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Exploring Therapeutic Potentials of Baicalin and Its Aglycone Baicalein for Hematological Malignancies

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Abstract

Despite tremendous advances in the targeted therapy for various types of hematological malignancies with successful improvements in the survival rates, emerging resistance issues are startlingly high and novel therapeutic strategies are urgently needed. In addition, chemoprevention is currently becoming an elusive goal. Plant-derived natural products have garnered considerable attention in recent years due to the potential dual functions as chemotherapeutics and dietary chemoprevention. One of the particularly ubiquitous families is the polyphenolic flavonoids. Among them, baicalin and its aglycone baicalein have been widely investigated in hematological malignancies because both of them exhibit remarkable pharmacological properties. This review focuses on the recent achievements in drug discovery research associated with baicalin and baicalein for hematological malignancy therapies. The promising anticancer activities of these two flavonoids targeting diverse signaling pathways and their potential biological mechanisms in different types of hematological malignancies, as well as the combination strategy with baicalin or baicalein as chemotherapeutic adjuvants for recent therapies in these intractable diseases are discussed. Meanwhile, the biotransformation of baicalin and baicalein and the relevant approaches to improve their bioavailability are also summarized.

Keywords

flavonoids; baicalin; baicalein; hematological malignancies; cancer targets

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1. Introduction

Hematological malignancies as a group of highly heterogeneous diseases affect the production and function of blood or blood-forming tissues including lymphatic system and bone marrow. These life threatening illnesses comprise various distinct disease types including leukemia, lymphoma, multiple myeloma, myeloproliferative neoplasms (MPN), myeloproliferative syndrome (MPS), and myelodysplastic syndromes (MDS) [1]. Each type has diverse incidence, prognosis, etiology, different features, particular treatment pathways and clinical outcomes [2].

The etiology of most of the hematological malignancies is not yet known. Radiation, exposure to chemicals and dusts, industrial exposures, viral infections, genetic predisposition and Down's syndrome are all associated with the increasing risk of one or several of these diseases. As the functions of blood or blood-forming tissues are closely connected through the immune system, when one of them is affected by a disease, the others will often be simultaneously affected. For instance, lymphoma is a disease of the lymph nodes; however, it often spreads to bone marrow, occasionally producing a paraprotein and affecting the blood.

Great advances have been made in early detection or in development of effective targeted and combination therapies for hematological malignancies in recent years. In spite of these advances having had favorable impact on survival, several types of hematological malignancies remain incurable [3]. In addition, although some patients having significant improvement in survival are now living longer with their disease, they are often suffering the associated symptoms. Furthermore, many patients ultimately develop resistance to currently available treatments. Meanwhile, the existing chemotherapeutic agents often have significant toxicities [4]. Because patients with hematological malignancies already suffer from compromised immune systems, the side effects of the chemotherapeutic agents are always intolerable. Not only that, the premium pricing of these promising drugs is becoming one of the major burdens for cancer patients [5]. Therefore, novel effective treatment options with less toxicity, higher tolerability, and more affordable price are urgently needed.

2.1. Dietary Polyphenolic Flavonoids

Natural products especially plant-derived traditional medicines have been utilized for the prevention and treatment of various human diseases since time immemorial [6,7]. About 65% of people around the world mainly rely on herbal medicines for their primary health care. There is an indisputable fact that more than 50% of the drugs currently in clinical application are of natural product origin. Utilization of plant-derived traditional medicines has a long history for cancer therapies. Jonathan Hartwell published his monumental work which contains over 3,000 plant species for the treatment of various cancers [8]. Despite the fact that the pharmaceutical industry appears to be shifting from the research direction on the natural product-inspired drug discovery, there is an increasing interest on the development of low toxic natural antioxidants as promising leads, especially those compounds that are available in extremely large quantities. Polyphenolic flavonoids, one unique family in dietary plants, are widely distributed in vegetables, fruits, and many

traditional Chinese herbal medicines [9]. Flavonoids exhibit diverse biological properties including antifungal, antioxidant, antiallergic, antiinflammatory, anticancer, antiobesity, antidiabetic, and immune-modulating effects [10-12]. Recently, the remarkable multifunctional antiproliferative effects of flavonoids against various cancer cells including an array of different malignancies are intensively investigated. Accumulating evidence has demonstrated that flavonoids exhibit potential anticancer properties *in vivo*, resulting in several bioflavonoids in preclinical and clinical trials [13].

2.2. *Scutellaria baicalensis*, Baicalin and Baicalein

Scutellaria baicalensis (*S. baicalensis*, common name: Huang Qin in China, Figure 1A) as one of the fifty fundamental herbs in traditional Chinese herbal medicine is widely used for the prevention and treatment of various ailments including cardiovascular diseases, hypertension, bacterial infection, inflammation, and cancer [14]. More than 50 flavonoids have been purified and identified from *S. baicalensis* [15]. The major components (Figures 1B and 1C) are baicalin (baicalein-7-*O*-glucoside), and its aglycone baicalein (5,6,7-trihydroxyfavone) [16]. Accumulating evidence has demonstrated that both of them exhibit extensive pharmacological effects. Due to their relatively low toxicity and the abundance in the root of *S. baicalensis*, baicalin and baicalein became the most extensively researched components in recent years [16]. Over the past decade, a considerable amount of studies has demonstrated that baicalin and baicalein display potent anticancer effects in various types of hematological malignancies [17]. Significant progress has been made in identifying the precise targets and elucidating relevant biological mechanisms of baicalin and baicalein involved in the inhibition of hematological malignancies.

In this concise review, we seek to summarize the recent achievements in drug discovery research on baicalin and baicalein in hematological malignancies and discuss the associated diverse signaling pathways and the potential biological mechanisms. In addition, we also discuss the combination strategy with baicalin or baicalein as chemotherapeutic adjuvants for recent therapies in these intractable diseases, and summarize their biotransformation and the relevant approaches to improve their bioavailability.

2.3. Biotransformation pathways and bioavailability

Baicalin belongs to Class IV of Biopharmaceutical Classification System (BCS) due to the extremely low hydrophilicity (solubility 0.052 mg/mL in water) and lipophilicity (Papp = 0.037×10^{-6} cm/s) [18]. Baicalein is highly permeable (Papp = 1.7×10^{-5} cm/s) but poorly water soluble, which is classified as a Class II compound according to BCS [19,20]. The poor solubility results in both baicalin and baicalein very low bioavailability [21]. Extensive studies have been conducted to explore the *in vivo* processes of these two drugs. The serum profiles and pharmacokinetics of orally administered baicalein and baicalin were compared. Baicalin was absorbed more slowly and had lower C_{max} than baicalein [22]. There exists wide complicated biotransformation of baicalin and baicalein *in vivo* (Figure 2). As a natural glycoside, baicalin possesses more favorable aqueous solubility than baicalein. However, baicalin is difficult to be absorbed as its parent form due to the poor lipophilicity. When baicalin was orally administered, only a small portion was absorbed as its original form by the body, and most was hydrolyzed to baicalein by intestinal bacterial [23]. The recovered

baicalein was then extensively subjected to Phase 2 metabolism, and glucuronides and/or sulfates of baicalein were exclusively presented in the plasma. Notably, the circulating baicalin is not the administered parent drug but one of the conjugated metabolites of baicalein after oral administration of baicalin. The circulating baicalin reenters the gastrointestinal tract via the biliary excretion mechanism [24]and undergoes enterohepatic circulation [21]. After oral administration of baicalein, it is subjected to the extensive first-pass metabolism in liver and small intestine [25,26], and therefore, glucuronides/sulfates of baicalein including baicalin are predominant in the plasma [22]. The biotransformation of baicalin and baicalein and the enterohepatic circulation of baicalin can keep a balance in the systemic levels. With the oral administration of baicalin and baicalein, dominantly circulating in the plasma are the glucuronides/sulfates of baicalein, and therefore, the conjugated metabolites are actually responsible for the *in vivo* effects. Because baicalin itself is one of the conjugated metabolites after oral administration of baicalin or baicalein, the activity of baicalin reported in *in vitro* studies can only partially explain the *in vivo* effects of baicalin and baicalein [22].

A sound knowledge of the pharmacokinetic characteristics of baicalin and baicalein enables scientists to further optimize use of these agents. Various formulations have been developed to improve the oral bioavailability of baicalin and baicalein. Baicalein nanocrystal [27], baicalein-hydroxypropyl-β-cyclodextrin inclusion complex [28], baicalein self-microemulsifying drug delivery system [29], and baicalein solid dispersion [30]have been developed to improve dissolution and oral bioavailability of baicalein. Some nano-based formulations such as solid nanocrystals [31], nanoemulsions [32], and solid lipid nanoparticles [33]have been designed for increasing baicalin's solubility and absorption rate and improving its oral bioavailability. Besides, change administration route of baicalein may be employed to avoid the first-pass effect of the gastrointestinal tract or liver and enhance its bioavailability. For example, pulmonary administration of baicalein nanocrystal can obtain similar pharmacokinetic parameters to intravenous injection of baicalein solution [27].

2.4. Leukemia

Leukemia is a cancer of the bone marrow or blood where the blood cells – mostly leukocytes abnormally proliferate. It is estimated that over 52,380 new cases will be diagnosed and over 24,090 patients will die from leukemia in 2014 in America. The research over the past few decades yielded remarkable improvements in chemotherapy for patients with leukemia. However, drug resistance and serious toxicity remain to be major challenges. Natural antioxidants have gained an increasing interest due to their potential to be developed as low toxic antileukemic compounds [34]. Accumulating studies support that flavonoids isolated from *Scutellaria baicalensis* exhibit promising antileukemic activity [35-39]. Numerous reports have shown that baicalin and baicalein as the major components display remarkable antiradical, antioxidative and antileukemic effects [40,41]. Romanouskaya et al. chose 11 flavonoids and investigated their antiproliferative effects on chronic myeloid leukemia K562 cells and healthy peripheral blood mononuclear cells [42]. Among 11 flavonoids, baicalein displayed the specific cytotoxic effect on leukemia cells. Dong et al. revealed that baicalein could arrest K562 cells in the S phase and selectively induce apoptosis via upregulating caspase-3 and Fas [43]. In addition, Wang et al. found that

baicalin and baicalein might target endogenous CBF1-dependent Notch signal pathway to affect tumorigenesis of K562 cells [44].

Baicalein was also found to inhibit the proliferation of human T-lymphoid leukemia cells (CEM cells) with an IC_{50} value of 4.7 μM [45]. Baicalein significantly inhibited the protein tyrosine kinase in a dose-dependent manner and reduced the expression of PDGF-A mRNA. All these data indicate that baicalein may affect cell proliferation by direct inhibition of growth-related signal, reduction of mRNA expression of PDGF-A, and inhibition of protein tyrosine kinase. Lin et al. also reported that baicalein is capable of suppressing the holoenzyme activity of CK2 with an IC_{50} of 2.54 μM, indicating that baicalein may target protein kinase CK2 [46].

Despite several studies revealing the possible biological targets of baicalin and baicalein, the signaling pathways are substantially distinct in different cancer cell lines, and partial signaling pathways may be regulated successively or simultaneously. In CCRF-CEM leukemic cells, baicalin exhibits a potent anticancer effect with an IC_{50} value of 10.6 μg/mL [47]. The apoptosis of CCRF-CEM induced by baicalin is Bcl-2-dependent, but not p53-dependent pathway. Chen et al. further investigated the biological mechanisms of baicalein in inducing CCRF-CEM apoptosis [48]. They found that baicalein could induce cleavage of caspases-9 and -3 and PARP, and decrease the expression of IAP family proteins, XIAP, and survivin. They also found that baicalein might trigger a convergence of the intrinsic and extrinsic apoptotic pathways via the death receptor-caspase 8-tBid signaling cascade.

The anticancer activity and the mechanism of action of baicalein in human promyelocytic leukemia HL-60 cells have been studied by several research groups. Li et al. demonstrated that baicalein activates caspase-3 and induces the cleavage of PARP and DNA fragmentation [49]. They further demonstrated that baicalein can affect *N*-acetylation of 2-aminofluorene in HL-60 cells, indicating that baicalein can affect the *N*-acetyltransferase (NAT) activity *in vitro* [50]. Wang et al. confirmed that baicalein is capable of inducing apoptosis in HL-60 cells [51]. By finding that baicalein can induce the cleavage of Bid protein, release of cytochrome c from mitochondria into cytosol, activate caspase-3, -8 and -9, and elevate the intracellular hydrogen peroxide level, they concluded that baicalein might trigger the apoptotic death program through ROS-mediated mitochondrial dysfunction pathway. Chow et al. also studied the anticancer effects of baicalein in HL-60 [52]. However, they found that apoptosis induced by baicalein is independent of the production of ROS. Intriguingly, Zheng et al. demonstrated that baicalin displays promising anticancer effect in drug-resistant HL-60/ADR cells through PI3K/Akt signaling pathway [53]. Taken together, all these results encourage further investigation of baicalin and baicalein as potential drug candidates for patients with leukemia.

2.5. Lymphoma

Lymphomas as one kind of the intractable cancers are developed from the uncontrolled proliferation of cells in the lymphatic system. The lymphatic cells are able to overcrowd, invade, and destroy lymphoid tissues and metastasize to other organs. Several studies have demonstrated that *S. baicalensis*, baicalin and baicalein display antiproliferative and apoptotic effects against lymphoma [17,54,55]. Huang et al. reported that baicalin is capable

of suppressing the growth of CA46 Burkitt lymphoma cells via induction of apoptosis with an IC_{50} value of 10 μM [56]. In addition, baicalin almost completely inhibits colony formation at 10 μM. CA46 cells undergo apoptosis in response to baicalin induced apoptosis via up-regulating the cleaved forms of caspase-9, caspase-3, and PARP. Furthermore, baicalin is capable of downregulating antiapoptotic and upregulating apoptotic components of the PI3K/Akt signaling pathway [56].

2.6. Myeloma

Although the current cancer treatments have progressed rapidly, myeloma remains incurable because most patients may eventually relapse or become refractory to available therapies [57]. In order to search more effective adjuvant therapies for the treatment of myeloma, Ma et al. investigated the effects of several traditional Chinese herbal medicines on the proliferation and apoptosis of myeloma cells [58]. They found that Huang-Lian-Jie-Du-Tang (HLJDT) inhibits the proliferation of either myeloma cell lines or primary myeloma cells, especially MPC-1-immature myeloma cells, and induces myeloma cell apoptosis through reduction of mitochondrial membrane potential and activation of caspase-9 and caspase-3. The *Scutellaria* radix was confirmed to be responsible for the suppressive effect of HLJDT on myeloma cell proliferation. Baicalein as one of the major components in *Scutellaria* radix took the lead in the antiproliferation effects in comparison with baicalin or wogonin. Biological mechanistic studies revealed that baicalein inhibits the phosphorylation of IkB-α, and decreases the expression of the IL-6 and XIAP genes.

Lin et al. examined the active effects of *Scutellaria* extract and its main flavonoids constituents on the proportion of side population cells in human multiple myeloma (MM) cell line RPMI 8226 cells [59]. Gu et al. further revealed that baicalein inhibits RPMI 8226 cells with an IC_{50} value of 168.5 μM [60]. They found that baicalein can significantly decrease the expression level of ABCG2 protein. The molecular docking investigation demonstrated that baicalein and fumitremorgin C may share similar binding sites in TM domain of ABCG2, indicating baicalein decreases the proportion of side population through inhibition of ABCG2 protein in RPMI 8226 cells. Li et al. found that baicalein inhibits proliferation and induces apoptosis of RPMI 8226 cells and causes G0/G1-phase arrest [61]. They also confirmed that baicalein is able to inhibit 12-LOX protein expression.

IL-6 is one of the most important growth factors for myeloma cells. IL-6 promotes the proliferation and survival of MM cells through the phosphorylated proteins, including STAT3, Akt, and MAPK. Chemical components that suppress the phosphorylation of signaling proteins might have a potential therapeutic effects for the treatment of MM. Liu et al. investigated the therapeutic effects of baicalein in four myeloma cell lines, namely U266, NOP2, AMO1, and ILKM2, and demonstrated that baicalein suppresses proliferation and induces apoptosis of myeloma cells by blocking IkB-α degradation, resulting in down-regulation of IL-6 and XIAP gene expression [62]. They also found that baicalein not only inhibits IL-6-mediated phosphorylation of signaling proteins, such as Akt, Jak, MAPK, and STAT3, but also inhibits the expression of their target genes, such as Bcl-XL. In addition, baicalein exhibits a stronger inhibitory effect on Erk(1/2) phosphorylation. In contrast, baicalin has no significant effect on IL-6-mediated protein phosphorylation. All these results

suggest that baicalein is a potent inhibitor of protein phosphorylation induced by IL-6. Xu et al. further revealed that baicalein simultaneously inhibits β-catenin protein level to resist the effect of IL-6 on inducing MM cell proliferation, and results in decrease of β-catenin, c-myc, cyclinD1 and integrin β7 mRNA levels [63]. They also found that baicalein decreases migration ability of MM cells in a dose-dependent manner by SDF-1.

The representative *in vitro* studies of baicalin and baicalein on various hematological cancer cell lines are summarized in Table 1. Despite these findings have demonstrated the significant biological promise, further mechanistic investigations of baicalin and baicalein are imperative to provide helpful insights for the advancement into the potential clinical trials.

2.7. Combination strategy

Some cancers remain susceptible to other drugs even though they are resistant to one drug. Based on this view, the concept of combination therapy is well recognized in oncology. As discussed above, baicalin and baicalein have demonstrated the potential therapeutic effects for hematological malignancies treatment. Because the mode of actions of baicalin and baicalein are different from that of conventional cytotoxic agents, combination regimens may show particular promise in early trials.

Combination of baicalein and vincristine yields a synergistic antileukemic efficacy [48]. This combination strategy is applicable to future clinical trials in the treatment of pediatric leukemia because baicalein has beneficial effects in alleviating the vomiting, nausea, and skin rashes caused by chemotherapy. Hexamethylene bisacetamide (HMBA) and baicalin both exert potent antileukemic activity. Ren et al. indentified that the combination of HMBA and baicalin cooperatively inhibits the proliferation of AML cell lines [64]. The combination treatment triggers apoptosis through the intrinsic pathway, as well as through the extrinsic pathway, which involves loss of matrixmetalloproteinase, decreased Bcl-2/Bax ratio and Bcl-XL/Bax ratio, and activation of caspase-8, caspase-9, and Fas. Notably, combination of baicalin and HMBA shows little toxic effect on healthy peripheral blood mononuclear cells. Otsuyama et al. revealed that the synergistic growth suppression of dexamethasone and baicalein in myeloma cells may be useful for myeloma therapy [65]. Interestingly, this combinatory treatment may overcome the dexamethasone resistance in either primary myeloma cells or myeloma cell lines. Baicalein combined with dexamethasone can induce the activation of PPARb and glucocorticoid receptor (GR), which synergistically suppresses the transcriptional activity of nuclear NF-kB. Recently, Zhang et al. reported that baicalein in combination with lenalidomide exhibits synergistic effect via inducing apoptosis of myeloma cells [66]. Further clinical trials are anticipated to rapidly evaluate the utility of combinatory treatments in relapsed and refractory hematological disorders.

3. Conclusions and future perspectives

There is an increasing interest concerning the application of natural antioxidants as low toxic anticancer agents. Some flavonoids from dietary sources have shown to exhibit antioxidative activity, coronary heart disease prevention, free-radical scavenging capacity, and anticancer activity. *S. baicalensis* has been clinically used as a major component in traditional Chinese

medicines to treat various diseases including hematologic malignancies. Notably, baicalin and baicalein are the main bioactive constituents in *S. baicalensis* and have been subjected to extensive investigations as potential candidates for the treatment of cancers. This review summarizes the recent progress of studies on baicalin and baicalein in hematological malignancies. Evidence from various *in vitro* studies suggests that both natural products can indeed suppress multiple molecular targets, induce cell cycle arrest and differentiation on various hematological cancer cell lines. However, very few *in vivo* experiments were conducted to exploit their efficacy for the treatment of hematological malignancies. Our preliminary *in vivo* studies revealed that baicalin can suppress the tumor growth of CA46 cell xenografts in nude mice at a dose of 60 mg/kg (unpublished data).

Over the past decade, accumulating evidence from pharmacokinetics studies suggests that baicalin and baicalein are orally bioavailable despite the limited capability. Further pharmaceutical research indicates that development of appropriate delivery systems can significantly enhance their bioavailability and efficacy. Despite aforementioned advances, more detailed investigations are needed to extensively understand their exact mechanisms of biological effects against different hematological malignancies. In addition, with respect to their limited bioavailability and low toxicity, extensive *in vivo* studies are required to fully exploit their efficacy. Furthermore, as *S. baicalensis* has already been clinically utilized as the traditional medicines and the nutritional supplements, additional clinical trials of baicalin and baicalein are warranted to prove their possibility as potential drug candidates for chemoprevention and treatment of hematological malignancies in clinic. It is worthy to note that chemical modification of baicalein results in several promising compounds in preclinical studies [67-69]. Due to the chemical complexity, structural optimization of baicalin and baicalein remains sparse. Nevertheless, overcoming such challenges represents a promising research direction for further explorations to yield better anticancer agents and provides a great opportunity to identify novel drug targets for treatment of hematological malignancies.

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Abbreviations

PDGF-A	platelet-derived growth factor-A
CK2	casein kinase 2
Bcl-2	B-cell lymphoma-2
PARP	poly-(ADP-ribose) polymerase
IAP	inhibitor of apoptosis protein
XIAP	X-linked inhibitor of apoptosis protein
8-tBid	caspase-8-cleaved Bid
CBF1	C-repeat binding factor 1
NAT	N-acetyltransferase
ROS	reactive oxygen species
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
Akt	protein kinase B

HLJDT	Huang-Lian-Jie-Du-Tang
MM	multiple myeloma
TM	transmembrane
ABCG2	ATP-binding cassette sub-family G member 2
12-LOX	12-lipoxygenase
STAT3	signal transducer and activator of transcription 3
MAPK	Mitogen-activated protein kinases
IL-6	interleukin-6
Jak	Janus kinase
Bcl-XL	B-cell lymphoma-extra large
Erk(1/2)	extracellular-signal-regulated kinase (1/2)
SDF-1	stromal cell-derived factor 1
HMBA	hexamethylene bisacetamide
AML	acute myeloid leukemia
Bax	Bcl-2-associated X protein
NF-κB	nuclear factor-κB
GR	glucocorticoid receptor
BCS	biopharmaceutical classification system

Highlights

- Baicalin and baicalein display therapeutic potentials for hematological malignancies.
- They are associated with diverse cancer targets and signaling pathways.
- Potential biological mechanisms in various hematological malignancies are discussed.
- Biotransformation and approaches to improve their bioavailability are summarized.
- Combination with baicalin or baicalein offers promise as chemotherapeutic adjuvants.

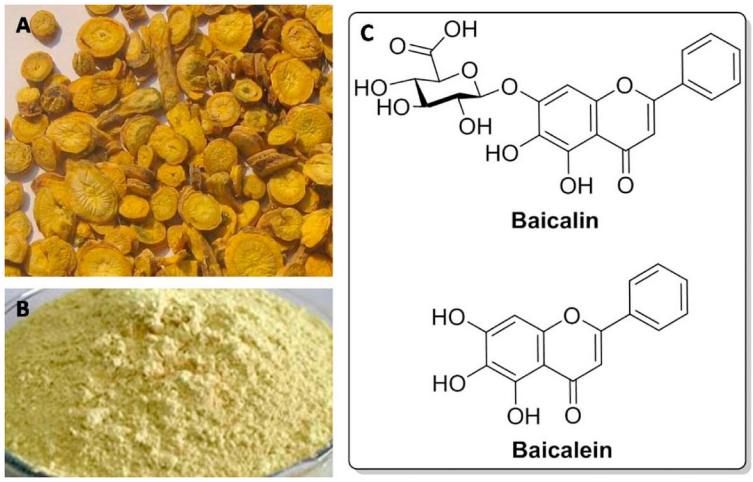

Figure 1.
(A) The roots of *Scutellaria baicalensis*; (B) The powder of baicalin; (C) Chemical structures of baicalin and baicalein.

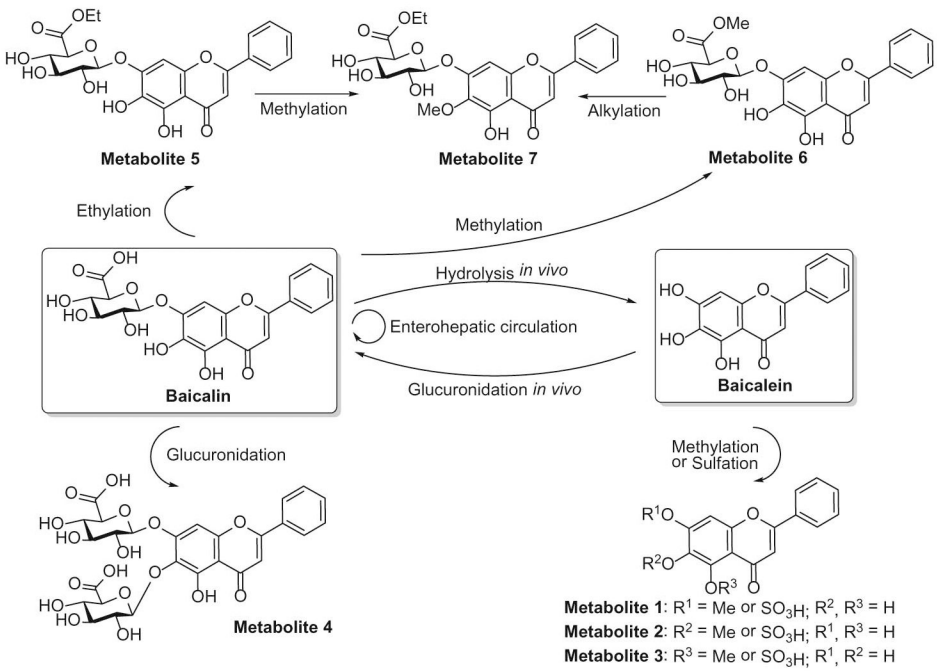

Figure 2. The potential biotransformation pathways of baicalin and baicalein *in vivo*

Baicalin is hydrolyzed to baicalein by intestinal bacterial and is absorbed as baicalein by the body. The recovered baicalein is extensively subjected to Phase 2 metabolism. Baicalin is one of the conjugated metabolites after oral administration of baicalein. The circulating baicalin reenters the gastrointestinal tract via the biliary excretion mechanism and undergoes enterohepatic circulation.

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Table 1

Summary of *In Vitro* Studies with Baicalin and Baicalein on Various Hematological Cancer Cell Lines

Origin	Cell lines	Biological effects	Molecular mechanisms	Ref.
Leukemia	CEM	Baicalein inhibits CEM cell proliferation with an IC_{50} value of 4.7 μM	direct inhibition of growth-related signal, protein tyrosine kinase, and reduction of mRNA expression of PDGF-A	[45]
	CCRF-CEM	Baicalein triggers mitochondria-mediated apoptosis	Baicalein induces mitochondria-dependent cleavage of caspases-9 and -3 and PARP with concomitant decreases in IAP family proteins, survivin, and XIAP	[48]
	CCRF-CEM	Baicalin exhibits remarkable anticancer effect with an IC_{50} value of 10.6 μg/mL	Baicalin induces apoptosis by Bcl-2-dependent, but not p53-dependent pathway	[47]
	K562	Baicalein exhibits the specific cytotoxic effect on leukemia cells	not disclosed	[42]
	K562	Baicalein arrests K562 cells in the S phase and selectively induces apoptosis	upregulating caspase-3 and Fas	[43]
	K562	Baicalin and baicalein affects tumorigenesis of K562 cells	induction of Notch signal pathway	[44]
	HL-60	Baicalein induces *in vitro* apoptosis	Baicalein activates caspase-3, resulting in the cleavage of PARP and DNA fragmentation; Baicalein affects the NAT activity	[49,50]
	HL-60	Baicalein is capable of inducing apoptosis	Baicalein induces the cleavage of Bid protein, cytochrome c release from mitochondria into cytosol, and activation of	[51]
			caspase-3, -8 and -9; Baicalein causes elevation of intracellular hydrogen peroxide level; through ROS-mediated mitochondrial dysfunction pathway	
	HL-60	Baicalein induces apoptosis, suppresses mitochondrial dysfunction	Baicalein-induced apoptosis is independent of the production of ROS, activation of PKC and JNKs participated in TPA's prevention	[52]
	HL-60/ADR	Baicalin induces apoptosis	PI3K/Akt signaling pathway	[53]
Lymphoma	CA46	Baicalin is capable of suppressing the growth of CA46 cells via induction of apoptosis with an IC_{50} value of 10 μM	up-regulate the cleaved forms of caspase-9, caspase-3, and PARP; down-regulate anti-apoptotic and up-regulate apoptotic components of the PI3K/Akt signaling pathway signaling pathway	[56]
Myeloma	U266, NOP-2, AMO1, ILKM2	Baicalein induces apoptosis	Baicalein inhibits the phosphorylation of IkB-alpha, followed by decreased expression of the IL-6 and XIAP genes and activation of caspase-9 and caspase-3	[58]
	MM cells	Baicalein inhibits proliferation and migration	Its molecular mechanisms are associated with inhibition of proliferation related genes β-catenin, c-myc, cyclin D1 and integrin β7 expression	[63]
	RPMI 8226	Baicalein inhibits proliferation and induces apoptosis and causes G0/G1-phase arrest	Baicalein inhibits 12-LOX protein expression	[61]
	RPMI 8226	Baicalein inhibits RPMI 8226 cells with an IC_{50} value of 168.5 μM	Baicalein significantly decreases the expression level of ABCG2 protein; Baicalein and fumitremorgin C might share similar binding sites in TM domain of ABCG2	[59,60]
	U266, NOP2, AMO1,	Baicalein suppresses proliferation and induces apoptosis of various	blocking IkB-α degradation followed by down-regulating IL-6 and XIAP gene expression; Baicalein not only inhibits	[62]

Origin	Cell lines	Biological effects	Molecular mechanisms	Ref.
	ILKM2	myeloma cells	IL-6-mediated phosphorylation of signaling proteins, such as Jak, STAT3, MAPK, and Akt, but also inhibits the expression of their target genes, such as Bcl-XL; Baicalein exhibits a potent inhibitory effect on Erk(1/2) phosphorylation	