

From *Scutellaria barbata* to BZL101 in Cancer Patients: Phytochemistry, Pharmacology, and Clinical Evidence

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Abstract

Scutellaria barbata D. Don is a popular Chinese medicinal plant documented to treat cancer patients in traditional Chinese medicine (TCM). A botanical new investigational drug for breast cancer BZL101 (FDA IDN# 59521) was previously developed in the United States from the aqueous extract of the aerial parts from *S. barbata*. The early phase 1A and 1B clinical trials show its favorable toxicity profiles, good clinical tolerance, and promising efficacy for patients with metastatic breast cancer. To further evidence the phytopharmacology research, drug development, and anticancer use of this herb, a systematic literature review was performed herein on the phytochemistry, pharmacology, and specifically anticancer clinical evidence. A systematic review of the literature on phytochemical and pharmacological properties of the plant related to cancer treatment employed several web-based scientific databases including Wanfang (Chinese), Pubmed, Web of Science, and Elsevier. Key words included *Scutellaria barbata*, Ban Zhi Lian, cancer, and tumor. Based on critical quality criteria, only 8 out of 69 reports related to clinical studies of cancer patients in China. This review covered the available literature up to July 2019. The anticancer effects of *S. barbata* can be explained by the presence of various flavonoids and diterpenoids alkaloids. The underlying mechanisms are primarily summarized as cyclin/cyclin-dependent kinase (CDK)-modulated cell cycle arrest and mitochondria-mediated apoptotic death. The highly cancer-cell selective cytotoxicity and detoxifying effects of *S. barbata* contribute to a favorable clinical profile and enhanced quality of life for the cancer patient, thereby demanding further study as an adjuvant or alternative to conventional chemotherapy. The phytochemical and pharmacological studies reviewed strongly underpin a fundamental understanding of the anticancer activity of *S. barbata* and support ongoing clinical trials. The further safety verification and clinical trials are expected to progress *S. barbata*-based development to finally transform the traditional TCM herb *S. barbata* to the valuable anticancer drug.

Keywords

Scutellaria barbata D. Don, BZL101, anticancer, selective cytotoxicity, mitochondria-mediated apoptosis

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Scutellaria barbata D. Don (*S. barbata*), commonly known as Ban Zhi Lian in China and belong to the family *Lamiaceae*, is a popular medicinal plant (Figure 1) with a long history of use in traditional Chinese medicine (TCM). The plant name was first documented in “Wai Ke Zheng Zong” by Shigong Chen in 1617 AD.¹ In China through the centuries, the whole herb of *S. barbata* has been traditionally used as a source of drugs for treating symptoms associated with carbuncle, scrofula, haematemesis, epistaxis, ascites, traumatic injuries, and especially tumors (mainly lung, breast, and digestive system cancers).^{2,3} Data from the Taiwan National Health Insurance Research Database report *S. barbata* as one of the most common herbs used for the core treatment of TCM prescriptions in breast cancer patients.⁴ According to bibliographic investigation using peer-reviewed articles in the Wanfang (Chinese literature), Pubmed, Web of Science, and Elsevier database, scientific

interest in the medicinal activities of *S. barbata* rose significantly during the 1990s mainly in the United States and East Asian countries especially China. The antitumor activity and the underlying mechanisms have been the most researched

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Figure 1. *Scutellaria barbata* D.Don.

aspect of *S. barbata*. Moreover, phytochemistry studies have isolated and identified from *S. barbata* over a hundred metabolites with medicinal value. Antibacterial activities, anti-oxidant, liver protective, and immune regulation functions were also characterized in many in vitro or in vivo models. One of the most significant outcomes of all this knowledge, which may yet translate to the clinical application of *S. barbata* in cancer treatment, is the development of BZL101 for breast cancer patients beyond China.

BZL101 (FDA IDN# 59521) is an aqueous extract of the aerial part of *S. barbata* that shows a favorable toxicity profile and is well tolerated by patients, and demonstrates promising efficacy for metastatic breast cancer in phase I clinical trials.^{5,6} Moreover, the further clinical development of BZL101 has been solidly advanced by continued phytochemistry and mechanistic investigations following clinical trials in patients with advanced breast cancer. In in vitro studies, BZL101 has demonstrated selective cytotoxicity to breast cancer cells over non-transformed mammary epithelial cells.^{7,8} This cancer-specific killing might account for its favorable toxicity profile and good tolerance observed in early clinical trials when compared to chemotherapeutic agents such as cyclophosphamide, thiotepa, and 5-fluorouracil (5-FU). The mechanisms underlying anti-cancer activities of BZL101 were revealed as the mitochondria-targeted inhibition of metabolic pathways in a combined proteomic and metabolomic study.^{7,9,10} On treatment with *S. barbata* extract, the mitochondria of tumor cells were shown to

progressively respire high levels of superoxide and peroxide-type reactive oxygen species (ROS). BZL101 thus inhibits oxidative phosphorylation and depletes mitochondrial reserve capacity depriving the abilities of cancer cells to produce ATP followed by the inhibition of glycolysis and then cell death.⁹ Flavonoids, mainly scutellarein as well as carthamidin, were determined as active anticancer constituents of BZL101 in a recent study. However, the maximal activity of BZL101 appears to need a combination of compounds as the synergistic effect is observed experimentally.¹¹

Though the significant progress achieved during the development of BZL101, the development of this *S. barbata*-based medicine was halted due to insufficient funding. To provide further evidence for the phytopharmacological research, drug development, and anticancer use of this herb, we performed a systematic literature review on the phytochemistry, pharmacology, and especially anticancer aspects of *S. barbata*.

Materials and Methods

The authors searched a number of electronic databases, including Wanfang (Chinese), Pubmed, Web of Science, and Elsevier up to July 30, 2019. The keywords for searching include *Scutellaria barbata*, Ban Zhi Lian, cancer, and tumor. These keywords were searched individually and in combination. The titles and abstracts of each of the articles were assessed to delete duplication data. Searching was limited to articles only in the English or Chinese language. The articles with the contents unrelated to cancer were excluded. Patents, abstracts, case reports, and abstracts in symposia and congress were excluded due to insufficient information for evaluation and comparison with other studies. Review articles were also excluded as the data of them were not original. Based on the above criteria, 69 scientific articles were eligible for evaluation in this study.

No clinical reports were found in the selected English databases, including Pubmed, Web of Science, and Elsevier database. The keywords (in Chinese) “Ban Zhi Lian” with “antitumor” and “anticancer” were used to retrieve peer-reviewed clinical reports in the Chinese Wanfang database. The criteria for selecting quality publications for clinical trials included only the reports that (1) clearly indicated the composition of a formula, (2) daily dose of each herbs, and (3) reports that employed the internationally accepted clinical criteria: Response Evaluation Criteria in Solid Tumors (RECIST)¹² or WHO Response Evaluation Criteria¹³ or years’ survival rates to evaluate treating results is referred to here. Only 8 scientific articles passed the quality criteria on reporting clinical trials and were considered for clinical outcomes.

Phytochemical and Pharmacological Properties of *Scutellaria barbata*

The bioactive secondary metabolites are the basic functional units of medicinal plants. To date, multiple classes of

Table 1. Active Compounds Isolated From *Scutellaria barbata*.

Chemical classification	Phytochemicals	Pharmacological activity	References
Flavonoid	Scutellarin	Anticancer (breast cancer cells MDAMB231, hepatoma cells Hep3B, colon cancer cells HCT-116)	11,14,15
	Carthamidin		
	Apigenin	Anticancer and antimicrobial	16
	Luteolin		16,17
Essential oil	Hexahydrofarnesylacetone	Antimicrobial (myometrium and leiomyomal cells; Lewis lung carcinoma cells)	18
	3,7,11,15-Tetramethyl-2-hexadecen-1-ol		
	Menthol		
Diterpenoid alkaloid	1-Octen-3-ol		
	Scutebarbatines A-L, X	Anticancer (HONE-1 nasopharyngeal, KB oral epidermoid carcinoma, A549 lung cancer, HT29 colorectal carcinoma, LoVo colon cancer, LNCaP prostate cancer, SK-MEL-2 melanoma, MCF-7 breast cancer, SCG7901 gastric cancer, HL-60 leukemia, SMMC-7721 hepatoma cancer and HCT-116 colon cancer cells)	19-25
	6,7-Di-O-nicotinoylscutebarbatine G		21,25
	6-O-Nicotinoyl-7-O-acetylscutebarbatine G		
	7-O-NicotinoylscutebarbatineH		
	Scutehenanine H		26
	6-(2,3-Epoxy-2-isopropyl-n-propoxy)barbatin C		
	Barbatellarines B		27
	Barbatins A, C		20,24
	Barbatins B-H		20,24,28
	Scuteliquanines A-D		29,30
	Scutebatas A-E, G, H, L-N, P-Q, C1	24,31-34	
	Scutehenanines A-D	35	
	6-O-Acetylscutehenanine A		
	6-O-(2-Carbonyl-3-methylbutanoyl)scutehenanine A		
	Scutebarbatines M-O	36,37	
	6-Acetoxybarbatin C	30	
	6-O-Nicotinoylscutebarbatine G	36	
	Scutebarbalactone VN	38	
	Scutebarbatolides A, B	39	
Scubatines F	40		
Polysaccharide	SBPW3, SPS2p	Anticancer (colon cancer)	41,42

phytochemicals, including flavonoids, essential oils, polysaccharide, and terpenoid alkaloids, have been identified from *S. barbata* herb. Table 1 lists the identified phytochemicals accounting for pharmacological activities of *S. barbata*.

Flavonoids, the class of chemicals with anti-inflammatory, antioxidant, and anticancer properties, are the main bioactive components in *S. barbata*. Among them, scutellarin is reported as the highest content according to high performance liquid chromatography-ultraviolet (HPLC-UV) analysis.² The presence of scutellarin has been considered as the major effector of the anticancer effects of BZL101.¹¹ On HCT-116 human colon cancer cells, scutellarin could reduce the cell viability and induce apoptosis by regulating p53 and Bcl-2/Bax expression.¹⁴ More recently, Scutellarein was found to induce Fas-mediated extrinsic apoptosis by modulating the caspase-8, caspase-3, poly-ADP-ribose polymerase and death receptor 4, and G2/M cell cycle arrest by inhibiting the expression of the

proteins Cdc25C, CDK1, and Cyclin B1 in Hep3B hematoma cells.¹⁵ Besides scutellarin, carthamidin, apigenin, and luteolin (Figure 2) are the other antitumor flavonoids identified in *S. barbata*.^{11,16,17,43,44} Scutellarin and carthamidin induced DNA damage and oxidative cell death in breast cancer cells in vitro,¹¹ while luteolin exerted the inhibitory and apoptotic effects via caspase activation and extracellular signal-regulated kinase (ERK)/AKT suppression.¹⁷ Moreover, anti-angiogenic effects of total flavonoids within *S. barbata* were confirmed⁴⁵ and these may play a role in the matrix metalloproteinase (MMP)/tissue inhibitor of metalloproteinase related inhibition of tumor metastasis.⁴⁶ Total flavonoids of *S. barbata* could also induce the apoptosis of human hepatocarcinoma MHCC97-H cells in a concentration-dependent manner via the mitochondrial pathway. The 48-hour treatment led to the significant upregulated expression of apoptotic proteins including Smac,

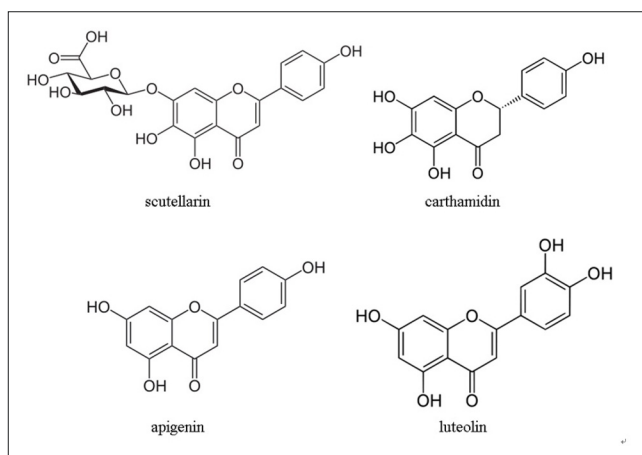


Figure 2. Antitumor flavonoids identified from *Scutellaria barbata*.

apoptotic protease activating factor-1, cytochrome *c*, caspase-9, and caspase-3.⁴⁷

As terminal stage cancer patients often suffer serious microbial infection, the presence of flavonoids also contributes to the antimicrobial activity of *S. barbata*. Luteolin and apigenin were reported in vitro to be selectively active against *Staphylococcus aureus*, including both methicillin-resistant (MRSA) and -sensitive strains.⁴⁸ Essential oils are another class of components that exhibit antimicrobial activity in *S. barbata*. A broad antimicrobial spectrum is observed but with stronger effects on gram-positive bacteria (including MRSA) than gram-negative bacteria or yeasts.¹⁸ The antibacterial activities may arise from the main oil constituents such as hexahydrofarnesyl acetone (11.0%), 3,7,11,15-tetramethyl-2-hexadecen-1-ol (7.8%), menthol (7.7%), and 1-octen-3-ol (7.1%),¹⁸ whose effects had been reported elsewhere.⁴⁹⁻⁵¹

Polysaccharides isolated from *S. barbata* (PSB) could inhibit the proliferation of human lung cancer 95-D cell line with IC₅₀ at 35.2 μg/mL. In vivo, PSB inhibited tumor growth in the 95-D subcutaneous xenograft model in a dose-dependent manner. The treatment of once-daily intraperitoneal injection (100 mg/kg) for 3 weeks was able to inhibit 42.72% tumor growth.⁵² Li et al also isolated a water-soluble polysaccharide, SBPW3, composed of rhamnose, arabinose, xylose, mannose, glucose, and galactose. SBPW3 was found to effectively suppress transforming growth factor-beta (TGF-β) 1-induced migration and invasion by regulating the expression of epithelial and mesenchymal markers through blocking the Smad2/3 signaling pathway in colon cancer cells. It could prevent cancer metastasis in animal model in vivo as well.⁴¹ SPS2p, another water-soluble polysaccharide isolated from *S. barbata*, was also reported to promote the apoptosis in HT29 colon cancer cells through regulating the phosphoinositide 3-kinase (PI3K)/AKT pathway.⁴² This demonstrated the potential antitumor activity for polysaccharides of *S. barbata*.

Diterpenoid alkaloids are the most widely reported compounds from *S. barbata* with cytotoxic activities tested on

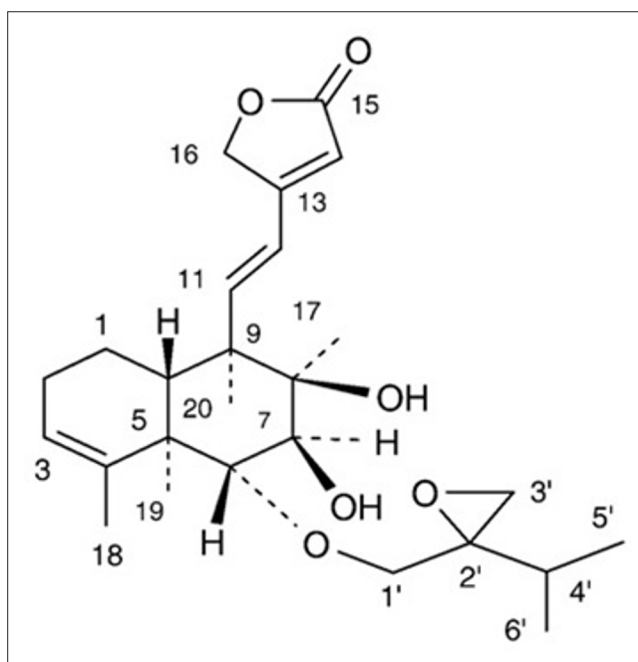


Figure 3. 6-(2,3-Epoxy-2-isopropyl-*n*-propoxy)barbatin C.

cancer cell lines. Their in vitro cytotoxicities have been identified on at least one of the following cancer cell lines including HONE-1 nasopharyngeal, KB oral epidermoid carcinoma, HT29 colorectal carcinoma,^{19-22,29,30,35-37,39,53,54} HL-60 leukemia,^{27,31,32,40} SK-BR-3 breast adenocarcinoma,³² K562 erythromyeloblastoid leukemia, HepG2 and SMMC-7721 hepatocellular carcinoma,^{3,23,24,39} A549 lung adenocarcinoma,^{3,23} LNCaP prostate cancer, SK-MEL-2 melanoma,³⁹ MCF-7 breast adenocarcinoma,^{24,37,39} SGC7901 gastric cancer,³³ LoVo,²⁴ HCT-116,^{24,28} and SW480 colon adenocarcinoma cells³² with IC₅₀ values ranging from 2.0 to over 100 μM. The 6-(2,3-epoxy-2-isopropyl-*n*-propoxy) barbatin C (Figure 3) was the most cytotoxic neo-clerodane diterpenoid reported so far with IC₅₀ as low as 2.0 μM to KB oral epidermoid cancer cells.²⁶

Rationale for the Use of *Scutellaria barbata* to Treat Cancer Patients

Though still at an early stage of clinical validation the existing evidence already defines the anticancer potential of *S. barbata*, this conclusion is supported mainly by evidence from (1) the traditional use and therapeutic evaluation; (2) pharmacology data established by both in vitro and in vivo models; and (3) ongoing clinical trials.

Clinical Uses of *Scutellaria barbata* Formulae in Cancer Treatment Across China

The herbal formulae, usually decoctions comprising dozens of medicinal plants of differing amounts, are the typical dosage

form of TCM. Numerous herbal formulas of TCM have been empirically developed over the centuries and claim to treat cancer-like symptoms in Chinese hospitals and private clinics. As one of the most popular anticancer herbs in TCM, *S. barbata* is widely used in many such formulae. However, the medicinal value of such formulas is extremely hard to evaluate due to the lack of authoritative clinical reports. In this review, we evaluated Chinese language scientific reports concerning the clinical research on anticancer herbs.

As shown in Table 2, out of a total of 69 eligible papers evaluated through the systematic review, only 8 clinical reports of none of the random control test (RCT) double blind studies in Chinese on *S. barbata*-containing herbal formulae complied with our quality screening criteria.⁵⁵⁻⁶² In all 8 clinical studies, herbal metabolites were delivered as decoctions to the target location by oral administration. The weight of *S. barbata* used to prepare the decoction is between 10 and 30 g/day. According to the Chinese Pharmacopeia, the quality standard for *S. barbata* must contain over 0.20% scutellarin.² The daily dosage of scutellarin, claimed to be the major anticancer constituent of *S. barbata*,¹¹ is thus estimated in the range 20 to 60 mg within those herbal formulae. However, the determination of actual concentration of scutellarin is an impossible task due to the variation of drug preparation and complex chemical composition within decoctions. The cancer patients are typically instructed by TCM doctors to prepare the decoction at home by boiling herbal mixtures in water (once or twice to produce 300-400 mL). The decoctions are then self-administered 2 to 3 times daily. Clearly, the multiple factors, such as preboiling procedures (washing and grinding), boiling time, herbal quality, starting liquid volume, and chemical reactions during boiling, can influence the composition and concentration of active compounds in the resulting beverage. To better understand the phytochemical basis underlying the application of such herbal formulae, chemical fingerprinting for drug metabolites in the decoction formulations and in vivo biological fluid sampling (serum or urine from patients) is strongly suggested for future clinical experiments.

Moreover, the therapeutic evaluations of antitumor effects in cancer patients are usually made over a 2-month treatment. In 8 clinical trials reported here, herbal formulae were used either alone or as the adjuvant to the conventional chemo/radiotherapy. The complete response (CR) and partial response (PR) used as indicators of tumor size reduction were used to evaluate the short-term effects and the years' survival rate represented the long-term outcome. As shown in Table 2, the herb plus treatment demonstrated statistically significant improvement on either or both of the evaluating parameters compared to the parallel chemo/radiotherapy. The trials without parallel treatment also partly showed therapeutic effects in cancer therapy.

Taken together, despite issues concerning the quality of 8 identified TCM clinical reports, including that of herbal authentication, no provided chemical profiles (by HPLC-UV or liquid chromatography-mass spectrometer [LC-MS for

example) and limited patient numbers (all less than 100 cases), the anticancer potential of reported formulae including *S. barbata* is claimed. The positive treatment outcomes as judged by objective parameters (CR, PR, or year survival rate) has constructed the basis for further developing the anticancer use of *S. barbata* in both the laboratory and the clinic.

In Vitro Effects of *Scutellaria barbata* on Human Cell Lines

According to reports published since 2003, the *S. barbata* extract has been identified as a growth inhibitor on a broad range of cancer cells in vitro (Table 3).⁶³⁻⁷¹ Aqueous extract of *S. barbata* showed inhibitory effects for the growth of 11 ovarian, 2 breast cancer cell lines, leukemia cells, hepatoma cells as well as leiomyoma cells through inducing mitochondria-mediated apoptosis and arresting the cell cycle at G₁ stages.⁶³⁻⁶⁷ This inhibition is commonly achieved through regulating the CDK/cyclin cascade and apoptotic proteins.⁶⁴⁻⁶⁷ Specially, methanol extracts of *S. barbata* were reported in inducing the G₂/M phase arrest of lung cancer cell CL1-5 through reducing the levels of Cdc25C, cyclin A, cyclin B1, and Cdc2.⁷¹ The actively proliferating cells were more sensitive to the treatment, which suggests the potential selectivity of *S. barbata* on cancers over normal tissues. This is consistent with fewer side-effects of BZL101 observed in clinical trials. Moreover, sensitivities of treatment varied among different cell lines, leading to different survival rates of cancer cells under Bcl-2 transfection.⁶³ The ethanol extract of *S. barbata* could significantly suppress the activation of STAT3, ERK, and p38 signalings through regulation of multiple critical genes expression such as Bcl-2, Bax, Cyclin D1, CDK4, caspase 3/9, and p21 in colon and ovarian cancer cells.⁶³⁻⁷³ The chloroform fraction of *S. barbata* increased the ratio of the pro-apoptotic Bax/Bcl-2, and decreased the expression of the pro-proliferative cyclin D1 and cyclin-dependent kinase 4 and tumor suppressor miR-34a in human colon cancer cells.^{74,75} Compared to the other organic solvent fractions, the methylene chloride fraction was the most cytotoxic demonstrating concentration-dependent effects with IC₅₀ as low as 10 µg/mL on leukemia cells. The mechanism featured as typically mitochondria-mediated apoptotic progress including caspases activation and bcl proteins modulation.⁶⁸ *Scutellaria barbata* was also characterized as an effective regulator for AKT/protein kinase B (PKB), whose disruption frequently occurred in numerous types of human cancers. This regulation was believed to be the critical part of the *S. barbata*'s antitumor and anti-angiogenic functions.⁷⁰ The ethanol extract of *S. barbata* could effectively promote the growth inhibition and apoptosis of human colon carcinoma cells HT-29 via modulation of the interleukin (IL)-6/STAT3 signaling pathway and its target genes.⁷⁶ The apoptosis induced by ethanol extract of *S. barbata* was also found to be mediated through mitochondria-, caspase- and Mitogen-Activated Protein Kinase (MAPK) dependent pathways in MKN-45 gastric adenocarcinoma cells. It enhanced ROS generation and increased the chemosensitivity of MKN-45 cells.⁷⁷ In addition,

Table 2. The Clinical Therapeutic Effects of Herbal Formulae Containing *Scutellaria barbata*.

Herbal formulae (daily dose)	Cancer types	Chemo/radiotherapy	Therapeutic effects	References
Scutellaria barbata (15 g) ; <i>Astragalus membranaceus</i> (30 g); <i>Adenophora tetraphylla</i> (30 g); <i>Hedyotis diffusa</i> (15 g); <i>Solanum nigrum</i> (15 g); <i>Coix lacryma-jobi</i> (15 g); <i>Carcuma phaeocaulis</i> (10 g)	Non-small cell lung cancer	Non	CR + PR ^a : 10.7% (herb ⁺ treatment); 5-y survival rate: 23.2% (herb ⁺ treatment)	55
Scutellaria barbata (20 g) ; <i>Pseudostellaria heterophylla</i> (20 g); <i>Gynostemma pentaphyllum</i> (20 g); <i>Ganoderma lucidi</i> (20 g); <i>Paonia sterniana</i> (15 g); <i>Manis pentadactyla</i> (10 g); <i>Amorphophallus rivieri</i> (10 g)	Liver cancer	Non	CR + PR ^a : 12.5% (herb ⁺ treatment) vs 6.25% (herb ⁻ treatment)	56
Scutellaria barbata (30 g) ; <i>Codonopsis pilosula</i> (20 g); <i>Poria cocos</i> (15 g); <i>Atractylodes macrocephala</i> (15 g); <i>Pinellia ternate</i> (15 g); <i>Raphanus sativus</i> (15 g); <i>Perilla frutescens</i> (15 g); <i>Ligusticum chuanxiong</i> (15 g); <i>Gallus gallus domesticus</i> (15 g); <i>Citrus reticulata</i> (12 g); <i>Astragalus membranaceus</i> (30 g); <i>Carcuma veyujin</i> (30 g); <i>Vinapis alba</i> (10 g); <i>Sophora subprostrata</i> (10 g)	Lung cancer	Femoral artery puncture: etoposide 100 mg, cis-platinum 30 mg, mitomycin 6 mg, and hydroxycamptothecine 5 mg	CR + PR ^a : 58.3% (herb ⁺ treatment) vs 48.3% (herb ⁻ treatment)	57
Scutellaria barbata (30 g) ; <i>Astragalus membranaceus</i> (30 g); <i>Ligustrum lucidum</i> (30 g); <i>Psoralea corylifolia</i> (30 g); <i>Coix lacryma-jobi</i> (30 g); <i>Carcuma veyujin</i> (30 g); <i>Codonopsis pilosula</i> (15 g); <i>Poria cocos</i> (15 g); <i>Angelica sinensis</i> (10 g); <i>Epimedium davidii</i> (10 g)	Liver cancer	Non	CR + PR ^a : 38.9% (herb ⁺ treatment); 1-y survival rate: 55.6% (herb ⁺ treatment)	58
Scutellaria barbata (30 g) ; <i>Astragalus membranaceus</i> (30 g); <i>Carcuma veyujin</i> (30 g); <i>Carcuma phaeocaulis</i> (30 g); <i>Pinellia ternate</i> (15 g); <i>Rabdosia rubescens</i> (15 g); <i>Coix lacryma-jobi</i> (15 g); <i>Gallus gallus domesticus</i> (15 g); <i>Sophora subprostrata</i> (10 g)	Esophagus cancer	Femoral artery puncture: 5-FU 1 g and dodecyl phthalate (DDP) 60 mg or VP-16 200 mg and DDP 60 mg	CR + PR ^a : 65.8% (herb ⁺ treatment) vs 47.1% (herb ⁻ treatment)	59
Scutellaria barbata (15 g) ; <i>Astragalus membranaceus</i> (30 g); <i>Coix lacryma-jobi</i> (30 g); <i>Pseudostellaria heterophylla</i> (20 g); <i>Ligustrum lucidum</i> (15 g); <i>Lycium barbarum</i> (15 g); <i>Crematula appendiculata</i> (15 g); <i>Carcuma phaeocaulis</i> (15 g); <i>Salvia miltiorrhiza</i> (10 g); <i>Achyranthes bidentata</i> (6 g); <i>Atractylodes macrocephala</i> (6 g); <i>Poria cocos</i> (6 g); <i>Pinellia ternate</i> (6 g); <i>Citrus reticulata</i> (6 g)	Rectal and cervical cancer	6MV-X ray linear accelerator irradiation, 3-4/week	CR + PR ^a : 94.8% (herb ⁺ treatment) vs 70.7% (herb ⁻ treatment); 5-y survival rate: 51.7% (herb ⁺ treatment) vs 32.8% (herb ⁻ treatment)	60
Scutellaria barbata (10 g) More recently, <i>Scutellarein</i> was; <i>Angelica sinensis</i> (30 g); <i>Astragalus membranaceus</i> (30 g); <i>Codonopsis pilosula</i> (30 g); <i>Polygonum multiflorum</i> (30 g); <i>Rhizoma dioscoreae</i> (30 g); <i>Liquiritia glycyrrhiza</i> (30 g); <i>Rhizoma polygonati</i> (30 g); <i>Rhenum officinale</i> (30 g); <i>Radix scrophulariae</i> (30 g); <i>Paonia lactiflora pallas</i> (30 g); <i>Fructus Aurantii Immaturus</i> (30 g); <i>Crataegus pinnatifida</i> (35 g); <i>Adenophora stricta</i> (35 g); <i>Pseudobulbus cremanstrae</i> (10 g); <i>Lobelia chinensis</i> (10 g); <i>Scandent schefflera</i> (15 g)	Breast cancer	Paclitaxel 175 mg/m ² and adriamycin 60 mg/m ²	CR + PR ^a : 47.1% (herb ⁺ treatment)	61
Scutellaria barbata (15 g) ; <i>Astragalus membranaceus</i> (30 g); <i>Adenophora stricta</i> (15 g); <i>Ophiopogon japonicus</i> (15 g); <i>Lycium chinensis</i> (15 g); <i>Trichosanthes kirilowii</i> (10 g); <i>Poria cocos</i> (10 g); <i>Fritillaria thunbergii</i> (15 g); <i>Hedyotis diffusa</i> (20 g); <i>Salvia chinensis</i> (10 g); <i>Solanum nigrum</i> (10 g); <i>Parsipolphylla</i> (10 g)	Non-small cell lung cancer	Gemcitabine, 1000 mg/m ² and DDP, 75 mg/m ²	CR + PR ^a : 57.9% (herb ⁺ treatment)	62

5-FU, 5-fluorouracil.

^aCR (complete response); tumors completely disappear for 1 month and above; PR (partial response); tumor size reduces over 50% for 1 month and above.

Table 3. The Anticancer Activities of *Scutellaria barbata* Extracts.

Extract types	Cancer types	Cell lines	IC ₅₀ (μg/mL)	Mechanisms	References
Water	Ovarian	SKOV3	-	G ₁ arrest; apoptosis	63
		A2780 PARENT			
		A2780 CP70			
		A2780 V			
		A2780 MP53			
		HA8			
		HEY			
		HEY C2			
		OVCAR-3			
		CAOV3			
Breast	SKBR3				
	MCF7				
Leiomyoma		LM-1/2	-	G ₁ arrest; apoptosis; caspase-3 activity↑; cyto- <i>c</i> release; α-smooth muscle actin↑; calponin h1↑; p27↑	64,65
Leukemia		HL-60	-	G ₁ arrest; apoptosis; cyclin A↓; cyclin D↓; cyclin E↓; CDK2↓; CDK4↓; CDK6↓; p21↑; pRb↓	66
Hepatoma		H22	-	G ₁ arrest; apoptosis; mitochondrialtransmembrane potential↓; caspase-3 activation; cyto- <i>c</i> release	67
Methylene chloride	Leukemia	U937	10	Apoptosis; caspase-3/9 activation; Bax/Bcl-2↑; cyto- <i>c</i> release	68
Ethanol	Lung	A549	210	Apoptosis; DNA damage; cell cycle control; nucleic acid binding; protein phosphorylation	69
	Colon	HT-29	-	Apoptosis; caspase-3/9 activation; cyclin D1↓; CDK4↓; Bcl-2↓	76
		HCT-8/5-FU	-	Cyclin D1↓; Bcl-2↓; ABCG2↓; p21↑; Bax↑; suppression of the PI3K/AKT pathway	79
	Gastric	MKN-45	105.6	Apoptosis; caspase-3/9 activation; MAPK dependent; ROS generation	77
	Ovarian	A2780	-	Apoptosis; caspase-3/9 activation; Bcl-2↓; MMP-2/9↓	72
	Colorectal	HCT-8	-	MMPs↓; PI3K/AKT, and TGF-beta/Smad pathways suppression	78
Methanol	Colorectal	LoVo	-	Phosphorylated AKT↓	70
	Lung	CL1-5	-	G ₂ /M arrest; Cdc25C↓; cyclin A↓; cyclin B1↓; Cdc2↓; apoptosis, caspase 7↑; caspase 3↑; PARP↑; caspase 4↑; Bcl-2↓; Bcl-xs↑; FasL↑; SIRT1↓; phosphorylation of P38 ↑	71
Chloroform	Colon	HCT-8	-	Apoptosis; miR-34a↑; Bcl-2↓; Notchl/2↓; Jagged1↓	74

MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; PI3K, phosphoinositide 3-kinase.

ethanol extract of *S. barbata* decreased the expression of MMP-1, MMP-2, MMP-3/10, MMP-9, and MMP-13, and proteins in the PI3K/AKT and TGF-β/Smad pathways, thus inhibiting cell metastasis of colorectal cancer.⁷⁸ Importantly, the anticancer effect of ethanol extract of *S. barbata* was presented in a 5-FU-resistant colorectal cancer cell line HCT-8/5-FU by regulating PI3K/AKT pathway. It indicated the potentials of *S. barbata* against chemoresistance, which was a major obstacle in clinical treatment of cancers.⁷⁹ In a global genomics screening study using cDNA microarray analysis, the *S. barbata*-induced apoptotic death of cancer cells was determined as multiple genes involved in mechanisms including control of DNA damage, cell

cycle, nucleic acid binding, and protein phosphorylation.⁶⁹ However, to the best of our knowledge, further details on the anticancer mechanistic network of *S. barbata* has not been reported in the literature.

Taken together, the in vitro studies reported to date have indicated the cytotoxicity of *S. barbata* extracts on most of the cancer cell lines tested. The anticancer mechanisms were primarily identified as antiproliferative growth arrest and then mitochondria-mediated apoptotic death. However, the detailed molecular mechanisms are still far from clear at both proteomic and genomic levels and thus remain an ongoing challenge. The level of such understanding would expand our knowledge regarding

the anticancer properties of natural products and further aid the development of anticancer drug from those sources.

In Vivo Antitumor Effects of Scutellaria barbata in Animal Models

On the basis of the above in vitro studies, the antitumor effects of *S. barbata* or its fractions were gradually reported in recent years. The polysaccharide fraction of *S. barbata* inhibited by up to 34.35% growth of tumors in the hepatocarcinoma H22-bearing mice^{80,81} with similar inhibition also observed in S180 sarcoma-bearing mice.⁸² Meanwhile, immune defences of experimental animals were strengthened, as characterized by increased weight of immune organs, promoted serum IL-2 levels, and improved function of monocyte-macrophages.^{80,82} Similarly, the tumor growth of hepatoma H22-bearing mice was also significantly controlled by crude extracts of *S. barbata*. It could increase the efficacy of spleen NK cells, downregulate the amount of Treg cells and Th17 cells in tumor tissue, and decrease serum IL-10, TGF γ , and IL-17A levels whereas increase IL-2 and IFN γ levels.⁸³ Without loss of body weight (a key indicator for side-effects), the size of colorectal tumor and angiogenesis were significantly reduced in *S. barbata*-treated xenograft mice.^{73,84} The blockage of the Sonic Hedgehog and the Wnt/beta-catenin pathway was then involved in the anti-angiogenic activity of *S. barbata* through suppressed expression of key mediators such as sonic hedgehog, patched-1, β -catenin, c-Myc, surviving, smoothed, and the glioma-associated oncogene homolog 1.^{84,85} Moreover, Chen et al recently reported that the methanol extracts of *S. barbata* suppress tumor growth in mouse CL1-5 (lung cancer cell) xenograft models through apoptosis, autophagy, anti-angiogenesis, and antiproliferation, which were similar to those of *S. barbata*-treated CL1-5 cells in vitro.⁷¹ Besides inhibiting the tumor growth, *S. barbata* also presented protective effects against tumorigenesis. In diethylnitrosamine-stimulated animal models, the liver tumorigenesis was significantly inhibited after exposure to *S. barbata* extracts, featuring a reduced number of tumor nodules, elevated activities of serum alanine aminotransferase and aspartate aminotransferase, and inhibited levels of tumor markers including gamma-glutamyl transferase, glutathione-S-transferase, and alpha-L-fucosidase.⁸⁶ As a currently used adjuvant of conventional chemotherapy, *S. barbata* greatly synergized the antitumor effect of low dose 5-FU (2 μ g/mL or 8 mg/kg) both in vitro (Bel-7402 and HCT-8 cell lines) and in vivo (H22 transplanted hepatocarcinoma Kunming mice). Apoptotic death of cancer cells was induced under such combined treatment through the activation of caspase-3 and the modulation of apoptotic proteins including p53, Bcl-2, Bax, and bid.⁸⁷ Moreover, *S. barbata* polysaccharides were recently found to inhibit the growth of Calu-3 xenograft tumors through blocking the HER2 pathway and angiogenesis.⁸⁸

In summary, the antitumor effects of *S. barbata* have been confirmed in several in vivo models. The data obtained from these in vivo experiments are greatly in agreement with *S. barbata* traditional uses and in vitro activity. These and in vivo pre-clinical animal experiments also offer the foundations for proposed BZL101 clinical trials.

Phase 1A and 1B Clinical Trials

As described above, the safety and efficacy of BZL101 (the drug developed from crude aqueous extracts of *S. barbata*) for treating metastatic breast cancers has been assessed in early phases of clinical trials in the United States. In a phase 1A trial, the crude herb *S. barbata* was extracted in hot water and the crude liquids produced were orally administered to patients. According to Common Toxicity Criteria,⁸⁹ no grade III or IV adverse events occurred during the BZL101 treatment. The grade I and II side events related to BZL101 were mainly gastrointestinal symptoms including nausea (48%), vomiting (10%), gagging (5%) as well as diarrhea, constipation, bloating, gas, and abdominal cramping.⁶ These effects were thought to be caused by the bitterness and insoluble plant roughage from unprocessed herbal materials in the study. In the subsequent phase 1B trial, the reformulation of BZL101 using sweeteners and taste-enhancing excipients significantly improved the patient's acceptance and achieved excellent tolerability with a median compliance of 92%. Compared to the conventional chemotherapeutic drugs capecitabine and lapatinib, BZL101 (maximum at 40 g daily) demonstrated more favorable toxicological profiles and thus represents a clear advancement in options for patients with metastatic breast cancers.⁵

In both the phase 1A and 1B trials, treatment with BZL101 shows early indications of biological antitumor activity and a potential to delay disease progression. According to the Response Evaluation Criteria in Solid Tumors (RECIST),¹² 4 out of 16 patients enrolled in trial 1A have stable disease (SD) for over 90 days and 3 had SD for over 180 days. Moreover, 5 patients demonstrated a minimal response with one having 1 mm in tumor size reduction.⁶ In the further 1B trial with patients suffering metastatic breast cancers who had already undergone surgery, chemotherapy or radiotherapy before the trial, 5 of 14 experienced long periods of SD and 3 were classified as SD for over 120 days. One patient was treated with BZL101 for 449 days and remained stable for over 700 days.⁵

In summary, the recent phase 1 clinical trials demonstrated that BZL101, especially with the improved organoleptic formula, is safe, well tolerated with beneficial therapeutic activities for patients with metastatic breast cancers. Although the development of BZL101 was halted due to funding problems, the further development of the *S. barbata*-based anticancer drug formula and advanced phase clinical trials remains promising.

Safety and Drug Interactions

Though the systemic toxicity and safety evaluations are still inadequate for drug development, the lower toxicity of *S. barbata* in cancer treatment was evidenced in the early phase clinical trials.^{5,6} In preclinical animal research, *S. barbata* has been determined as an effective synergistic and toxicity-reducing agent for chemotherapy in both in vitro and in vivo cancer models.^{87,90-92} In the hepatoma H22 tumor-bearing mice undergoing 5-FU treatment, the co-administration of *S. barbata* could significantly enhance the tumor inhibition rate, reduce toxic effects including abdominal distention, listlessness, and emaciation, prolong the survival time and upregulate immune function.⁹⁰ Moreover, *S. barbata* demonstrated protective and recovery effects against cisplatin-induced nephrotoxicity in mice. *Scutellaria barbata* pretreatment could ameliorate renal dysfunction as indicated by serum creatinine and blood urea nitrogen level, as well as reduce pro-inflammatory cytokines secretion and tubular injury in cisplatin-treated mice.^{91,92} The cisplatin-induced damage could be strongly recovered by *S. barbata* on Human Embryonic Kidney 293 cells.⁹² However, the toxicology and co-efficacy activities of *S. barbata* need further assessment along with the commonly used chemo-drugs and experimental models in preclinical tests and then clinical trials, which would lead to its application as an adjuvant drug for cancer treatment.

Conclusion

As one of the first botanical investigational new drugs approved by FDA, BZL101 (*S. barbata*) has been of increasing interest in recent years. The numerous phytochemical and pharmacological studies reviewed in this article help to validate the anticancer potential of *S. barbata* and strongly support ongoing and any further clinical trials proposed. Its cytotoxicity effects can be explained by the presence of various flavonoids and diterpenoid alkaloids. The mechanisms underlying anticancer effects could be summarized as cyclin/CDK-modulated cell cycle arrest and mitochondria-mediated apoptotic death. The highly selective cytotoxicity and detoxifying effects of *S. barbata*, which denote a favorable clinical profile, may receive more interest as an adjuvant medicine to conventional chemotherapy.

Based on the review of current research, there is a need to further detail the anticancer mechanisms of *S. barbata* at both genomic and proteomic levels. Efforts should also be made to determine the identity, pharmacokinetics, bioavailability, and physiological pathways of functionally anticancer constituents in *S. barbata*. Further safety verification and clinical trials are expected to progress *S. barbata*-based anticancer drug development and finally succeed in transforming *S. barbata* the traditional Chinese medicine to a new drug for women suffering from breast cancer.

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