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Mini-review

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.

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

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.

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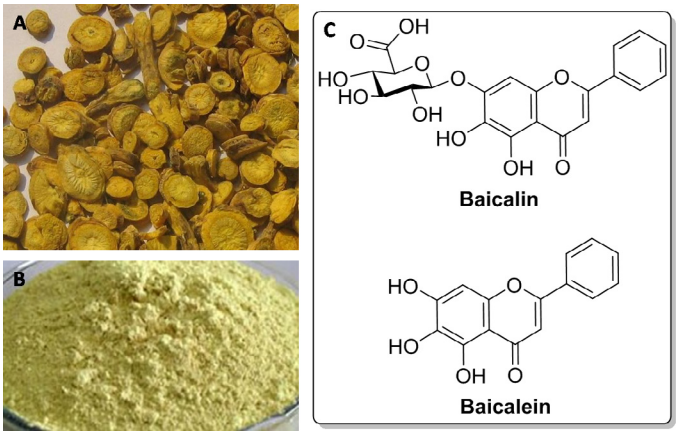

Fig. 1. (A) The roots of *Scutellaria baicalensis*; (B) the powder of baicalin; (C) chemical structures of baicalin and baicalein.

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.

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 3000 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].

Scutellaria baicalensis, *baicalin and baicalein*

Scutellaria baicalensis (*S. baicalensis*, common name: Huang Qin in China, Fig. 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 (Fig. 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 study 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.

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's 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* (Fig. 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 bacteria [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],

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