma characterized by an increase of malignant CD4+ T cells in the skin, may be effectively and safely treated with baicalein, a natural substance. By blocking HDAC1 and HDAC8, baicalein decreased CTCLs, according to Xiaoxuan Yu et al., and its tumor-inhibiting properties outperformed those of conventional HDAC inhibitors [98]. By blocking the Wnt/β-catenin signaling pathway, baicalein also decreased the growth of acute T-lymphoblastic leukemia (TLL) Jurkat cells [99]. Baicalein and baicalin increased tumor regression via reducing PD-L1 expression in HCC cells, in addition to its direct cytotoxicity to different cancer cells [100]. By improving T lymphocyte immunological dysfunction, bailalein may help lessen severe sepsis. By lowering TNFα and IL-6 expression while raising IL-10 and galectin 9, baicalein significantly boosted the proportions of CD3+CD4+ T cells and the ratios of CD4+/CD8+ T cells in the peripheral blood and spleen of caecal ligation and puncture (CLP)-induced septic rats [101]. Additionally, baicalin demonstrated potent antiviral action against influenza virus A (H1N1), the causative agent of the common respiratory illness, by triggering the JAK/STAT-1 pathway and causing CD4+ and CD8+ T cells to secrete IFN-γ, therefore preventing the replication of influenza virus A [102]. There is little information available on baicalein's immune-modulation of T cells in a cancerous setting. When extrapolating T-cell anticancer immunity from T-cell lymphomas and acute inflammation, care should be used. The equilibrium between Treg and Th17 is crucial for inflammation and autoimmune. Th17 and Treg serve different purposes. By producing IL-17, IL-22, and IL-23, which attract neutrophils and stimulate inflammation at the infection site, Th17 cells induce autoimmunity and inflammation. On the other hand, Tregs secrete the anti-inflammatory cytokines TGF-β and IL-10, which suppress a range of immune cells and preserve immunological homeostasis. In ulcerative colitis [103,104], inflammatory bowel disease [105], red blood cell (RBC) immunization [106], allergic asthma [107], sepsis-associated pancreatic damage [108], and allergic rhinitis [109], baicalin controls the balance of Treg/Th17 and alleviates the symptoms of the illness. The majority of these conditions may cause or encourage the development of tumors, the spread of cancer, and metastases. By increasing the expression of the Foxp3 protein, baicalin may also encourage the differentiation of Tregs [110,111]. Humoral immunity is regulated by B cells, and autoimmune disease-related immune responses may be suppressed by regulatory B cells, or Bregs [112]. By activating macrophages via immune complex deposition and blocking T cells' antitumor immune response through antigen-nonspecific pathways, B cells contribute to the progression of colon cancer [113]. In B-ALL cell lines that frequently have gene rearrangements in the mixed-lineage leukemia 1 (MLL1) or Pre-B-cell leukemia transcription factor 1 (PBX1), baicalin has been demonstrated to inhibit cell proliferation, induce cell cycle arrest at the G0/G1 phase, and induce cell death. Baicalin also has antitumor activity against acute B-lymphoblastic leukemia (B-ALL), the most common blood cancer in children [114]. By upregulating activating transcriptionally active p63 (TAp63) and downregulating NFκB and CD74/CD44 signaling, baicalein triggers the ASK1/JNK pathway and mitochondria-associated apoptosis. B cells altered by EBV [115]. It is yet unknown how baicalin and baicalein affect B cell humoral immunity, particularly in relation to antigen presentation, antibody generation, and differentiation and proliferation. When combined, they show promise in using the anti-oxidative and anti-inflammatory properties of baicalin and baicalein to prevent and cure cancer by modifying various lymphocyte types. However, further research is required to determine how the effects of baicalin and baicalein on T cells and B cells, including their potential danger of causing cancer, may be directly transferred to cancer therapy. Determining how certain subtypes of tumor-promoting and tumor-inhibitory lymphocytes that are targeted by baicalein and baicalin contribute

ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

to the TME for a given cancer situation is crucial. Understanding the TME landscape and the combined effects of baicalein and baicalin on a particular cancer scenario is crucial.

6. The neutrophils In the innate arm of the immune system, neutrophils, also referred to as polymorphonuclear leukocytes (PMN), are crucial effector cells that perform three primary antimicrobial tasks: phagocytosis, degranulation, and the release of nuclear material in the form of neutrophil extracellular traps (NETs) [116]. Tumor associated neutrophils (TANs), commonly known as neutrophils, make up the majority of the inflammatory cells seen in solid tumors. A high intra-tumor density of TANs is related with lymph node metastases, tumor grade, and tumor stage [117]. TANs are an essential component of the TME and may develop pro-tumor (N2 neutrophils) or antitumor (N1 neutrophils) activity. Through their mastery of angiogenesis, ECM remodeling, metastasis, and immunosuppression, TANs' conflicting roles in TME control tumor-associated inflammation [118]. Neutrophil functions are regulated by baicalein and baicalin (Table 1). By triggering the NRF2-induced heme oxygenase-1 (HO-1) signaling pathway [119], a potent antioxidant and anti-inflammatory signaling pathway [19,34], baicalin reduced the lung infiltration of neutrophils and improved the LPS-induced inflammatory lung disorders in the mouse model of acute lung injury (ALI). By preventing NFκB activation, baicalin decreased lung accumulation of neutrophils and inflammatory cytokines IL-1β, TNFα, and IL-6 in the chicken ALI model caused by avian pathogenic Escherichia coli (APEC) [120]. By activating NRF2 and blocking the MAPK pathway, baicalin also decreased inflammation and symptoms of diabetic nephropathy (DN) [78]. A higher risk of HCC is linked to nonalcoholic fatty liver disease (NAFLD) [121], and baicalin improved hepatic histopathological changes and decreased neutrophil infiltration in mice with methionine and choline deficient diet (MCD)-induced NAFLD [122] by inhibiting TLR4 signaling and the production of inflammatory mediators. Furthermore, baicalein inhibited the NFκB and MAPK pathways, which decreased neutrophil infiltration and the generation of liver-inflammatory cytokines, therefore protecting against polymicrobial sepsis-induced liver damage [123]. The various cell types that flavones target show a coordinated outcome of reduced inflammation, and it would be a promising method to treat the transformation from inflammation to cancer, despite the lack of direct evidence that these flavones reduce the malignancy of cancer by directly inhibiting the accumulation of TANs.

7. Regulation of non-immune cells and cancer ECM in the TME by baicalin and baicalein

There are many cell types in the TME that might affect the immune system; as a result, these cells may be further targets for cancer treatment. Studies on inflammation during the last several decades have mostly focused on immune cells. Nonetheless, an increasing amount of research indicates that mesenchymal stromal cells are equally crucial for the inflammatory response [96,124]. Fibroblasts are regarded as an essential component of

Baicalin and baicalein can control fibroblast activity and a portion of TME (Table 1).

7.1. CAFs

Fibroblasts are the primary source of connective tissue extracellular matrix (ECM) and are crucial for stromagenesis, wound healing, and TME modification [125]. CAFs are often a unique subset of cells that are devoid of the mutations seen in cancer cells, have an elongated shape, a contractile cytoskeleton, and are negative for epithelial, endothelial, and leukocyte markers [126]. CAFs have a variety of roles in the tumor stroma, such as remodeling and matrix deposition, extensive signaling interaction with cancer cells, and leukocyte infiltration [127]. Flavones may alter the activity of CAFs, and fibroblasts aid in the growth of tumors. Baicalin shields fibroblasts against cyclobutane pyrimidine dimers (CPDs), the most prevalent DNA photoproducts that result in DNA mutations and the

ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

development of skin cancer, which are caused by ultraviolet (UV) B [128]. In a different research, baicalein inhibited the oxidative stress in a human skin fibroblast cell line, therefore reducing skin damage caused by UVB exposure [129]. By controlling fibroblasts, this study suggests that baicalein and baicalin have therapeutic potential for skin cancer. Furthermore, baicalein is thought to inhibit lip-oxygenases (LOXs). Baicalein may cause apoptosis and reduce the growth of epidermoid carcinoma cells by blocking LOX, which in turn suppresses PI3K-Akt and ERK signaling [130]. When cocultured with lung cancer cells, which stimulate the fibroblasts by paracrine signaling, Hongmei Chen et al. discovered that baicalein prevented the activation of fibroblasts [131]. By controlling the CAFs, baicalin and baicalein together have the potential to treat lung and skin cancer. Although their functions in other malignancies are yet unknown, it wouldn't be shocking if they had comparable impacts on CAF inactivation in other tumors.

7.2. Angiogenesis and tumor endothelium

Because it facilitates the supply of nutrients, the elimination of waste for cancer, and the creation of metastases, angiogenesis is crucial for the development and spread of neoplasms. When a carcinoma lesion is larger than a few millimeters, angiogenic switch, which is brought on by hypoxia and nutrition restriction, may stimulate tumor development [135]. In addition to providing the neoplasm with oxygen and nutrition, angiogenesis is a sign that a tumor has progressed beyond its size constraint and reached an advanced stage of malignant malignancy. In addition to fibrosis and growth and dissemination [140]. The primary causes of VEGF-induced harmful activities are its effects on vascular permeability and neoangiogenesis [141]. VEGF expression and signaling can be controlled by baicalin and baicalein (Table 2).
It has been shown that baicalin inhibits VEGF expression, which inhibits the PI3K/AKT/mTOR pathway and lowers the migration and proliferation of human mesothelioma cells [142]. Baicalein inhibited numerous cancers, including non-small cell lung cancer (NSCLC) [143–145], ovarian cancer [146], colorectal cancer [147], prostate cancer [148], glioma [149], and bladder cancer [150], by attenuating the production of VEGF, much as baicalin did. Baicalein suppressed inhibitor of differentiation 1 (Id1), which is necessary for VEGFA production, in NSCLC via increasing Rap1-GTP binding and decreasing alpha 7 nicotinic acetylcholine receptor (α7nAChR)-SR-C/AKT signaling [145]. The mechanism by which Id1 controls VEGFA expression is unclear. Furthermore, 12-lipoxygenase, which suppresses the activity of transcription factor Sp1 in prostate cancer to limit VEGF production, was preferentially suppressed by baicalein [148]. Sp1 is a VEGF gene regulatory protein that binds to the promoter of the VEGF gene to trigger transcription of the gene [148]. Additionally, by downregulating the production of HIF-1α, a master regulator for angiogenesis, baicalein may suppress the development of VEGF [149]. In addition to inhibiting VEGF production, baicalein may also prevent VEGF-induced angiogenesis by downregulating the VEGFR/ERK signaling pathway and upregulating p53/Rb, which leads to G1/S cell cycle arrest and decreased endothelial cell migration and proliferation [151]. Baicalein mediated the suppression of VEGF to reduce UVB-induced skin hyperplasia by reducing the expression of COX-2 and NF-κB/p65 [152]. Zhang Keqiang et al. demonstrated that baicalin enhanced VEGF expression and angiogenesis by activating expression of estrogen-related receptor α (ERRα), which binds to the promoter region of VEGF in a glioma cell line and human lung fibroblasts, independent of HIF-1α [153], in contrast to baicalein's inhibition of VEGF in an orthotopic glioma model [149]. Consequently, it is worthwhile to do more research on the situations in which baicalin and baicalein selectively stimulate or inhibit angiogenesis in order to enhance their therapeutic potential.

VEGF Baicalin causes S phase cell cycle arrest by inhibiting the PI3K/AKT/mTOR pathway;
regulates the formation of vascular endothelium and the architectural structure of tumor vasculature in the

ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

TME by activating the ERRα signaling pathway and expressing and secreting pro-angiogenic molecules. In order to carry out this intricate process, angiogenesis needs a variety of components, including vascular endothelial growth factor (VEGF), extracellular matrix (ECM), MMPs, and platelets. Baicalein reduces the production of NF-κB/p65 and COX-2, regulates the p53/Rb signaling pathway and G1/S cell cycle arrest, increases Rap1-GTP binding, and activates Akt and Src via attenuating a7nAChR signaling.

.2.1. Vascular endothelial growth factor

The VEGF family of proteins is encoded by five distinct genes in ECM Baicalin inhibits the TGF-β1 signaling pathway; stimulates expression of HIF-1α; Baicalein inhibits the TGF-β1 signaling pathway MMPs Baicalin inhibits the p38 MAPK signaling;

humans and other mammals, VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF). Each VEGF can

be roughly categorized as being hemangiogenic (VEGF-A, PlGF, and VEGF-B) or lymphangio-genic (VEGF-C and VEGF-D). They interact with three major VEGF re- inhibits the PKC/STAT3 signaling Pathway; Baicaleininhibits the p38 MAPK-dependent NF-κB signaling; ceptors (VEGFR), VEGFR— 1, — 2 and — 3, and co-receptors in inhibits the p38 signaling pathway; inhibits the ERK signaling pathway; endothelial cells to mediate their effects [139]. VEGF is considered as an indispensable composition for physiologic homeostasis, such as blood volume and pressure, interstitial volume and drainage, signal process- ing, and immunity. It serves as an important regulator for tumor Platelets Baicalein inhibits the activity of ERK2, p38, and Akt;

inhibits platelet-type 12-LOX expression and TCIPA;

is made up of a network of biochemically different components, such as polysaccharides, fibrous proteins, glycoproteins, and proteoglycans [163]. Changes in the total content or composition of the extracellular matrix (ECM) during tumor growth display its biophysical and biological signals, which affect the features of stromal cells and neoplasms (such as their mobility and proliferation) and modify the characteristics of cancer [164]. All of the cells in the TME produce extracellular matrix (ECM), which is a complex fibrous network that gathers local signals and provides structural support [165]. ECM also affects the immune system, fibroblasts, endothelial cells, and tumor cells' motility, proliferation, and differentiation [166]. Tumor tissue becomes more rigid due to force-mediated ECM remodeling and matrix-crosslinking enzymes generated by CAFs in the ECM. Matrix proteases, on the other hand, enable the reorganization of the tumor extracellular matrix (ECM), resulting in the creation of permissive tracks that permit the invasion of cancer cells and the movement of infiltrating leukocytes. This has consequences for the tumor immune surveillance [167].

By reducing the expression of ECM, baicalin and baicalein may improve a variety of fibrotic disorders (Table 2). In renal fibroblast cells, baicalein has more potent anti-fibrotic effects than baicalin, as shown by the downregulation of collagen production, endogenous TGF-β1 expression, and the TGFβ-Mothers against decapentaplegic homolog 3 (SMAD3) signaling pathway [154]. Baicalein encapsulated in liposomes reduces the production of extracellular matrix (ECM) in human dermal Hs68 fibroblasts and prevents fibroblast lipogenesis and differentiation into the skin adipose layer, which is mediated by conditional adipogenic differentiation medium [168]. Although the exact mechanism behind baicalein's inhibitory impact on skin fibroblasts is unknown, it is most likely linked to the inhibition of lipogenesis and the inflammatory response. Remarkably, baicalin has also been shown to promote autophagy via the MiR-766–3p/AIFM1 axis in chondrocytes [169] or to enhance ECM formation and reduce ECM breakdown by activating HIF-1α signaling [155]. It is still unknown what

ISSN:0976-0172
Journal of Bioscience And Technology
www.jbstonline.com

processes underlie the possible conflicting effects of baicalin and baicalein. The possible hazards of employing baicalin or baicalein to treat cancer, particularly their effects on the ECM formulation in a particular cancer setting, need additional research given their paradoxical effects on the extracellular matrix.

7.2.2. Matrix metalloproteinase

MMPs, also known as matrixins, are zinc-containing endopeptidases that are calcium-dependent and act in the extracellular milieu to break down matrix and non-matrix proteins. They have been shown to be the most representative protease family associated with carcinogenesis [170]. They control medication access, tumor mechanics, wound healing, tissue repair, and therapeutic response in conjunction with tissue inhibitors of metalloproteinases (TIMPs). Apart from their functions in ECM turnover and remodeling for cell migration, MMPs also alter signaling pathways linked to angiogenesis, immunological response, cell growth, and proliferation [171]. MMP expression can be controlled by baicalin and baicalein (Table 2). Baicalin inhibited MMP-7 expression, which probably helps to prevent the triple negative breast cancer cell line MDA-MB-231 from invading, migrating, and proliferating [172]. In a different research, baicalin inhibited MMP-2 and MMP-9 production by blocking p38MAPK signaling, which decreased the proliferation, invasion, and lung metastasis of breast cancer cells [156]. Furthermore, baicalin suppressed the proliferation and advancement of cervical cancer cells HeLa and SiHa by blocking Protein Kinase C/Signal Transducer and Activator of Transcription 3 (PKC/STAT3) signaling, which in turn decreased the protein levels of MMP-2 and MMP-9 [157]. Downregulation of MMP-2 and MMP-9 expression brought on by baicalin helps to prevent ovarian cancer cells [173] and non-small cell lung cancer cells [174] from proliferating and migrating. The SIRT1/AMPK signaling pathway is activated to suppress the production of MMP-2 and MMP-9 in NSCLC cells. Likewise, baicalein decreased the expression of MMP-2 by blocking the NFκB signaling in human ovarian cancer cells that is reliant on p38MAPK [158]. Baicalein inhibited the invasion of gastric cancer cells by reducing the expression of MMP-2 and MMP-9 via the inhibition of the p38 signaling pathway [159]. Baicalein also decreased the expression of MMP-2 and MMP-9 via inhibiting the ERK signaling pathway, which inhibited the metastasis of colorectal cancer [176], osteosarcoma [175], and HCC [160]. Baicalein boosted TIMP-1 and TIMP-2 expression while simultaneously decreasing MMP-2 and MMP-9 expression [160]. Baicalein suppressed tumor invasion and death by inhibiting the expression of MMP-2 and MMP-9 in bladder cancer [178] and Ewing's sarcoma [177]. Those investigations did not examine the signaling mechanisms that underlie the suppression of MMP-2 and MMP-9. When combined, baicalin and baicalein have the ability to suppress the production of MMPs in a variety of malignancies, which may lead to the therapy of cancer. More research should be done on the interactions between the upstream growth factor signaling pathways and the essential transcription factors and transcriptional activities needed for the production of MMPs.

7.2.3. Platelets

Small, anucleate, discoid cells that circulate in the blood, platelets have the remarkable ability to alter shape and have potent secretion qualities that control inflammation linked to cancer and hemostasis. Through a variety of methods, cancer cells may stimulate platelet activation and aggregation. Both pro-tumor and anti-tumor actions are shown by platelets [179]. Platelets may produce a variety of proteins, including as lipids, cytokines, growth factors, and proteases, which either directly or indirectly control angiogenesis. They also play a crucial role in the circulating angiogenesis-associated components [180].

Baicalein alters platelet function to treat cancer, according to many research (Table 2). Collagen, thrombin, or ADP are ligands that can promote platelet aggregation and granule secretion, [Ca2+]i mobilization, P-selectin expression through PI3K-AKT signaling induction, and activated platelets that aggregate with cancer cells

ISSN:0976-0172
Journal of Bioscience And Technology
www.jbstonline.com

to shield them from immune surveillance and blood shear forces. Baicalein suppressed the pulmonary metastasis of CT26 colon cancer cells by blocking ligand-induced platelet aggregation and granule production [161]. Mechanistically, baicalein suppressed tumor metastasis by attenuating PI3K-AKT signaling and promoting PKA-dependent VASP phosphorylation, which in turn prevented platelet activation and aggregation [161]. Through a variety of processes, circulating tumor cells promote tumor cell survival and metastasis by inducing platelet activation (TCIPA), also known as tumor cell-induced platelet aggregation (TCIPA) [181]. Additionally, baicalein reduced platelet/tumor cell contacts and TCIPA produced by rat C6 glioma cells [161]. In that research, the mechanism by which baicalein inhibits TCIPA was not examined. Additionally, tumor cells with elevated integrin β4-platelet-type 12-lipoxygenase (12-LOX) signaling may release 12-lipoxygenase (12-LOX) and its enzymatic product 12-hydroxyeicosatetraenoic acid (12S-HETE), which may promote TCIPA [162,182]. In several malignancies, the 12-LOX/12S-HETE axis is crucial for angiogenesis, carcinogenesis, and cell migration [162,182]. Furthermore, in a platelet-independent way, baicalein prevented the increase of mouse epidermal cell cloning efficiency mediated by 12-LOX and 12S-HETE [183]. Baicalein increased ROS generation via 12-LOX in melanoma cells, which inhibited the progression of malignancy, as shown by Duen-Suey Chou et al. [184]. To describe the effects of baicalin and baicalein in both platelet-dependent and independent pathways in each cancer context, further mechanistic research is required. Antiplatelet medications that target TCIPA may pave the door for the creation of novel cancer therapies.

According to these findings, the natural phytochemicals baicalin and baicalein that were separated from Scutellaria baicalensis may be able to cure cancerous tumors by reducing the tumor metastases brought on by platelet activation.

8. Future directions

With both direct and indirect actions, the naturally occurring flavonoids carry out their tasks on a variety of targets and cell types. Both baicalin and baicalein have a number of notable anticancer properties. There are still some crucial issues that need to be addressed. 1. What are baicalin and baicalein's immediate molecular targets? 2. How do baicalin and baicalein manage the intricate, multidimensional cellular networks to control the treatment outcomes? 2. What are the intercellular interaction networks that govern cancer pathogenesis? 3. Which techniques to increase their bioavailability for the clinical anticancer targeted treatment are the most dependable, biocompatible, and biodegradable? Identifying a novel drug's target (TID) and determining its mechanism of action (MoA) are crucial steps in the early stages of drug development and continue to be a bottleneck for moving hits along the discovery pipeline. There is now a wealth of pharmacological information on baicalin and baicalein in cellular and animal-based research in various illness states. We will have a better understanding of how baicalin and baicalein function in a particular illness context once the molecular target or targets of these flavones are discovered. Future research on TID for these flavones will benefit from the precise identification of protein-ligand complexes using a variety of high-resolution mass spectrometry (MS) techniques. Human clinical studies will significantly progress thanks to the many advantages this information offers.

Cancer is an intricate illness. Even in the age of precision medicine, a treatment is seldom effective because, in addition to cancer cells, many other cells and their extracellular matrix (ECM) in the TME entangle with one another during the course of the lengthy developing process. To carry out their cancer therapeutic operations, we must comprehend how their complex signaling networks cooperate (Fig. 4). Knowing the cellular targets of baicalein and baicalin in various illness scenarios is essential to using their advantageous roles for cancer prevention and therapy, since neutrophils, macrophages, and platelets have both tumor-inhibiting and tumor-promoting functions. In the future, the complex cellular and signal pathway landscape that is

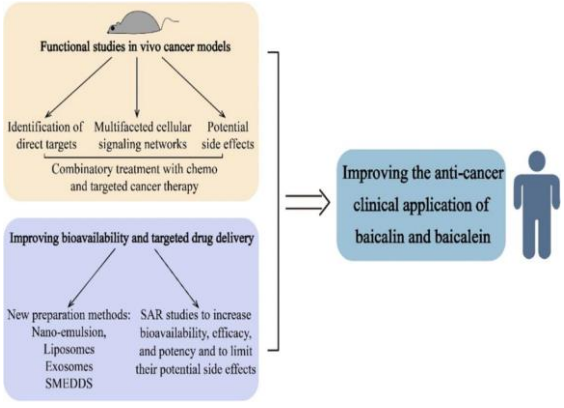
ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

essential for a particular cancer type and stage will be identified with the aid of mass cytometry, single cell-omics, spatiotemporal proteomics or transcriptomics, and sliced tissue culture or organoid culture. The majority of research to date has been conducted using in vitro assays based on cancer cell lines; thus, it is vital to examine the roles of these flavonoids in animal cancer models that more closely resemble the characteristics and genesis of human malignancies. Furthermore, it is unknown how combination medication treatments, such as chemotherapy or targeted therapy, in conjunction with these flavonoids may be used to improve the anticancer effect. To further improve their potency, effectiveness, and bioavailability while reducing any possible negative effects, structure and activity (SAR) investigations are required. When TID is known, it becomes much more significant. Future drug research and development will make excellent use of computer-aided drug design (CADD) and the newly developed artificial intelligence (AI), particularly for the optimization of baicalin and baicalein. Baicalin's clinical uses are currently limited by its poor bioavailability. New techniques for production have been devised to increase the bioavailability of baicalin and improve its pharmacological effects. Since they may increase the general solubility of insoluble medications, nano-emulsions and self-microemulsifying drug delivery systems (SMEDDS) are potential preparation techniques for enhancing their bioavailability. For poorly soluble medications like baicalin, liposomes and exosomes that can encapsulate them are also known to improve drug solubility and stability and may function as an efficient drug delivery mechanism (Fig. 4). Improved cellular targeting and uptake have been achieved via the use of modified liposomes and nanoparticles. Exosomes primarily collect in the liver, lungs, and spleen, much as the majority of drug-carrying nanoparticles. However, they also have a predilection for the tissues from where they were initially extracted and exhibit a homing feature, which lowers the possibility of adverse consequences. The quantity of a chemotherapeutic medication that reaches the tumors may be increased by loading it into the exosomes of cancer cells. To enhance these flavonoids for the therapeutic use of anticancer therapy, those challenges will be addressed.

9. Conclusion

10. Because of their phytochemicals and traditional herbal medicine, which has been used for hundreds of years to effectively treat a variety of ailments, plant species from all over the globe are emerging as new instruments for therapeutic uses. One of the most popular botanicals used in many traditional Chinese and Japanese medicines, Scutellaria baicalensis has garnered more attention recently because of its encouraging clinical outcomes and reduced adverse effects when used to treat cancer. The two main flavonoids extracted from Scutellaria roots, baicalein and baicalin, have been regarded as potential cancer therapeutic options. The genesis and course of cancer are significantly influenced by the interaction between TME and cancer. By controlling the tumor cells and stromal cells in the TME, including fibroblasts, platelets, neutrophils, macrophages, lymphocytes, and tumor endothelium, as well as the extracellular matrix, flavones may prevent the development of cancer.



Baicalin and baicalein's future directions for enhancing its therapeutic uses. For its anticancer uses, it is crucial to identify direct molecular and cellular targets in a particular malignancy. Baicalin and baicalein's bioavailability, cancer-targeted administration, and metastasis are all improved by the development of novel techniques. To sum up, future research will resolve the issues and release the nature and evolution's amazing potential for the good of human health.

References

ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (2021)
209–249.

[2] H. Rumgay, M. Arnold, J. Ferlay, O. Lesi, C.J. Cabasag, J. Vignat, et al., Global burden of primary liver cancer in 2020 and predictions to 2040, J. Hepatol. 77 (2022) 1598–1606.

[3] Y. Chen, K.M. McAndrews, R. Kalluri, Clinical and therapeutic relevance of cancer-associated fibroblasts, Nat. Rev. Clin. Oncol. 18 (2021) 792–804.

[4] C.S. Cheng, J. Chen, H.Y. Tan, N. Wang, Z. Chen, Y. Feng, Scutellaria baicalensis and cancer treatment: recent progress and perspectives in biomedical and clinical studies, Am. J. Chin. Med 46 (2018) 25–54.

[5] L. Zhao, F. He, H. Liu, Y. Zhu, W. Tian, P. Gao, et al., Natural diterpenoid compound elevates expression of Bim protein, which interacts with antiapoptotic protein Bcl-2, converting it to proapoptotic Bax-like molecule, J. Biol. Chem. 287 (2012) 1054–1065.

[6] M. Bruno, F. Piozzi, S. Rosselli, Natural and hemisynthetic neoclerodane diterpenoids from scutellaria and their antifeedant activity, Nat. Prod. Rep. 19 (2002) 357–378.

[7] W.H. Organization, WHO global report on traditional and complementary medicine 2019, World Health Organization,, 2019.

[8] Q. Zhao, Y. Zhang, G. Wang, L. Hill, J.K. Weng, X.Y. Chen, et al., A specialized flavone biosynthetic pathway has evolved in the medicinal plant, Scutellaria baicalensis, Sci. Adv. 2 (2016), e1501780.

[9] S. Chen, Z. Wang, S. Wan, H. Huang, H. Liang, Effect of modified Xiaochaihu decoctioncontaining serum on HepG2.2.15 cells via the JAK2/STAT3 signaling pathway, Mol. Med Rep. 16 (2017) 7416–7422.

[10] B. Bie, J. Sun, Y. Guo, J. Li, W. Jiang, J. Yang, et al., Baicalein: a review of its anti- cancer effects and mechanisms in Hepatocellular Carcinoma, Biomed. Pharm. 93 (2017) 1285–1291.

[11] R. Koes, W. Verweij, F. Quattrocchio, Flavonoids: a colorful model for the regulation and evolution of biochemical pathways, Trends Plant Sci. 10 (2005) 236–242.

[12] Q. Zhao, X.Y. Chen, C. Martin, Scutellaria baicalensis, the golden herb from the garden of Chinese medicinal plants, Sci. Bull. (Beijing) 61 (2016) 1391–1398.

[13] H.Z. Wang, C.H. Yu, J. Gao, G.R. Zhao, Effects of processing and extracting methods on active components in Radix Scutellariae by HPLC analysis, Zhongguo Zhong Yao Za Zhi 32 (2007) 1637–1640.

[14] Q.Y. Lu, L. Zhang, A. Moro, M.C. Chen, D.M. Harris, G. Eibl, et al., Detection of baicalin metabolites baicalein and oroxylin-a in mouse pancreas and pancreatic xenografts, Pancreas 41 (2012) 571–576.

[15] G.F. Meresman, M. Gotte, M.W. Laschke, Plants as source of new therapies for endometriosis: a review of preclinical and clinical studies, Hum. Reprod. Update (2020).

[16] I. Shimizu, Y.R. Ma, Y. Mizobuchi, F. Liu, T. Miura, Y. Nakai, et al., Effects of Sho- saiko-to, a Japanese herbal medicine, on hepatic fibrosis in rats, Hepatology 29 (1999) 149–160.

[17] M. Li-Weber, New therapeutic aspects of flavones: the anticancer properties of Scutellaria and its main active constituents Wogonin, Baicalein and Baicalin, Cancer Treat. Rev. 35 (2009) 57–68.

[18] F. Klemm, J.A. Joyce, Microenvironmental regulation of therapeutic response in cancer, Trends Cell Biol. 25 (2015) 198–213.

[19] F. He, X. Ru, T. Wen, NRF2, a transcription factor for stress response and beyond, Int J. Mol. Sci. 21 (2020).

[20] W.Y. Gong, Z.X. Zhao, B.J. Liu, L.W. Lu, J.C. Dong, Exploring the chemopreventive properties and perspectives of baicalin and its aglycone baicalein in solid tumors, Eur. J. Med Chem. 126 (2017) 844–852.

[21] H. Wu, X. Long, F. Yuan, L. Chen, S. Pan, Y. Liu, et al., Combined use of phospholipid complexes and self-emulsifying microemulsions for improving the oral absorption of a BCS class IV compound, baicalin, Acta Pharm. Sin. B 4 (2014) 217–226.

[22] W. Li, J. Pi, Y. Zhang, X. Ma, B. Zhang, S. Wang, et al., A strategy to improve the oral availability of baicalein: The baicalein-theophylline

ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

cocrystal, Fitoterapia 129 (2018) 85–93.

[23] H. Chen, Y. Gao, J. Wu, Y. Chen, B. Chen, J. Hu, et al., Exploring therapeutic potentials of baicalin and its aglycone baicalein for hematological malignancies, Cancer Lett. 354 (2014) 5–11.

[24] T. Akao, Y. Sakashita, M. Hanada, H. Goto, Y. Shimada, K. Terasawa, Enteric excretion of baicalein, a flavone of Scutellariae Radix, via glucuronidation in rat: involvement of multidrug resistance-associated protein 2, Pharm. Res 21 (2004) 2120–2126.

[25] T. Akao, K. Kawabata, E. Yanagisawa, K. Ishihara, Y. Mizuhara, Y. Wakui, et al., Baicalin, 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. Pharm. 52 (2000) 1563–1568.

[26] K. Noh, Y. Kang, M.R. Nepal, K.S. Jeong, D.G. Oh, M.J. Kang, et al., Role of intestinal microbiota in baicalin-induced drug interaction and its pharmacokinetics, Molecules 21 (2016) 337.

[27] T. Huang, Y. Liu, C. Zhang, Pharmacokinetics and bioavailability enhancement of baicalin: a review, Eur. J. Drug Metab. Pharm. 44 (2019) 159–168.

[28] M.Y. Lai, S.L. Hsiu, S.Y. Tsai, Y.C. Hou, P.D. Chao, Comparison of metabolic pharmacokinetics of baicalin and baicalein in rats, J. Pharm. Pharm. 55 (2003) 205–209.

[29] B. Dinda, M. Dinda, S. Dinda, U.C. De, An overview of anti-SARS-CoV-2 and anti-inflammatory potential of baicalein and its metabolite baicalin: Insights into molecular mechanisms, Eur. J. Med Chem. 258 (2023), 115629.

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

[31] S. Tian, G. He, J. Song, S. Wang, W. Xin, D. Zhang, et al., Pharmacokinetic study of baicalein after oral administration in monkeys, Fitoterapia 83 (2012) 532–540.

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

[33] W. Liang, X. Huang, W. Chen, The effects of baicalin and baicalein on cerebral ischemia: a review, Aging Dis. 8 (2017) 850–867.

[34] F. He, L. Antonucci, M. Karin, NRF2 as a regulator of cell metabolism and inflammation in cancer, Carcinogenesis 41 (2020) 405–416.

[35] N. Yang, R. Sun, X. Liao, J. Aa, G. Wang, UDP-glucuronosyltransferases (UGTs) and their related metabolic cross-talk with internal homeostasis: a systematic review of UGT isoforms for precision medicine, Pharm. Res 121 (2017) 169–183.

[36] M. Li, A. Shi, H. Pang, W. Xue, Y. Li, G. Cao, et al., Safety, tolerability, and pharmacokinetics of a single ascending dose of baicalein chewable tablets in healthy subjects, J. Ethnopharmacol. 156 (2014) 210–215.

[37] X. Sun, M. Pisano, L. Xu, F. Sun, J. Xu, W. Zheng, et al., Baicalin regulates autophagy to interfere with small intestinal acute graft-versus-host disease, Sci. Rep. 12 (2022), 6551.

[38] Y.Y. Li, X.J. Wang, Y.L. Su, Q. Wang, S.W. Huang, Z.F. Pan, et al., Baicalein ameliorates ulcerative colitis by improving intestinal epithelial barrier via AhR/ IL-22 pathway in ILC3s, Acta Pharm. Sin. 43 (2022) 1495–1507.

[39] J.Y. Jang, E. Im, N.D. Kim, Therapeutic potential of bioactive components from Scutellaria baicalensis Georgi in inflammatory bowel disease and colorectal cancer: a review, Int. J. Mol. Sci. 24 (2023).

[40] Q. Hu, W. Zhang, Z. Wu, X. Tian, J. Xiang, L. Li, et al., Baicalin and the liver-gut system: Pharmacological bases explaining its therapeutic effects, Pharm. Res 165 (2021), 105444.

[41] N. Zhu, J.C. Li, J.X. Zhu, X. Wang, J. Zhang, Characterization and bioavailability of wogonin by different administration routes in beagles, Med. Sci. Monit. 22 (2016) 3737–3745.

[42] C.P. Yu, C.S. Shia, S.Y. Tsai, Y.C. Hou, Pharmacokinetics and Relative Bioavailability of Flavonoids between Two Dosage Forms of Gegen-Qinlian-Tang in Rats, Evid. Based Complement Altern. Med 2012 (2012), 308018.

[43] J. Xing, X. Chen, D. Zhong, Stability of baicalin in biological fluids in vitro, J. Pharm. Biomed. Anal. 39 (2005) 593–600.

[44] M.J. Mitchell, M.M. Billingsley, R.M. Haley, M.E. Wechsler, N.A. Peppas, R. Langer, Engineering precision nanoparticles for drug delivery, Nat. Rev. Drug Discov. 20 (2021)

ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

101–124.

[45] A. Gupta, H.B. Eral, T.A. Hatton, P.S. Doyle, Nanoemulsions: formation, properties and applications, Soft Matter 12 (2016) 2826–2841.

[46] L. Zhao, Y. Wei, Y. Huang, B. He, Y. Zhou, J. Fu, Nanoemulsion improves the oral bioavailability of baicalin in rats: in vitro and in vivo evaluation, Int J. Nanomed. 8 (2013) 3769–3779.

[47] J. Xie, Y. Luo, Y. Liu, Y. Ma, P. Yue, M. Yang, Novel redispersible nanosuspensions stabilized by co-processed nanocrystalline cellulose-sodium carboxymethyl starch for enhancing dissolution and oral bioavailability of baicalin. Int J. Nanomed. 14 (2019) 353–369.

[48] S. Han, W. Wang, S. Wang, S. Wang, R. Ju, Z. Pan, et al., Multifunctional biomimetic nanoparticles loading baicalin for polarizing tumor-associated macrophages, Nanoscale 11 (2019) 20206–20220.

[49] L. Karapetyan, J.J. Luke, D. Davar, Toll-Like Receptor 9 Agonists in Cancer, Onco Targets Ther. 13 (2020) 10039–10060.

[50] Q. Xu, A. Zhou, H. Wu, Y. Bi, Development and in vivo evaluation of baicalin- loaded W/O nanoemulsion for lymphatic absorption, Pharm. Dev. Technol. 24 (2019) 1155–1163.

[51] L.C. Chen, W.J. Cheng, S.Y. Lin, M.T. Hung, M.T. Sheu, H.L. Lin, et al., CPT11 with P-glycoprotein/CYP 3A4 dual-function inhibitor by self-nanoemulsifying nanoemulsion combined with gastroretentive technology to enhance the oral bioavailability and therapeutic efficacy against pancreatic adenocarcinomas, Drug Deliv. 28 (2021) 2205–2217.

[52] W. Dong, J. Ye, J. Zhou, W. Wang, H. Wang, X. Zheng, et al., Comparative study of mucoadhesive and mucus-penetrative nanoparticles based on phospholipid complex to overcome the mucus barrier for inhaled delivery of baicalein, Acta Pharm. Sin. B 10 (2020) 1576–1585.

[53] T. Rawal, S. Patel, S. Butani, Chitosan nanoparticles as a promising approach for pulmonary delivery of bedaquiline, Eur. J. Pharm. Sci. 124 (2018) 273–287.

[54] A. Prete, A. Matrone, C. Gambale, L. Torregrossa, E. Minaldi, C. Romei, et al., Poorly differentiated and anaplastic thyroid cancer: insights into genomics, microenvironment and new drugs, Cancers (Basel) 13 (2021).

[55] J.A. Joyce, J.W. Pollard, Microenvironmental regulation of metastasis, Nat. Rev. Cancer 9 (2009) 239–252.

[56] K.E. de Visser, J.A. Joyce, The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth, Cancer Cell 41 (2023) 374–403.

[57] Y. Wang, H. Guo, F. He, Circadian disruption: from mouse models to molecular mechanisms and cancer therapeutic targets, Cancer Metastas-.-. Rev. 42 (2023) 297–322.

[58] D. Hanahan, L.M. Coussens, Accessories to the crime: functions of cells recruited to the tumor microenvironment, Cancer Cell 21 (2012) 309–322.

[59] D.F. Quail, J.A. Joyce, Microenvironmental regulation of tumor progression and metastasis, Nat. Med 19 (2013) 1423–1437.

[60] S. Guo, C.X. Deng, Effect of stromal cells in tumor microenvironment on metastasis initiation, Int. J. Biol. Sci. 14 (2018) 2083–2093.

[61] F.R. Greten, S.I. Grivennikov, Inflammation and cancer: triggers, mechanisms, and consequences, Immunity 51 (2019) 27–41.

[62] M. Schafer, S. Werner, Cancer as an overhealing wound: an old hypothesis revisited, Nat. Rev. Mol. Cell Biol. 9 (2008) 628–638.

[63] M.D. Wellenstein, S.B. Coffelt, D.E.M. Duits, M.H. van Miltenburg, M. Slagter,
I. de Rink, et al., Loss of p53 triggers WNT-dependent systemic inflammation to drive breast cancer metastasis, Nature 572 (2019) 538–542.

[64] S.M. Crusz, F.R. Balkwill, Inflammation and cancer: advances and new agents, Nat. Rev. Clin. Oncol. 12 (2015) 584–596.

[65] F. He, P. Zhang, J. Liu, R. Wang, R.J. Kaufman, B.C. Yaden, et al., ATF4 suppresses hepatocarcinogenesis by inducing SLC7A11 (xCT) to block stress- related ferroptosis, J. Hepatol. 79 (2023) 362–377.

[66] N. Nagarsheth, M.S. Wicha, W. Zou, Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy, Nat. Rev. Immunol. 17 (2017) 559–572.

[67] F. Veglia, E. Sanseviero, D.I. Gabrilovich, Myeloid-derived suppressor cells in the era of

ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

increasing myeloid cell diversity, Nat. Rev. Immunol. (2021).

[68] G.P. Dunn, C.M. Koebel, R.D. Schreiber, Interferons, immunity and cancer immunoediting, Nat. Rev. Immunol. 6 (2006) 836–848.

[69] T. Kitamura, B.Z. Qian, J.W. Pollard, Immune cell promotion of metastasis, Nat. Rev. Immunol. 15 (2015) 73–86.

[70] B.Z. Qian, J.W. Pollard, Macrophage diversity enhances tumor progression and metastasis, Cell 141 (2010) 39–51.

[71] W. Zhu, Z. Jin, J. Yu, J. Liang, Q. Yang, F. Li, et al., Baicalin ameliorates experimental inflammatory bowel disease through polarization of macrophages to an M2 phenotype, Int Immunopharmacol. 35 (2016) 119–126.

[72] K.E. Cochran, N.G. Lamson, K.A. Whitehead, Expanding the utility of the dextran sulfate sodium (DSS) mouse model to induce a clinically relevant loss of intestinal barrier function, PeerJ 8 (2020), e8681.

[73] C.G. Li, L. Yan, F.Y. Mai, Z.J. Shi, L.H. Xu, Y.Y. Jing, et al., Baicalin Inhibits NOD- Like Receptor Family, Pyrin Containing Domain 3 Inflammasome Activation in Murine Macrophages by Augmenting Protein Kinase A Signaling, Front Immunol. 8 (2017), 1409.

[74] C.S. Zhong, B. Zeng, J.H. Qiu, L.H. Xu, M.Y. Zhong, Y.T. Huang, et al., Gout- associated monosodium urate crystal-induced necrosis is independent of NLRP3 activity but can be suppressed by combined inhibitors for multiple signaling pathways, Acta Pharm. Sin. (2021).

[75] M. Ishfaq, Z. Wu, J. Wang, R. Li, C. Chen, J. Li, Baicalin alleviates Mycoplasma gallisepticum-induced oxidative stress and inflammation via modulating NLRP3 inflammasome-autophagy pathway, Int Immunopharmacol. 101 (2021), 108250.

[76] H.Y. Tan, N. Wang, K. Man, S.W. Tsao, C.M. Che, Y. Feng, Autophagy-induced RelB/p52 activation mediates tumour-associated macrophage repolarisation and suppression of hepatocellular carcinoma by natural compound baicalin, Cell Death Dis. 6 (2015), e1942. K.R. Paudel, D.W. Kim, Microparticles-Mediated Vascular Inflammation and its Amelioration by Antioxidant Activity of Baicalin, Antioxid. (Basel) 9 (2020).

[77] L. Ma, F. Wu, Q. Shao, G. Chen, L. Xu, F. Lu, Baicalin Alleviates Oxidative Stress and Inflammation in Diabetic Nephropathy via Nrf2 and MAPK Signaling Pathway, Drug Des. Devel Ther. 15 (2021) 3207–3221.

[78] R. Wang, L. Liang, M. Matsumoto, K. Iwata, A. Umemura, F. He, Reactive Oxygen Species and NRF2 Signaling, Friends or Foes in Cancer? Biomolecules 13 (2023).

[79] F. He, L. Antonucci, S. Yamachika, Z. Zhang, K. Taniguchi, A. Umemura, et al., NRF2 activates growth factor genes and downstream AKT signaling to induce mouse and human hepatomegaly, J. Hepatol. 72 (2020) 1182–1195.

[80] Y.S. Lai, R. Wahyuningtyas, S.P. Aui, K.T. Chang, V.E.G.F. Autocrine, signalling on M2 macrophages regulates PD-L1 expression for immunomodulation of T cells,
J. Cell Mol. Med 23 (2019) 1257–1267.

[81] Junior, Y.S. Lai, H.T. Nguyen, F.P. Salmanida, K.T. Chang, MERTK(+/hi) M2c Macrophages Induced by Baicalin Alleviate Non-Alcoholic Fatty Liver Disease. Int
J. Mol. Sci. 22 (2021).

[82] X. Zhao, J. Qu, X. Liu, J. Wang, X. Ma, X. Zhao, et al., Baicalein suppress EMT of breast cancer by mediating tumor-associated macrophages polarization, Am. J. Cancer Res 8 (2018) 1528–1540.

[83] W.L. Pu, Y.Y. Luo, R.Y. Bai, A.W. Guo, K. Zhou, Y.S. Zhang, et al., Baicalein inhibits acinar-to-ductal metaplasia of pancreatic acinal cell AR42J via improving the inflammatory microenvironment, J. Cell Physiol. 233 (2018) 5747–5755.

[84] C. Jiang, J. Zhang, H. Xie, H. Guan, R. Li, C. Chen, et al., Baicalein suppresses lipopolysaccharide-induced acute lung injury by regulating Drp1-dependent mitochondrial fission of macrophages, Biomed. Pharm. 145 (2022), 112408.

[85] Z. Qi, F. Yin, L. Lu, L. Shen, S. Qi, L. Lan, et al., Baicalein reduces lipopolysaccharide-induced inflammation via suppressing JAK/STATs activation and ROS production, Inflamm. Res 62 (2013) 845–855.

[86] T. Xu, X. Wang, C. Ma, J. Ji, W. Xu, Q. Shao, et al., Identification of potential regulating effect

ISSN:0976-0172

Journal of Bioscience And Technology
www.jbstonline.com

of baicalin on NFkappaB/CCL2/CCR2 signaling pathway in rats with cerebral ischemia by antibody-based array and bioinformatics analysis.
J. Ethnopharmacol. 284 (2022), 114773.

[87] X. Cai, Y. Shi, Y. Dai, F. Wang, X. Chen, X. Li, Baicalin clears inflammation by enhancing macrophage efferocytosis via inhibition of RhoA/ROCK signaling pathway and regulating macrophage polarization, Int Immunopharmacol. 105 (2022), 108532.

[88] M. Xu, X. Li, L. Song, Baicalin regulates macrophages polarization and alleviates myocardial ischaemia/reperfusion injury via inhibiting JAK/STAT pathway, Pharm. Biol. 58 (2020) 655–663.

[89] D.A.M. Mustafa, R. Pedrosa, M. Smid, M. van der Weiden, V. de Weerd, A.L. Nigg, et al., T lymphocytes facilitate brain metastasis of breast cancer by inducing Guanylate-Binding Protein 1 expression, Acta Neuropathol. 135 (2018) 581–599.

[90] X. Liu, J. Zheng, W. Sun, X. Zhao, Y. Li, N. Gong, et al., Ferrimagnetic Vortex Nanoring-Mediated Mild Magnetic Hyperthermia Imparts Potent Immunological Effect for Treating Cancer Metastasis, ACS Nano 13 (2019) 8811–8825.

[91] Z. Jiang, J. Chen, X. Du, H. Cheng, X. Wang, C. Dong, IL-25 blockade inhibits metastasis in breast cancer, Protein Cell 8 (2017) 191–201.

[92] N. Syafni, S. Devi, A.M. Zimmermann-Klemd, J.K. Reinhardt, O. Danton, C. Grundemann, et al., Immunosuppressant flavonoids from Scutellaria baicalensis, Biomed. Pharm. 144 (2021), 112326.

[93] M. Yang, X. Zhu, F. Fu, Q. Guo, X. Zhu, Y. Xu, et al., Baicalin ameliorates inflammatory response in a mouse model of rhinosinusitis via regulating the Treg/Th17 balance, Ear Nose Throat J. 101 (2022) 8S–16S.

[94] H. Liao, J. Ye, L. Gao, Y. Liu, The main bioactive compounds of Scutellaria baicalensis Georgi. for alleviation of inflammatory cytokines: a comprehensive review, Biomed. Pharm. 133 (2021), 110917.

[95] B.Z. Qian, Inflammation fires up cancer metastasis, Semin Cancer Biol. 47 (2017) 170–176.

[96] R.S. Patwardhan, D. Pal, R. Checker, D. Sharma, S.K. Sandur, Baicalein induces cell death in murine T cell lymphoma via inhibition of thioredoxin system, Int J. Biochem Cell Biol. 91 (2017) 45–52.

[97] X. Yu, H. Li, M. Zhu, P. Hu, X. Liu, Y. Qing, et al., Involvement of p53 acetylation in growth suppression of cutaneous T-cell lymphomas induced by HDAC inhibition, J. Invest Dermatol. 140 (2020) 2009–2022, e2004.

[98] X. Liu, S. Liu, J. Chen, L. He, X. Meng, S. Liu, Baicalein suppresses the proliferation of acute T-lymphoblastic leukemia Jurkat cells by inhibiting the Wnt/beta-catenin signaling. Ann. Hematol. 95 (2016) 1787–1793.

[99] M. Ke, Z. Zhang, B. Xu, S. Zhao, Y. Ding, X. Wu, et al., Baicalein and baicalin promote antitumor immunity by suppressing PD-L1 expression in hepatocellular carcinoma cells, Int Immunopharmacol. 75 (2019), 105824.

[100] H.Y. Chen, S. Zhang, J. Li, N. Huang, J. Sun, B.H. Li, et al., Baicalein attenuates severe polymicrobial sepsis via lleviating immune dysfunction of T lymphocytes and inflammation, Chin. J. Integr. Med (2022).

[101] M. Chu, L. Xu, M.B. Zhang, Z.Y. Chu, Y.D. Wang, Role of baicalin in anti-influenza virus A as a potent inducer of IFN-gamma, Biomed. Res Int 2015 (2015), 263630.

[102] L. Zhu, L.Z. Xu, S. Zhao, Z.F. Shen, H. Shen, L.B. Zhan, Protective effect of baicalin on the regulation of Treg/Th17 balance, gut microbiota and short-chain fatty acids in rats with ulcerative colitis, Appl. Microbiol Biotechnol. 104 (2020) 5449–5460.

[103] Y. Zou, S.X. Dai, H.G. Chi, T. Li, Z.W. He, J. Wang, et al., Baicalin attenuates TNBS-induced colitis in rats by modulating the Th17/Treg paradigm, Arch. Pharm. Res 38 (2015) 1873–1887.

[104] Y. Chang, L. Zhai, J. Peng, H. Wu, Z. Bian, H. Xiao, Phytochemicals as regulators of Th17/Treg balance in inflammatory bowel diseases, Biomed. Pharm. 141 (2021), 111931.

[105] X. Jiang, L. Liu, J. Sun, J. Yang, D. Xiang, Y. Yang, et al., Baicalin inhibits IgG production by regulating Treg/Th17 axis in a mouse model of red blood cell transfusion, Int Immunopharmacol. 66 (2019) 282–287.

[106] L. Xu, J. Li, Y. Zhang, P. Zhao, X. Zhang, Regulatory effect of baicalin on the imbalance of Th17/Treg responses in mice with allergic asthma,
J. Ethnopharmacol. 208 (2017) 199–206.

[107] P. Liu, Z. Xiao, H. Yan, X. Lu, X. Zhang, L. Luo, et al., Baicalin suppresses Th1 and Th17 responses and promotes Treg response to ameliorate sepsis-associated pancreatic injury via the RhoA-ROCK pathway, Int Immunopharmacol. 86 (2020), 106685.

[108] J. Li, X. Lin, X. Liu, Z. Ma, Y. Li, Baicalin regulates Treg/Th17 cell imbalance by inhibiting autophagy in allergic rhinitis, Mol. Immunol. 125 (2020) 162–171.

[109] J. Yang, X. Yang, M. Li, Baicalin, a natural compound, promotes regulatory T cell differentiation, BMC Complement Alter. Med 12 (2012), 64.

[110] P. Liao, L. Liu, B. Wang, W. Li, X. Fang, S. Guan, Baicalin and geniposide attenuate atherosclerosis involving lipids regulation and immunoregulation in ApoE-/- mice, Eur. J. Pharm. 740 (2014) 488–495.

[111] S. Nishimura, I. Manabe, S. Takaki, M. Nagasaki, M. Otsu, H. Yamashita, et al., Adipose Natural Regulatory B Cells Negatively Control Adipose Tissue Inflammation, Cell Metab. 18 (2013) 759–766.

[112] S. Shah, A.A. Divekar, S.P. Hilchey, H.M. Cho, C.L. Newman, S.U. Shin, et al., Increased rejection of primary tumors in mice lacking B cells: inhibition of anti- tumor CTL and TH1 cytokine responses by B cells, Int J. Cancer 117 (2005) 574–586.

[113] B.U. Orzechowska, G. Wrobel, E. Turlej, B. Jatczak, M. Sochocka, R. Chaber, Antitumor effect of baicalin from the Scutellaria baicalensis radix extract in B- acute lymphoblastic leukemia with different chromosomal rearrangements, Int Immunopharmacol. 79 (2020), 106114.

[114] G.B. Park, Y.S. Kim, H.K. Lee, J.W. Yang, D. Kim, D.Y. Hur, ASK1/JNK-mediated TAp63 activation controls the cell survival signal of baicalein-treated EBV- transformed B cells, Mol. Cell Biochem 412 (2016) 247–258.

[115] B. Gierlikowska, A. Stachura, W. Gierlikowski, U. Demkow, Phagocytosis, Degranulation and Extracellular Traps Release by Neutrophils-The Current Knowledge, Pharmacological Modulation and Future Prospects, Front. Pharmacol. 12 (2021).

[116] A.J. Templeton, M.G. McNamara, B. Seruga, F.E. Vera-Badillo, P. Aneja, A. Ocana, et al., Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis, J. Natl. Cancer Inst. 106 (2014) dju124.

[117] S. Jaillon, A. Ponzetta, D. Di Mitri, A. Santoni, R. Bonecchi, A. Mantovani, Neutrophil diversity and plasticity in tumour progression and therapy, Nat. Rev. Cancer 20 (2020) 485–503.

[118] X. Meng, L. Hu, W. Li, Baicalin ameliorates lipopolysaccharide-induced acute lung injury in mice by suppressing oxidative stress and inflammation via the activation of the Nrf2-mediated HO-1 signaling pathway, Naunyn Schmiede Arch. Pharm. 392 (2019) 1421–1433.

[119] L.Y. Peng, M. Yuan, K. Song, J.L. Yu, J.H. Li, J.N. Huang, et al., Baicalin alleviated APEC-induced acute lung injury in chicken by inhibiting NF-kappaB pathway activation. Int Immunopharmacol. 72 (2019) 467–472.

[120] J.Y. Kim, F. He, M. Karin, From Liver Fat to Cancer: Perils of the Western Diet, Cancers (Basel) 13 (2021).

[121] J. Liu, Y. Yuan, X. Gong, L. Zhang, Q. Zhou, S. Wu, et al., Baicalin and its nanoliposomes ameliorates nonalcoholic fatty liver disease via suppression of TLR4 signaling cascade in mice, Int Immunopharmacol. 80 (2020), 106208.

[122] A. Liu, W. Wang, H. Fang, Y. Yang, X. Jiang, S. Liu, et al., Baicalein protects against polymicrobial sepsis-induced liver injury via inhibition of inflammation and apoptosis in mice, Eur. J. Pharm. 748 (2015) 45–53.

[123] W.N. Brennen, S.R. Denmeade, J.T. Isaacs, Mesenchymal stem cells as a vector for the inflammatory prostate microenvironment, Endocr. Relat. Cancer 20 (2013) R269–290.

[124] R. Kalluri, The biology and function of fibroblasts in cancer, Nat. Rev. Cancer 16 (2016) 582–598.

[125] E. Sahai, I. Astsaturov, E. Cukierman, D.G. DeNardo, M. Egeblad, R.M. Evans, et al., A framework for

advancing our understanding of cancer-associated fibroblasts, Nat. Rev. Cancer 20 (2020) 174–186.

[126] N. Dumont, B. Liu, R.A. Defilippis, H. Chang, J.T. Rabban, A.N. Karnezis, et al., Breast fibroblasts modulate early dissemination, tumorigenesis, and metastasis through alteration of extracellular matrix characteristics, Neoplasia 15 (2013) 249–262.

[127] B.R. Zhou, D. Luo, F.D. Wei, X.E. Chen, J. Gao, Baicalin protects human fibroblasts against ultraviolet B-induced cyclobutane pyrimidine dimers formation, Arch. Dermatol. Res 300 (2008) 331–334.

[128] T. Zhang, A. Sharma, Y. Li, Y. Zhou, X. Ding, Orthogonal Array composite design to study and optimize antioxidant combinations in the prevention of UVB-induced HSF damage, J. Photochem. Photobio. B 178 (2018) 568–576.

[129] S. Agarwal, C. Achari, D. Praveen, K.R. Roy, G.V. Reddy, P. Reddanna, Inhibition of 12-LOX and COX-2 reduces the proliferation of human epidermoid carcinoma cells (A431) by modulating the ERK and PI3K-Akt signalling pathways, Exp. Dermatol. 18 (2009) 939–946.

[130] H. Chen, W. Liu, B. Wang, Z. Zhang, In Situ Analysis of Interactions between Fibroblast and Tumor Cells for Drug Assays with Microfluidic Non-Contact Co- Culture, Micro (Basel) 9 (2018).

[131] Y. Fu, J. Shen, Y. Li, F. Liu, B. Ning, Y. Zheng, et al., Inhibition of the PERK/ TXNIP/NLRP3 Axis by Baicalin Reduces NLRP3 Inflammasome-Mediated Pyroptosis in Macrophages Infected with Mycobacterium tuberculosis, Mediat. Inflamm. 2021 (2021), 1805147.

[132] M. Zhang, L. Ye, C. Cheng, F. Shen, L. Niu, Y. Hou, et al., Dietary Flavone Baicalein Combinate with Genipin Attenuates Inflammation Stimulated by Lipopolysaccharide in RAW264.7 Cells or Pseudomonas aeruginosa in Mice via Regulating the Expression and Phosphorylation of AKT, Nutrients 13 (2021).

[133] S. He, S. Wang, S. Liu, Z. Li, X. Liu, J. Wu, Baicalein Potentiated M1 Macrophage Polarization in Cancer Through Targeting PI3Kgamma/ NF-kappaB Signaling. Front Pharm. 12 (2021), 743837.

[134] J. Folkman, D. Hanahan, Switch to the angiogenic phenotype during tumorigenesis, Prince Takamatsu Symp. 22 (1991) 339–347.

[135] S.M. Weis, D.A. Cheresh, Tumor angiogenesis: molecular pathways and therapeutic targets, Nat. Med. 17 (2011) 1359–1370.

[136] T. Cramer, P. Vaupel, Severe hypoxia is a typical characteristic of human hepatocellular carcinoma: Scientific fact or fallacy? J. Hepatol. 76 (2022) 975–980.

[137] J. Folkman, Role of angiogenesis in tumor growth and metastasis, Semin Oncol. 29 (2002) 15–18.

[138] P. Mabeta, V. Steenkamp, The VEGF/VEGFR Axis Revisited: Implications for Cancer Therapy, Int. J. Mol. Sci. 23 (2022).

[139] N. Ferrara, VEGF and Intraocular Neovascularization: From Discovery to Therapy, Transl. Vis. Sci. Technol. 5 (2016) 10.

[140] R.S. Apte, D.S. Chen, N. Ferrara, VEGF in Signaling and Disease: Beyond Discovery and Development, Cell 176 (2019) 1248–1264.

[141] W.F. Xu, F. Liu, Y.C. Ma, Z.R. Qian, L. Shi, H. Mu, et al., Baicalin Regulates Proliferation, Apoptosis, Migration, and Invasion in Mesothelioma, Med Sci. Monit. 25 (2019) 8172–8180.

[142] M.C. Cathcart, Z. Useckaite, C. Drakeford, V. Semik, J. Lysaght, K. Gately, et al., Anti-cancer effects of baicalein in non-small cell lung cancer in-vitro and in-vivo, BMC Cancer 16 (2016), 707.

[143] Z. Zhao, B. Liu, J. Sun, L. Lu, L. Liu, J. Qiu, et al., Baicalein Inhibits Orthotopic Human Non-Small Cell Lung Cancer Xenografts via Src/Id1 Pathway, Evid. Based Complement Altern. Med 2019 (2019), 9806062.

[144] Z. Zhao, B. Liu, J. Sun, L. Lu, L. Liu, J. Qiu, et al., Scutellaria Flavonoids Effectively Inhibit the Malignant Phenotypes of Non-small Cell Lung Cancer in an Id1-dependent Manner, Int J. Biol. Sci. 15 (2019) 1500–1513.

[145] S.S. Chen, A. Michael, S.A. Butler-Manuel, Advances in the treatment of ovarian cancer: a potential role of antiinflammatory phytochemicals, Discov. Med 13 (2012) 7–17.

[146] Y. Wang, L. Bian, T. Chakraborty, T. Ghosh, P. Chanda, S. Roy, Construing the Biochemical and Molecular Mechanism Underlying the In Vivo and In Vitro Chemotherapeutic Efficacy of Ruthenium-Baicalein Complex in Colon Cancer, Int

J. Biol. Sci. 15 (2019) 1052–1071.

[147] D. Nie, S. Krishnamoorthy, R. Jin, K. Tang, Y. Chen, Y. Qiao, et al., Mechanisms regulating tumor angiogenesis by 12-lipoxygenase in prostate cancer cells, J. Biol. Chem. 281 (2006) 18601–18609.

[148] F.R. Wang, Y.S. Jiang, Effect of treatment with baicalein on the intracerebral tumor growth and survival of orthotopic glioma models, J. Neurooncol 124 (2015) 5–11.

[149] C. Chestnut, D. Subramaniam, P. Dandawate, S. Padhye, J. Taylor 3rd, S. Weir, et al., Targeting Major Signaling Pathways of Bladder Cancer with Phytochemicals: A Review, Nutr. Cancer (2020) 1–23.

[150] Y. Ling, Y. Chen, P. Chen, H. Hui, X. Song, Z. Lu, et al., Baicalein potently suppresses angiogenesis induced by vascular endothelial growth factor through the p53/Rb signaling pathway leading to G1/S cell cycle arrest, Exp. Biol. Med (Maywood) 236 (2011) 851–858.

[151] Y. Kimura, M. Sumiyoshi, Effects of baicalein and wogonin isolated from Scutellaria baicalensis roots on skin damage in acute UVB-irradiated hairless mice, Eur. J. Pharm. 661 (2011) 124–132.

[152] K. Zhang, J. Lu, T. Mori, L. Smith-Powell, T.W. Synold, S. Chen, et al., Baicalin increases VEGF expression and angiogenesis by activating the ERR{alpha}/PGC-1 {alpha} pathway, Cardiovasc Res 89 (2011) 426–435.

[153] Q. Hu, L. Gao, B. Peng, X. Liu, Baicalin and baicalein attenuate renal fibrosis in vitro via inhibition of the TGF-beta1 signaling pathway. Exp. Ther. Med 14 (2017) 3074–3080.

[154] P. Wang, P. Zhu, R. Liu, Q. Meng, S. Li, Baicalin promotes extracellular matrix synthesis in chondrocytes via the activation of hypoxia-inducible factor-1alpha. Exp. Ther. Med 20 (2020) 226.

[155] X.F. Wang, Q.M. Zhou, J. Du, H. Zhang, Y.Y. Lu, S.B. Su, Baicalin suppresses migration, invasion and metastasis of breast cancer via p38MAPK signaling pathway, Anticancer Agents Med Chem. 13 (2013) 923–931.

[156] Q. Wang, H. Xu, X. Zhao, Baicalin Inhibits Human Cervical Cancer Cells by Suppressing Protein Kinase C/Signal Transducer and Activator of Transcription (PKC/STAT3) Signaling Pathway, Med Sci. Monit. 24 (2018) 1955–1961.

[157] H. Yan, S. Xin, H. Wang, J. Ma, H. Zhang, H. Wei, Baicalein inhibits MMP-2 expression in human ovarian cancer cells by suppressing the p38 MAPK- dependent NF-kappaB signaling pathway. Anticancer Drugs 26 (2015) 649–656.

[158] X. Yan, X. Rui, K. Zhang, Baicalein inhibits the invasion of gastric cancer cells by suppressing the activity of the p38 signaling pathway, Oncol. Rep. 33 (2015) 737–743.

[159] K. Chen, S. Zhang, Y. Ji, J. Li, P. An, H. Ren, et al., Baicalein inhibits the invasion and metastatic capabilities of hepatocellular carcinoma cells via down-regulation of the ERK pathway, PLoS One 8 (2013), e72927.

[160] S.D. Kim, Y.J. Lee, J.S. Baik, J.Y. Han, C.G. Lee, K. Heo, et al., Baicalein inhibits agonist- and tumor cell-induced platelet aggregation while suppressing pulmonary tumor metastasis via cAMP-mediated VASP phosphorylation along with impaired MAPKs and PI3K-Akt activation, Biochem Pharm. 92 (2014) 251–265.

[161] K. Tang, Y. Cai, S. Joshi, E. Tovar, S.C. Tucker, K.R. Maddipati, et al., Convergence of eicosanoid and integrin biology: 12-lipoxygenase seeks a partner, Mol. Cancer 14 (2015), 111.

[162] J. Winkler, A. Abisoye-Ogunniyan, K.J. Metcalf, Z. Werb, Concepts of extracellular matrix remodelling in tumour progression and metastasis, Nat. Commun. 11 (2020).

[163] D.M. Gilkes, G.L. Semenza, D. Wirtz, Hypoxia and the extracellular matrix: drivers of tumour metastasis, Nat. Rev. Cancer 14 (2014) 430–439.

[164] S. Srinivasan, T. Kryza, J. Batra, J. Clements, Remodelling of the tumour microenvironment by the kallikrein-related peptidases, Nat. Rev. Cancer 22 (2022) 223–238.

[165] R.O. Hynes, The extracellular matrix: not just pretty fibrils, Science 326 (2009) 1216–1219.

[166] N.V. Popova, M. Juecker, The functional role of extracellular matrix proteins in cancer, Cancers 14 (2022).

[167] C.L. Fang, Y. Wang, K.H. Tsai, H.I. Chang, Liposome-encapsulated baicalein suppressed lipogenesis and extracellular matrix formation in Hs68 human dermal fibroblasts, Front Pharm. 9 (2018), 155.

[168] Z. Li, J. Cheng, J. Liu, Baicalin protects human OA chondrocytes against IL-1beta- induced apoptosis and

ISSN:0976-0172
Journal of Bioscience And Technology
www.jbstonline.com

ECM degradation by activating autophagy via MiR-766- 3p/AIFM1 axis, Drug Des. Dev. Ther. 14 (2020) 2645–2655.

[169] S. Niland, A.X. Riscanevo, J.A. Eble, Matrix metalloproteinases shape the tumor microenvironment in cancer progression, Int. J. Mol. Sci. 23 (2022).

[170] K. Kessenbrock, V. Plaks, Z. Werb, Matrix metalloproteinases: regulators of the tumor microenvironment, Cell 141 (2010) 52–67.

[171] K. Yang, L. Zeng, A. Ge, Z. Chen, T. Bao, Z. Long, et al., Investigating the regulation mechanism of baicalin on triple negative breast cancer's biological network by a systematic biological strategy, Biomed. Pharm. 118 (2019), 109253.

[172] C. Gao, Y. Zhou, H. Li, X. Cong, Z. Jiang, X. Wang, et al., Antitumor effects of baicalin on ovarian cancer cells through induction of cell apoptosis and inhibition of cell migration in vitro, Mol. Med Rep. 16 (2017) 8729–8734.

[173] J. You, J. Cheng, B. Yu, C. Duan, J. Peng, Baicalin, a Chinese herbal medicine, inhibits the proliferation and migration of human non-small cell lung carcinoma (NSCLC) cells, A549 and H1299, by activating the SIRT1/AMPK signaling pathway, Med Sci. Monit. 24 (2018) 2126–2133.

[174] H. Lin, Y. Hao, X. Wan, J. He, Y. Tong, Baicalein inhibits cell development, metastasis and EMT and induces apoptosis by regulating ERK signaling pathway in osteosarcoma, J. Recept Signal Transduct. Res 40 (2020) 49–57.

[175] Y. Chai, J. Xu, B. Yan, The anti-metastatic effect of baicalein on colorectal cancer, Oncol. Rep. 37 (2017) 2317–2323.

[176] C. Ye, X. Yu, J. Zeng, M. Dai, B. Zhang, Effects of baicalein on proliferation, apoptosis, migration and invasion of Ewing's sarcoma cells, Int J. Oncol. 51 (2017) 1785–1792.

[177] H. Liu, Y. Dong, Y. Gao, Z. Du, Y. Wang, P. Cheng, et al., The fascinating effects of baicalein on cancer: a review, Int J. Mol. Sci. 17 (2016).

[178] L. Zhou, Z. Zhang, Y.Z. Tian, Z.F. Li, Z.L. Liu, S.B. Zhu, The critical role of platelet in cancer progression and metastasis, Eur. J. Med Res 28 (2023).

[179] M. Haemmerle, R.L. Stone, D.G. Menter, V. Afshar-Kharghan, A.K. Sood, The platelet lifeline to cancer: challenges and opportunities, Cancer Cell 33 (2018) 965–983.

[180] W. Strasenburg, J. Jozwicki, J. Durslewicz, B. Kuffel, M.P. Kulczyk, A. Kowalewski, et al., Tumor cell-induced platelet aggregation as an emerging therapeutic target for cancer therapy, Front. Oncol. 12 (2022).

[181] J. Yeung, B.E. Tourdot, P. Fernandez-Perez, J. Vesci, J. Ren, C.J. Smyrniotis, et al., Platelet 12-LOX is essential for FcγRIIa-mediated platelet activation, Blood 124 (2014) 2271–2279.

[182] Y.S. Piao, Y.C. Du, H. Oshima, J.C. Jin, M. Nomura, T. Yoshimoto, et al., Platelet- type 12-lipoxygenase accelerates tumor promotion of mouse epidermal cells through enhancement of cloning efficiency, Carcinogenesis 29 (2008) 440–447.

[183] D.S. Chou, G. Hsiao, Y.A. Lai, Y.J. Tsai, J.R. Sheu, Baicalein induces proliferation inhibition in B16F10 melanoma cells by generating reactive oxygen species via 12-lipoxygenase, Free Radic. Biol. Med 46 (2009) 1197–1203.