

Anti-Tumor Activities of Bioactive Phytochemicals in *Sophora flavescens* for Breast Cancer

This article was published in the following Dove Press journal:
Cancer Management and Research

Xianjiao Cao¹
Qingqing He² 

¹The First School of Clinical Medicine, Shandong University of Traditional Chinese Medicine, Jinan, Shandong 250011, People's Republic of China;

²Department of Thyroid and Breast Surgery, The 960th Hospital of the PLA Joint Logistics Support Force, Jinan, Shandong 250031, People's Republic of China

Abstract: Patients with breast cancer and breast cancer survivors are frequent users of botanicals and their bioactive phytochemicals. In China, active ingredients in *Sophora flavescens* like matrine (MT), oxymatrine (OMT), other *Sophora flavescens* alkaloids and Compound Kushen Injection (CKI) are extensively used for multiple malignant tumors. In vivo and in vitro studies have confirmed that these activities or injection have significant effects on relieving symptoms, alleviating side effects after chemotherapy and improving the quality of life of breast cancer patients, where there is evidence for efficacy. A large number of experimental studies have also revealed that they can inhibit the proliferation, invasion and migration of breast cancer cells according to different mechanisms. This provides promising valuable supportive therapies for prevention, treatment and postoperative recovery of breast cancer. Rigorous clinical research and experimental studies reflect integrative care as it is used in hospital is needed to responsibly move this field forward. This review summarizes an up to date knowledge of the available bioactive phytochemicals, their discovery, current clinical and experimental status.

Keywords: breast cancer, *Sophora flavescens*, CKI, matrine, oxymatrine

Introduction

Application of botanicals to treat solid tumors all over the world has a long history. Many anti-cancer agents have been identified from botanicals, although most of their anti-tumor mechanisms are under discussion. Botanicals are widely used in combination with radiotherapy or chemotherapy to improve the curative efficacy of cancer and reduce complications and side effect. Traditional Chinese Medicine (TCM), including herbal remedies, has been practised for more than five thousand years and many of the herbal medicines have been intensively investigated. In China, TCM formulas are extensively used for modulating immune function and improving the quality of life of cancer patients who undergoing chemotherapy or radiotherapy.¹ Because of the low toxicity and wide range of biological activities of botanicals, many natural products have been applied as alternative treatments for many cancers including breast cancer.²

Breast cancer is the most common noncutaneous malignancy among women worldwide, and the cure and prevention of cancer effects of botanicals are more and more thought highly of now. Although the mortality rate of breast cancer is decreasing and survival rate is increasing year by year, it is also estimated that more than 1000 thousand women are newly diagnosed with breast cancer each year worldwide and that over 400,000 cases will die from breast cancer. China National Cancer Center announced that the incidence of breast cancer is

Correspondence: Qingqing He
Department of Thyroid and Breast Surgery, The 960th Hospital of the PLA Joint Logistics Support Force, No. 25 Shifan Road, Jinan, Shandong 250031, People's Republic of China
Tel +86 13789828035
Fax +86 531666673
Email heqingqing@yeah.net

about 34,000 in 2015; Breast cancer accounted for 17.10% of all cancers and was the fifth leading cause of death in female malignant tumors, accounting for 8.16% of all cancer deaths. It has been a serious burden for societies of China and the whole world for a long time. The main treatment options for breast cancer cases include surgery, chemotherapy, hormone and immunological therapy, radiotherapy. Multidrug chemotherapy can reduce the recurrence rate while increase multidrug resistance. Even treated at an early stage, approximately 30% of breast cancer patients suffer from metastasis and relapse. Resistance to chemotherapy and subsequent recurrence and metastasis are two main intractable problems in most patients with breast cancer, which made patients bear additional economic and spiritual stress. The high toxicity of the treatments of breast cancer to normal tissues is practically inevitable. Seeking for effective and safe treatment strategies for breast cancer is an urgent task for medical researchers.^{3,4}

In the past several decades, many botanicals are used for breast cancer treatment. So far, it has been proved that there are many kinds of herbal extracts that have effects on the treatment of breast cancer, involving various mechanisms, such as Saikosaponin A, Emodin, Sanguisorba, Oridonin, Curcumol, Triptolide, artesunate, cycloartane triterpenoid derivative.⁵⁻¹⁴ Breast cancer prevention is equally important for high-risk women with older age and postmenopause status. Glycyrrhiza Species (Licorice) and its three medicinally used species of licorice (*G. glabra*, *G. uralensis*, and *G. inflata*), *Silybum marianum* (Milk Thistle) and its extract silibin B or silymarin, *Angelica sinensis* (Dong Quai) and its dong quai's phytoconstituents ferulic acid or Z-ligustilide, *Epimedium*, ginger, black cohosh and flaxseed have been reported for breast cancer prevention. These botanicals and their bioactive phytochemicals play the role of breast cancer prevention through four major mechanisms including hormonal, chemical, inflammatory, and epigenetic.¹⁵ Vinca alkaloids and taxol are two anticancer drugs extracted from naturally occurring compounds; however, toxic side effects place restrictions on their use. Therefore, developing novel natural with low toxicity and high therapeutic selectivity is clinically important. Novel molecular markers and genetic mutations are now comprehensively identified in breast cancer genome sequencing projects. At present, most studies on the underlying mechanisms of botanicals on breast cancer are limited to the molecular level, and the role of traditional medicine in gene level is less studied.

Sophora flavescens

Kushen (Radix *Sophorae Flavescentis*/*Sophorae flavescentis*), a traditional Chinese herbal medicine, is the dried root of *Sophora flavescens* Ai. In 200 A.D., Kushen was described in the traditional Chinese book *Shen Nong Ben Cao Jing* for the first time and it was used to treat inflammation, solid tumors, and other compounds. The main chemical components in Kushen include alkaloids, flavonoids, alkylxanthones, quinones, triterpene glycosides, fatty acids, and essential oils. Among them, Kushen alkaloids (KS-As) account for 3% and Kushen flavonoids (KS-Fs) account for 1.5%, which are two characteristic components of Kushen. MT and OMT consist of approximately 20% of the total alkaloids in Kushen. *Sophora flavescens* water decoction recorded in *Chinese Pharmacopoeia* can treat diseases such as leukorrhea, jaundice, enteritis, scabies, dysentery, carbuncles as well as pyogenic infections of the skin. KS-As or KS-Fs preparations from different manufacturers are more or less different, but their anti-tumor function was consistent with that in published reports.

Looking for the active substances is a critical approach to the development of new drugs to treat cancers. As unique tetracyclo-quinolizidine alkaloids, MT and OMT are found only in *Sophora* species thus far. Various patents of Kushen extracts have been applied in China, USA and other countries.¹⁶ In 2005, Kushen extracts were approved by the Chinese FDA for malignant tumor treatment. Kushen alkaloids are effective anticancer drugs and widely used in cancer treatment in China now. The mechanism of breast cancer treatment and prevention includes inhibition of cell proliferation, induction of cell differentiation or apoptosis, ant-inflammatory, antioxidant, and anti-angiogenesis. This literature will introduce the anti-cancer effects of CKI and other phytochemicals extracted from *Sophora flavescens* (Table 1).

Compound Kushen Injection

Compound Kushen Injection (CKI), commonly known as the Yanshu Injection, is exacted from Kushen (Radix *Sophorae Flavescentis*). The chemical fingerprint of CKI contains at least 8 different components, with primary 4 principles including MT, OMT, sophoridine and oxysophocarpine, which exhibit a variety of pharmacological activities. In China, CKI has been extensively used integrated with both TCMs and modern medicines when treating tumors, including cardiovascular and rheumatic diseases as

Table 1 General Information of Active Ingredients in *Sophora flavescens* for Breast Cancer

	Chemical Formula	Types of Cancer Cells	Optimum Experimental Concentration	Effects	Side Effects	Molecular Weight
Compound Kushen Injection	Include MT, OMT, sophoridine and oxysophocarpine, et al	MDA-MB-231, MCF-7	2 mg/mL	Reduce cell migration, induce cell apoptosis, reduce energy consumption, anti-angiogenesis, overcome the multidrug resistance, improve the efficiency of chemotherapy, reduce adverse reactions of chemotherapy	Unclear	N
Matrine	$C_{15}H_{24}N_2O$	Bcap-37, MCF-7/ADR, BT-474, MDA-MB-231, 4T1	In vivo: 10mg/Kg In vitro: 50–100 μ g/mL	Induce apoptosis of cells, inhibit the tumor vascular formation, protect liver function of breast cancer patients undergoing chemotherapy, down-regulate expression level of miRNA	Unclear	248.36g/mol
Oxymatrine	$C_{15}H_{24}N_2O_2$	MCF-7, MDA-MB-231	100 μ g/mL	Induce apoptosis of cells, inhibit epithelial-mesenchymal transformation of cells	Unclear	264.37g/mol
kurarinone	$C_{26}H_{30}O_6$	MDA-MB-453S, MCF-7, Bcap-37	7.3 and 31 μ g/mL	Enhance antitumor activities of taxol, suppress cell proliferation	Unclear	438.52 g/mol
2'-methoxy-kurarinone	$C_{27}H_{32}O_6$	MDA-MB-453S, MCF-7, Bcap-37	7.3 and 31 μ g/mL	Enhance antitumor activities of taxol, suppress cell proliferation	Unclear	452.55g/mol
Sophoridine	$C_{15}H_{24}N_2O$	MCF-7	30 μ g/mL	Antiproliferative activity	Unclear	248.37g/mol
Sophoridine+COCH ₂ Br	$C_{17}H_{26}N_2O_2Br$	MCF-7	20 μ g/mL	Antiproliferative activity, suspend the cell cycle	Unclear	370.31g/mol
9-methylanthracene +CH ₂ OH	$C_{16}H_{2}O$	MCF-7/AMD	1.25–5.0 μ g/mL	Block cell cycle	Unclear	210.19 g/mol
12-N-p-Chlorobenzyl sophoridinic-4',4'-chlorophenyl ketone	$C_{28}H_{34}ON_2Cl_2$	MCF-7/AMD	1.25–5.0 μ g/mL	Block cell cycle	Unclear	485.50 g/mol
-4'-4'-diethyl sophoridine bichloride	$C_{26}H_{39}N_2Cl_2 \cdot 2HCl$	MCF-7/AMD	1.25–5.0 μ g/mL	Block cell cycle	Unclear	486.98g/mol
Matrine+ methyl 6-bromo-2-naphthoate	$C_{26}H_{39}N_2O_2Br$	BT-20, MCF-7	12.5, 25, 50 μ M	Induce apoptosis and oxidative stress	Unclear	461.27 g/mol
5,7-D, 2',4'-tetrahydroxy-8-lavandulylflavono	$C_{35}H_{38}O_6$	MDA-MB-231	0-30 μ M	Increase cell apoptosis	Unclear	423.18 g/mol

well as viral hepatitis. CKI was approved for the treatment of cancer by the State Food and Drug Administration of China more than 20 years ago. Since 1995, it has been widely used to treat liver cancer, nonsmall cell lung carcinoma, and gastric cancer and acute leukaemia in combination with other antitumor drugs like cisplatin, vinorelbine et al.^{17–21} Experimental and clinical research has shown that CKI and its compounds exhibit anti-cancer actions, such as inhibiting cancer cell proliferation, metastasis and invasion, accelerating cell apoptosis, inducing cell differentiation and cycle arrest, restraining angiogenesis, reversing multidrug resistance, and reducing chemotherapy-induced toxicity. In China, the study of CKI is mostly focused on clinical practice. The involvement of CKI and its mechanisms of breast cancer treatment are reviewed below.

Uncontrolled migration of cells away from the primary tumor leads to cancer progression, which is the main cause of cancer-related deaths. Reconstitution and fractionation of CKI highlight the importance of combinations of multiple compounds for antitumor activity. Live-cell imaging confirmed CKI strongly reduced the migration of MDA-MB-231 cells, with down-regulation of actin cytoskeletal and focal adhesion genes.²² The cell cycle was identified as the potential primary target pathway of CKI in MCF-7 cells. CKI may induce apoptosis in MCF-7 cells via a p53 independent mechanism; furthermore, lncRNA H19, which over-expressed in breast cancer, was significantly down-regulated in cells treated with CKI.²³ In Hep G2 and MDA-MB-231 cells, protein levels in cell cycle pathway, DNA repair pathway and DNA double-strand breaks (DSBs) could be altered by CKI. It declined protein levels for cell cycle and DNA repair while increasing the level of DSBs. At the same time, energy metabolism was reduced because of reduced glucose consumption and cellular energy charge. These results support a model of action of CKI that multiple compounds rather than individual components affect multiple targets and the synergistic.²⁴ Breast cancer stem cells (CSCs) are the sources of oncogenesis, cancer metastasis and relapse. SP cells exhibit properties similar to CSCs because of the capabilities to proliferate more tumorigenic cells than other populations. Compared with cisplatin and saline (as a control) group, CKI suppressed the size of MCF-7 SP population (approximately 90%), and down-regulated the main genes of Wnt signaling pathway to suppress tumor growth, which suggested that CKI may serve as a novel drug targeting CSCs.²⁵ Anti-angiogenesis may be one of the important mechanisms of CKI in inhibiting tumor growth. Different doses of

CKI injected into the mice with tumor exhibited different angiogenesis effects: With the increase of compound Kushen injection dose, the tumor mass was decreased significantly, and the tumor inhibition rate was obviously increased.²⁶ Combination of CKI and doxorubicin could overcome the multidrug resistance in breast carcinoma MCF-7 cells. They showed an obvious synergistic effect, with an increase in the accumulation of doxorubicin and reduction of the expression of P-glycoprotein.²⁷ In two animal experiments, CMI could obviously decrease the levels of PDCD4, P53, E2, survivin and Ki67 in the model rats of breast cancer.^{28,29}

The detection of the expression level of Survivin was expected to be the predictive index of paclitaxel chemotherapy in breast cancer. For patients with high expression of Survivin, combining with CKI may improve the efficiency of chemotherapy, and even prolong PFS.³⁰ In addition, the serum level of VEGF-A decreased in breast cancer patients treated with CKI during radiotherapy, and the decrease was greater than that treated with radiotherapy alone.³¹

CKI is widely used in China. It is often used in combination with operative radiotherapy, chemotherapy and neoadjuvant chemotherapy. The effect is usually better than that of CKI alone, which may be related to improving the immune function of patients.^{32–34} Patients with CKI treatment had higher levels of CD3⁺, CD4⁺, CD4⁺/CD8⁺ and NK cells than those with only postoperative radiotherapy.^{35,36} Yasheng et al assessed relevant randomized controlled trials from 2000 to 2017 and the results showed that patients given CKI combined with chemotherapy (therapy group) had a higher performance status improvement rate than that given only chemotherapy (control group). In the analysis adverse drug reactions (ADRs), CKI combined with chemotherapy was indicated to significantly reduce the rate of liver dysfunction, kidney dysfunction, the reaction of fatigue, diarrhea, bone marrow suppression, hair loss, nausea and vomiting, oral mucositis, abnormal elevation of tumor marker CEA and CA153 and platelet decrease.^{37–40} Lymphocyte transformation ratio, immunoglobulin level,⁴¹ life quality, KPS and QOL score had also been improved.^{38–40} What's more, CKI had a good analgesic effect on bone and muscle pain caused by the paclitaxel chemotherapy for breast cancer patients, with their life quality improvement.⁴²

But these clinical studies face many problems to be solved urgently. Ongoing challenges include the inability to bind participants to the study, because most measures

are subjective, which are susceptible to suggestive biases. Patients who received it may perceive a benefit to the intervention.

Matrine

As one of the major quinolizidine alkaloids of *Sophora flavescens*, MT ($C_{15}H_{24}N_2O$) is extracted from the root of Kushen. MT has pharmacological effects such as anti-diuretic, anti-asthma, anti-bacterial, anti-inflammatory and immune suppressive activities. What's more, it has therapeutic effects on cardiac arrhythmia, hepatitis and various solid tumors. For years, MT has been reported to have promising pharmaceutical efficacies for various cancer cells, such as acute myeloid leukaemia, nasopharyngeal Carcinoma, hepatocellular carcinoma, cervical cancer, colorectal cancer, bladder cancer, prostate cancer, pancreatic cancer.^{43–54} However, the antitumor function about the molecular mechanism of MT still remains unclear. Like other extracts of botanicals, it has some moderate side effects, such as toxicity to the central nervous, coupled with system low water solubility, bioactivity and bioavailability. Opening of the D-ring and breaking of the amide bond can destroy the anti-proliferative activities, which mean amide bond may be required for the antitumor activities of MT. Annexin A2 has been identified as a direct-binding target of MT in cancer cells using the photo-affinity labeling approach.⁵⁵

Autophagy might cooperate, aggravate or antagonize apoptosis.⁵⁶ MT has been shown to promote autophagic cell death and induce autophagic in cancer cells in recent years. Autophagy was a protective cellular response to MT treatment;⁵⁷ therefore, inhibition of matrine-induced autophagy by treating the cancer cells with chloroquine enhanced the cytotoxicity. The molecular mechanism of autophagy induced by the effect of MT in human breast cancer Bcap-37 cells may be via down-regulating PI3K/Akt/mTOR signaling pathway.⁵⁸

Earlier studies suggest that the mechanism of inhibiting growth and inducing apoptosis of MCF-7/ADR cell growth is related to the blocking of S period cells.⁵⁹ Bcl-2, a novel anti-cancer target, is commonly associated with breast cancer. When treated with MT, three types of breast cancer cells (MCF-7 cells, BT-474 cells, MDA-MB-231) were all induced to death. The obvious effects on inhibiting the growth of MCF-7 cells and promoting the apoptosis might be achieved by up-regulating the expression of Fas protein, inhibiting telomerase activity, and down-regulating the expression of VEGF protein to inhibit the

tumor vascular formation. It displayed synergistic effects with trichostatin A, celecoxib and rosiglitazone against VEGF excretions and the cell proliferation via EGF/VEGF-VEGFR1-Akt-NF- κ B signaling pathway. Other studies revealed that the suppression of the cancer cell proliferation and invasion by MT is associated with inhibition of Akt signaling: downstream targets such as Bcl-2/Bax, NF- κ B, p-65, MMP-9 and MMP-2, and upstream targets such as EGF, VEGF and VEGFR1 in the breast cancer cells.⁶⁰ Compared to the controls, tumors treated with MT had a greater apoptosis index and a less microvessel density by downregulating the expression of Bcl-2/Bax, p53, VEGF and VEGFR-2, increasing the activation of caspase-3 and caspase-9.^{61–68} In another experimental study, MT inhibited the phosphorylation of AKT level to regulate the downstream apoptosis factors of PI3K/AKT signal pathway; the expressions of MRP1, P-GP, Bcl-2, p-AKT were down-regulated and PTEN level was up-regulated.⁶⁹ Conversely, in one study, Bax is overexpressed while Bcl-2 expression is decreased: MT inhibited the cell growth and induced apoptosis through up-regulation of Bax and down-regulation of Bcl-2 expression.⁷⁰ Animal research revealed that MT inhibited the expression of VEGF and downregulated the Wnt/ β -catenin signaling pathway in vivo. The 4T1-tumor-bearing mice treated with MT (100 mg/kg) exhibited a significant reduction in tumor volume and weight compared with the control group, and the expression levels of cytochrome c, cleaved caspase-9 and caspase-3 increased significantly.⁷¹

The treatment with MT resulted in the degradation of the inhibitor of κ B (I κ B) kinase β (IKK β), which is one of the activation of I κ B kinases (IKKs) and results in the phosphorylation of I κ B.⁷² The ER unfolded protein response (UPR) is a cellular signaling pathway in the ER, which is a survival mechanism utilized by tumors to buffer proteotoxic stress; overload ER stress is considered to be a key regulator of tumor cell death pathways in response to anticancer drugs. Endoplasmic reticulum stress is mainly involved in the cell apoptosis induced by MT. It could inhibit mitochondrial activity by promoting the release of cytochrome C and enhancing caspase-3 function to induce ER stress-mediated apoptosis. At the same time, MT inhibits the expression of hexokinase II and glycometabolism to down-regulate energy metabolism in MCF-7 cells.⁷³ The apoptosis induction effect may be caused by reducing mitochondrial transmembrane potential and leaving the MMP channel open.^{74,75} What's more, it may regulate the proliferation and apoptosis of 4T1 cells by

inhibiting the expression of ANXA3 mRNA and down-regulating the expression of ANXA3 protein.⁷⁶

Recent evidence has indicated that miRNAs can act as mediators of the therapeutic efficacy of botanicals. MiR-21 is overexpressed in the vast majority of cancers such as colorectal cancer, bladder cancer, lung cancer, prostate cancer and breast cancer. Inactivation of PTEN promoted the accumulation of PIP₃, resulting in phosphorylation of Akt, and this process is related to the high expression level of miR-21. An experimental study showed that MT up-regulated PTEN and down-regulated PTEN p21^{WAF1/CIP1} and p27^{KIP1}, which resulted in the inhibition of cell cycle progression and proliferation. It may inhibit breast cancer cell growth by interfering miR-21/PTEN/Akt signaling pathway.^{77,78} Upregulation of ZIC1 gene expression or MT alone can significantly inhibit the proliferation, adhesion and migration of MDA-MB-231 cells, and induce the apoptosis of human breast cancer cells, while the anti-tumor effect of ZIC1 gene combined with MT is more obvious.⁷⁹

Breast cancer patients receiving chemotherapy like anthracyclines and taxanes bear severe cumulative toxicities and tolerability disturbance. MT and chemotherapeutic drugs had synergistic effects and it reversed multidrug resistance in breast cancer, which involved regulating the downstream apoptosis factors (Bcl-2, p65, Bax, PARP, GSK-3 β , Caspase-3), inhibiting the activation of PI3K/AKT pathway, and reducing P-glycoprotein expression in breast carcinoma MCF-7 cells.^{80–82} MT injection has a protective effect on liver function of breast cancer patients undergoing chemotherapy after operation.⁸³ Other types of pharmaceutical preparations of Kushen such as *Sophora flavescens* alkaloid gels also can restrain cancer cell proliferation, inhibit metastasis and induce cellular apoptosis.⁸⁴ Further clinical studies with different concentrations and types of MT are warranted to obtain a better picture of antitumor activities of it.

Oxymatrine

Oxymatrine (molecular formula: C₁₅H₂₄N₂O₂) is another major alkaloid component extracted from the roots of Kushen, which belongs to quinolizidine alkaloid with relative molecular mass of 264.4. OMT has been shown a wide range of pharmacological effects, such as antitumor, anti-hypertension, anti-inflammation, heart strengthening, anti-pyresis and analgesia, anti-allergy, anti-arrhythmia, asthma relieving, sedation and hypnosis, inhibition of myocardial ischemia and infarction, antiviral and sterilization. Many

in vivo and in vitro experiments suggest that OMT exhibits antineoplastic properties in several cancers via different signaling pathways, including suppression of proliferation and promotion of apoptosis.⁸⁵

Previous study had confirmed that the antineoplastic effect of OMT was related to the induction of apoptosis of cancer cells by blocking the process of cell cycle, initiating cell self-regulation procedures.⁸⁶ A recent study revealed that it involved the inhibition of epithelial-mesenchymal transformation of cancer cells.⁸⁷ Similarly, one study demonstrated that it induced apoptosis in breast cancer cells by down-regulating apoptosis-related protein, including poly (ADP-ribose) polymerase (PARP) and cleaved Caspase-3, cleaved Caspase-9.⁸⁸ Like other antiapoptotic proteins (Bcl-XL, Mcl-1, Bcl-W), BCL-2 regulates cell differentiation and apoptosis through the intrinsic (or mitochondrial) pathway. Highest concentration of OMT (100 μ g/mL) regulated Bax mRNA abundance by 169% at 72 hrs, and regulated Bax mRNA abundance by 169%, resulting in promoting apoptosis in MCF-7 cells.⁸⁹ “side-population (SP)” cells, which are used for identification and analysis of the CSCs, show the characteristics of the cancer stem-like cells and represent a population with a capacity of limited maturation and self-renewal. Ying Zhang et al explored the effect of OMT on the SP of MCF-7 cells and this study demonstrated that OMT treatment increased the expression of phosphorylated β -catenin, which is related to the inactivation of Wnt signaling pathway, with the decrease of total β -catenin and deactivation of Wnt signaling pathway. It decreased the viability of MCF-7 cells in a time- and dose-dependent manner. What's more, compared with cisplatin, OMT showed a lower inhibitory effect on non-SP cells and a higher inhibitory effect on SP cells.⁹⁰ On the other hand, OM could clearly inhibit the proliferation and increases apoptosis of human MCF-7 cells, and the mechanism of this effect probably related to the activity of Wnt/ β -catenin signaling pathway,^{91,92} with the expression of downstream cytokines c-myc and cyclinD1 decreasing.

OM had direct anti-tumor effects and partly reversed MDR. The mechanism of reversing MDR was associated with the behavior of OMT down-regulating P-gP expression on the cell membrane.⁹³ OM enhanced the sensibility of MCF-7 cells to the cytotoxicity of NK-92MI cells, most likely through activating the NF- κ B signaling pathway, up-regulating the expression levels of ULBP1, ULBP2 and MICA/B in MCF-7 cells, promoting the secretion of TNF- α and IFN- γ by NK-92MI cells.⁹⁴

Other *Sophora flavescens* Alkaloids

Many flavonoids have been reported antitumor activities through anti-angiogenesis mechanism.^{95–97} Those isolated from Kushen have been demonstrated anti-inflammatory, anti-proliferative and antioxidant properties experimentally. Novel flavonoids isolated from *Sophora flavescens* had been identified as more potent antitumor activities than other Kushen alkaloids. 56 different flavonoids have been identified from KS-Fs, among which 21 of the KS-Fs have been described to have antitumor activities in vitro. KS-Fs consisted of kurarinone (Kur, 29%), 2'-methoxykurarinone (MeO-Kur, 5%), sophoraflavanone G (SFG, 2%) and other flavonoid species. The nonflavonoid compounds consist of alkylxanthenes, triterpene glycosides, quinones, essential oils and fatty acids. Recent studies illustrated the antineoplastic effects of novel *Sophora flavescens* alkaloids, including matrine derivative WM622, WM-127, matrine derivatives containing benzo- α -pyrone structure (6aS, 10S, 11aR, 11bR, 11cS)-10-methylamino-dodecahydro-3a,7a-diaza-benzo (de) (MASM), which beared therapeutic potentials for lung and hepatocellular carcinoma.^{98–101}

Kur and KS-Fs were able to enhance the effects of Taxol and adriamycin on tumor proliferation in vitro. Either combination of low dose of Taxol (5 mg/kg) or high dose of taxol (5 mg/kg), KS-Fs (200 mg/kg/day) were shown to enhance the effect of Taxol on tumor growth in vivo.¹⁰² Other matrine derivatives from sophoridine have also been developed. Many novel N-substituted sophoridinic acid derivatives were synthesized, and their cytotoxicity and anticancer activities were evaluated. An introduction of an aliphatic acyl on the nitrogen might enhance the antitumor activity. Among the synthesized derivatives, COCH₂Br bearing bromoacetyl side-chain inhibited the activity of DNA topo I to suspend the cell cycle at S-phase, which lead the breast cancer tumor cells to apoptosis.¹⁰³ A study revealed this (2S)-7,2',4'-trihydroxy-5-methoxy-8-dimethylallyl flavanone can inhibit proliferation, migration, adhesion, and tube formation of endothelial cells.¹⁰⁴ Because of its anti-angiogenesis activity and anti-proliferative properties this new flavonoid can be a good anticancer candidate. New sophoridinol derivatives and N-substituted sophoridinic acid/ester such as sophoridinol 7i (R1:9-methylanthracene, R2:CH₂OH) arrest the cell cycle at the G0/G1 phase and showed an antiproliferative activity with an IC₅₀ of 3.1 μ M.¹⁰⁵

It is well documented that several quinolizidine alkaloids have potential antitumor activity. A series of 12-chlorobenzyl

sophoridinic derivatives with novel chemical scaffolds such as compounds 5a(C₇H₄OCl-) and 7b (C₁₃H₈F₂p₂-) exhibited reasonable antiproliferative and anticancer activities; they displayed an equipotency in both adriamycin (AMD)-susceptible and resistant MCF-7 breast carcinoma cells.¹⁰⁶ In addition, three novel compounds (YF3-5, YF3-7 and YF3-9) all demonstrated anti-proliferation activity, of which YF3-5 showed the strongest anti-proliferation properties against the four human cancer cell lines (BT20 breast, MCF-7 breast, A549 lung and U2OS osteosarcoma cells).¹⁰⁷ Cell cycle arrest and induction of mitochondria-mediated apoptosis are common mechanisms of inhibiting cell proliferation. Recently, sophoraflavanone G (SG), a compound isolated from *Sophora flavescens*, induced reactive oxygen species, DNA fragmentation, nuclear condensation, showing anti-tumor and anti-inflammatory properties in MDA-MB-231. SG increased expression of cleaved caspase-3, caspase-9, caspase-8, and decreased Bcl-2 and Bcl-xL expression, which inhibited the migration and invasion of breast cancer cells.¹⁰⁸

Conclusions and Future Directions

Traditional medicine, such as Ayurvedic medicine, Chinese medicine, uses unidentified chemical entities with unknown mechanisms of action. TCM has been applied in many countries and regions and has achieved certain results. From the point of view of the basic principles of evidence-based medicine and the provision of clinical scientific evidence, there are still some problems to be solved in the practice of TCM application, such as the lack of sufficient experimental data on the effectiveness and safety of TCM, not an exhaustive study on side effects of TCM. The clinical trials of TCM are short of large sample randomized controlled data and exact evaluation index system and evaluation method in this field.

This review summarizes multiple anti-cancer effects of active ingredients in *Sophora flavescens*. Effective extracts of medicinal plants, such as MT, OMT and their derivatives, have been extensively studied in breast cancer. There is a growing body of evidence supporting the use of Kushen and its active ingredients as effective supportive care strategies during breast cancer treatment. CKI and other phytochemicals extracted from *Sophora flavescens* may become potential complementary and alternative therapy for breast cancer in the future. In China, patients with breast cancer commonly use them as supportive care during cancer treatment and to manage treatment-related side effects.

However, evidence supporting the application of MT, OMT and other *Sophora flavescens* alkaloids in the

oncology setting is limited. The specific anti-cancer mechanism of them needs further systematic studies. Some of the reported clinical studies about them were not well-controlled studies and not blinded. Although they are perceived as harmless, more studies are needed on safety rather than efficacy. What's more, little information is available on toxicities and cost effectiveness. Drug-botanical interactions, pharmacokinetic and distribution profile of active constituents have to be determined to help reach safe and efficacious concentrations in clinical settings. Evaluation and exploration of the clinical impact that is more truly generalizable must be made to avoid potentially toxic side effects or loss of activity of active ingredients. Additionally, seeking international cooperation in the research of them is also an important way to promote these compounds more widely used.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations

MT, matrine; OMT, oxymatrine; CKI, Compound Kushen Injection; TCM, Traditional Chinese Medicine; KS-As, Kushen alkaloids; KS-Fs, Kushen flavonoids; DSBs, double-strand breaks; CSCs, Breast cancer stem cells; I κ B, inhibitor of κ B; IKKs, I κ B kinases; UPR, unfolded protein response; SG, sophoraflavanone G.

Acknowledgments

Authors are thankful to the Department of Thyroid and Breast Surgery, the 960th Hospital of the PLA Joint Logistics Support Force for providing necessary support. We are greatly indebted to Dr. Xiaolei Li for the initial collaboration and Dr. Fang Yu for providing suggestions for the submission of this manuscript.

Funding

This work was supported by grants from the President Funding of Jinan Military General Hospital of PLA (Grants 2016ZD02 and 2018ZX01).

Disclosure

The authors report no conflicts of interest in this work.

References

- Chui CH, Lau FY, Tang JC, et al. Activities of fresh juice of *Scutellaria barbata* and warmed water extract of *Radix Sophorae Tonkinensis* on anti-proliferation and apoptosis of human cancer cell lines. *Int J Mol Med*. 2005;16:337–341.
- Greenlee H, DuPont-Reyes MJ, Balneaves LG, et al. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. *CA Cancer J Clin*. 2017;67:194–232. doi:10.3322/caac.21397
- Li J, Liu X, Chen H, et al. Multi-targeting chemoprevention of Chinese herb formula Yanghe Huayan decoction on experimentally induced mammary tumorigenesis. *BMC Complement Altern Med*. 2019;19:48. doi:10.1186/s12906-019-2456-1
- Zhuang SR, Chiu HF, Chen SL, et al. Effects of a Chinese medical herbs complex on cellular immunity and toxicity-related conditions of breast cancer patients. *Br J Nutr*. 2012;107:712–718. doi:10.1017/S000711451100345X
- Zhao X, Liu J, Ge S, et al. Saikosaponin A inhibits breast cancer by regulating Th1/Th2 balance. *Front Pharmacol*. 2019;10:624. doi:10.3389/fphar.2019.00624
- Iwanowycz S, Wang J, Hodge J, Wang Y, Yu F, Fan D. Emodin inhibits breast cancer growth by blocking the tumor-promoting feedforward loop between cancer cells and macrophages. *Mol Cancer Ther*. 2016;15:1931–1942. doi:10.1158/1535-7163.MCT-15-0987
- Wang Z, Loo WT, Wang N, et al. Effect of *Sanguisorba officinalis* L. on breast cancer growth and angiogenesis. *Expert Opin Ther Targets*. 2012;16(Suppl 1):S79–S89. doi:10.1517/14728222.2011.642371
- Li J, Wu Y, Wang D, et al. Oridonin synergistically enhances the anti-tumor efficacy of doxorubicin against aggressive breast cancer via pro-apoptotic and anti-angiogenic effects. *Pharmacol Res*. 2019;146:104313. doi:10.1016/j.phrs.2019.104313
- Huang L, Li A, Liao G, et al. Curcumin triggers apoptosis of p53 mutant triple-negative human breast cancer MDA-MB 231 cells via activation of p73 and PUMA. *Oncol Lett*. 2017;14:1080–1088. doi:10.3892/ol.2017.6273
- Patel A, Soni A, Siddiqi NJ, Sharma P. An insight into the anticancer mechanism of *Tribulus terrestris* extracts on human breast cancer cells. *3 Biotech*. 2019;9:58. doi:10.1007/s13205-019-1585-z
- Deng Y, Li F, He P, et al. Triptolide sensitizes breast cancer cells to Doxorubicin through the DNA damage response inhibition. *Mol Carcinog*. 2018;57:807–814. doi:10.1002/mc.v57.6
- Greenshields AL, Fernando W, Hoskin DW. The anti-malarial drug artesunate causes cell cycle arrest and apoptosis of triple-negative MDA-MB-468 and HER2-enriched SK-BR-3 breast cancer cells. *Exp Mol Pathol*. 2019;107:10–22. doi:10.1016/j.yexmp.2019.01.006
- von Hagens C, Walter-Sack I, Goeckenjan M, et al. Long-term add-on therapy (compassionate use) with oral artesunate in patients with metastatic breast cancer after participating in a phase I study (ARTIC M33/2). *Phytomedicine*. 2019;54:140–148. doi:10.1016/j.phymed.2018.09.178
- Li X, Wang W, Fan Y, et al. Anticancer efficiency of cycloartane triterpenoid derivatives isolated from *Cimicifuga yunnanensis* Hsiao on triple-negative breast cancer cells. *Cancer Manag Res*. 2018;10:6715–6729. doi:10.2147/CMAR.S185387
- Dietz BM, Hajrahimkhan A, Dunlap TL, Bolton JL. Botanicals and their bioactive phytochemicals for women's health. *Pharmacol Rev*. 2016;68:1026–1073. doi:10.1124/pr.115.010843
- Sun M, Cao H, Sun L, et al. Antitumor activities of Kushen: literature review. *Evid Based Complement Altern Med*. 2012;2012:373219. doi:10.1155/2012/373219

17. Jin Y, Yang Q, Liang L, et al. Compound Kushen Injection suppresses human acute myeloid leukaemia by regulating the Prdxs/ROS/Trx1 signalling pathway. *J Exp Clin Cancer Res*. 2018;37:277. doi:10.1186/s13046-018-0948-3
18. Tu H, Lei B, Meng S, et al. Efficacy of Compound Kushen Injection in combination with induction chemotherapy for treating adult patients newly diagnosed with acute leukemia. *Evid Based Complement Altern Med*. 2016;2016:3121402. doi:10.1155/2016/3121402
19. Zhang J, Qu Z, Yao H, et al. An effective drug sensitizing agent increases gefitinib treatment by down regulating PI3K/Akt/mTOR pathway and up regulating autophagy in non-small cell lung cancer. *Biomed Pharmacother*. 2019;118:109169. doi:10.1016/j.biopha.2019.109169
20. Wang XQ, Liu J, Lin HS, Hou W. A multicenter randomized controlled open-label trial to assess the efficacy of Compound Kushen Injection in combination with single-agent chemotherapy in treatment of elderly patients with advanced non-small cell lung cancer: study protocol for a randomized controlled trial. *Trials*. 2016;17:124.
21. Gao L, Wang KX, Zhou YZ, Fang JS, Qin XM, Du GH. Uncovering the anticancer mechanism of Compound Kushen Injection against HCC by integrating quantitative analysis, network analysis and experimental validation. *Sci Rep*. 2018;8:624. doi:10.1038/s41598-017-18325-7
22. Nourmohammadi S, Aung TN, Cui J, et al. Effect of Compound Kushen Injection, a natural compound mixture, and its identified chemical components on migration and invasion of colon, brain, and breast cancer cell lines. *Front Oncol*. 2019;9:314. doi:10.3389/fonc.2019.00314
23. Qu Z, Cui J, Harata-Lee Y, et al. Identification of candidate anti-cancer molecular mechanisms of Compound Kushen Injection using functional genomics. *Oncotarget*. 2016;7:66003–66019. doi:10.18632/oncotarget.v7i40
24. Cui J, Qu Z, Harata-Lee Y, et al. Cell cycle, energy metabolism and DNA repair pathways in cancer cells are suppressed by Compound Kushen Injection. *BMC Cancer*. 2019;19:103. doi:10.1186/s12885-018-5230-8
25. Xu W, Lin H, Zhang Y, et al. Compound Kushen Injection suppresses human breast cancer stem-like cells by down-regulating the canonical Wnt/beta-catenin pathway. *J Exp Clin Cancer Res*. 2011;30:103. doi:10.1186/1756-9966-30-103
26. Wang H, Hu H, Rong H, Zhao X. Effects of Compound Kushen Injection on pathology and angiogenesis of tumor tissues. *Oncol Lett*. 2019;17:2278–2282. doi:10.3892/ol.2018.9861
27. Li HY, Chen Y, He QY. Mechanisms of yanshu injection for overcoming multidrug resistance in breast carcinoma MCF-7 cells: an experimental research. *Chin J Integr Med*. 2014;34:324–328.
28. Long Y, Zeng ZT, Li YC, Li D. Effect of compound matrine injection in the model rats of breast cancer. *Chin J Clin Pharmacol*. 2018;34:141–144.
29. Lai MH. Improvement of compound matrine injection in breast cancer model rat. *Chin J Clin Pharmacol*. 2017;33:244–247.
30. Hou G, Li N, Zhang YP, Xiao CH, Wang C, Liu ZW. Expression of Survivin in breast cancer and study on the effectiveness of matrine. *Mod Oncol*. 2018;26:388–391.
31. Wen B, Yang ZH, Zheng WT. Clinical significance of changes of serum VEGF-A in breast cancer patients with combination with radiotherapy and matrine. *Chin J Lab Diagn*. 2011;15:1916–1917.
32. Fu FM, Luo SH, Wang Y, et al. Meta-analysis the effect of Fufangkushen injection combined with chemotherapy on immune function in patients with breast cancer. *Pract Clin J Integr Tradit Chin West Med*. 2018;18:1-4+22.
33. Gu XD, Zhao H, Xie XH. Effect of Compound Kushen Injection combined with neoadjuvant chemotherapy for locally advanced breast cancer. *Zhejiang J Tradit Chin Med*. 2015;50:74.
34. Zhai XJ. Effects of Compound Kushen Injection on immune function and toxicity reaction of patients with postoperative chemotherapy for breast cancer. *Chin J Basic Med Tradit Chin Med*. 2014;20:829–831.
35. Wei PF, Chen MX, Yang YY, Zhang YM, Wang J, Wang HC. Clinical effect of postoperative radiotherapy combined with compound matrine injection on the patients with breast cancer. *Prog Mod Biomed*. 2017;17:5255-7+66.
36. Maimaitiniyazi S, Ai XQ, Zhu XL, Wang YH, Mushajiang M. Effects of compound Kushen Injection combined with postoperative radiotherapy on immune function and quality of life for breast cancer. *Hainan MED J*. 2016;27:2283–2285.
37. Yasheng A, Ai XY, Zhang JZN, Tong Y, Wu J, Zhao B. Toxic and side effects of compound matrine injection in breast cancer adjuvant chemotherapy. *Liaoning J Tradit Chin Med*. 2016;43:2101–2102.
38. Chen LJ. Efficacy analysis of Compound Kushen Injection as adjunctive treatment for breast cancer. *China Pharm*. 2010;21:1866–1867.
39. An AJ, An GW, Wu YC. Observation of compound recipe light yellow sophora root injecta combined with chemotherapy in treatment of 35 postoperative patients with breast cancer. *Med Pharm J Chin PLA*. 2012;24:43–46.
40. Wang YX. Clinical observation of Compound Kushen Injection combined with chemotherapy in treatment of three negative breast cancer. *World Latest Med Inf*. 2018;18:3–4.
41. Gao QF. Clinical observation of Compound Kushen Injection combined with postoperative chemotherapy for breast cancer. *Liaoning J Tradit Chin Med*. 2015;42:1928–1929.
42. Bai ZQ. 63 cases of clinical observation research of zoleronic acid injection joint compound sophora injection on the treatment for breast cancer bone metastasis. *Chin J Hosp Pharm*. 2016;36:328–329.
43. Wu J, Hu G, Dong Y, et al. Matrine induces Akt/mTOR signalling inhibition-mediated autophagy and apoptosis in acute myeloid leukaemia cells. *J Cell Mol Med*. 2017;21:1171–1181. doi:10.1111/jcmm.2017.21.issue-6
44. Xie M, He G, Wang R, et al. Matrine-induced apoptosis of human nasopharyngeal carcinoma cells via in vitro vascular endothelial growth factor-A/extracellular signal-regulated kinase1/2 pathway inactivation. *Hormone Metab Res*. 2014;46:556–560. doi:10.1055/s-000000025
45. Qian L, Liu Y, Xu Y, et al. Matrine derivative WM130 inhibits hepatocellular carcinoma by suppressing EGFR/ERK/MMP-2 and PTEN/AKT signaling pathways. *Cancer Lett*. 2015;368:126–134. doi:10.1016/j.canlet.2015.07.035
46. Zhou H, Xu M, Gao Y, et al. Matrine induces caspase-independent program cell death in hepatocellular carcinoma through bid-mediated nuclear translocation of apoptosis inducing factor. *Mol Cancer*. 2014;13:59. doi:10.1186/1476-4598-13-59
47. Wang Y, Zhang S, Liu J, Fang B, Yao J, Cheng B. Matrine inhibits the invasive and migratory properties of human hepatocellular carcinoma by regulating epithelial mesenchymal transition. *Mol Med Rep*. 2018;18:911–919. doi:10.3892/mmr.2018.9023
48. Wu X, Zhou J, Cai D, Li M. Matrine inhibits the metastatic properties of human cervical cancer cells via downregulating the p38 signaling pathway. *Oncol Rep*. 2017;38:1312–1320. doi:10.3892/or.2017.5787
49. Gu YY, Chen MH, May BH, et al. Matrine induces apoptosis in multiple colorectal cancer cell lines in vitro and inhibits tumour growth with minimum side effects in vivo via Bcl-2 and caspase-3. *Phytomedicine*. 2018;51:214–225. doi:10.1016/j.phymed.2018.10.004
50. Yang Y, Guo JX, Shao ZQ, Gao JP. Matrine inhibits bladder cancer cell growth and invasion in vitro through PI3K/AKT signaling pathway: an experimental study. *Asian Pac J Trop Med*. 2017;10:515–519. doi:10.1016/j.apjtm.2017.05.009
51. Zhang P, Wang Z, Chong T, Ji Z. Matrine inhibits proliferation and induces apoptosis of the androgen independent prostate cancer cell line PC-3. *Mol Med Rep*. 2012;5:783–787. doi:10.3892/mmr.2011.701

52. Huang H, Wang Q, Du T, et al. Matrine inhibits the progression of prostate cancer by promoting expression of GADD45B. *Prostate*. 2018;78:327–335. doi:10.1002/pros.v78.5
53. Xie W, Lu J, Lu Q, et al. Matrine inhibits the proliferation and migration of lung cancer cells through regulation of the protein kinase B/glycogen synthase kinase-3 β signaling pathways. *Exp Ther Med*. 2018;16:723–729. doi:10.3892/etm.2018.6266
54. Cho YR, Lee JH, Kim JH, et al. Matrine suppresses KRAS-driven pancreatic cancer growth by inhibiting autophagy-mediated energy metabolism. *Mol Oncol*. 2018;12:1203–1215. doi:10.1002/1878-0261.12324
55. Wang D, Cao Y, Zheng L, et al. Identification of Annexin A2 as a target protein for plant alkaloid matrine. *Chem Commun*. 2017;53:5020–5023. doi:10.1039/C7CC02227A
56. Feng Q, Yang X, Hao Y, et al. Cancer cell membrane-biomimetic nanoplateform for enhanced sonodynamic therapy on breast cancer via autophagy regulation strategy. *ACS Appl Mater Interfaces*. 2019;11:32729–32738. doi:10.1021/acsami.9b10948
57. Ren LL, Lan T, Wang XJ. Antitumor effect of matrine in human breast cancer Bcap-37 cells by apoptosis and autophagy. *Chin Archiv Tradit Chin Med*. 2014;32:2756–2759.
58. Ren LL, Wang LL, Wang XJ. Relationship between matrine induced autophagy and mTOR in human breast cancer Bcap-37 cells. *Zhejiang JTCWM*. 2016;26:783–786.
59. Zhou BG, Sun JZ, Su G, Ma DQ. Apoptosis of human breast cancer MCF-7/ADR cells induced by matrine. *Chin J Exp Surg*. 2003;20:515–516.
60. Yu P, Liu Q, Liu K, Yagasaki K, Wu E, Zhang G. Matrine suppresses breast cancer cell proliferation and invasion via VEGF-Akt-NF- κ B signaling. *Cytotechnology*. 2009;59:219–229. doi:10.1007/s10616-009-9225-9
61. Li H, Tan G, Jiang X, et al. Therapeutic effects of matrine on primary and metastatic breast cancer. *Am J Chin Med (Gard City N Y)*. 2010;38:1115–1130. doi:10.1142/S0192415X10008512
62. Zheng RZ, Zhang JY, Shao XY, Wang XJ. Mechanism of matrine promoting apoptosis induced by tamoxifen in breast cancer cell Bcap-37. *J Chin Oncol*. 2012;18:840–843.
63. Zheng RZ, Zhang JY, Shao XY, Wang XJ. Inhibition of the growth of human breast cancer cell line Bcap-37 with matrine. *Zhejiang JTCWM*. 2012;22:945–947.
64. Li HJ, Zhao XX, Bai ML, Zhang LX, Liu H, Ge LP. Effects of matrine on proliferation and apoptosis in human breast cancer MCF-7 cells. *Jiangsu Med J*. 2011;37:396–8+68.
65. Xiao X, Ao M, Shi WD, et al. The effect of matrine on proliferation and apoptosis in breast cancer MCF-7 cells. *Chin Tradit Patent Med*. 2018;40:2750–2754.
66. Sui H. Effects of matrine on proliferation of human breast cancer cells. *China J Mod Med*. 2013;23:41–43.
67. Wang SQ, Guo Y, Li HJ, Zhang XL, Li YZ, Hao XQ. Matrine induces apoptosis in MCF-7 breast cancer cells and its effect on Bax. *Chin J Gerontol*. 2012;32:3489–3491.
68. Zhao WG, Sun Y, Zhuang J, Feng FB, Li J, Sun CG. Matrine with adriamycin has synergistic effect on human breast cancer cells. *Lishizhen Med Mater Med Res*. 2018;29:33–36.
69. Zhou BG, Wei CS, Zhang S, Zhang Z, Gao HM. Matrine reversed multidrug resistance of breast cancer MCF-7/ADR cells through PI3K/AKT signaling pathway. *J Cell Biochem*. 2018;119:3885–3891. doi:10.1002/jcb.26502
70. Li H, Li X, Bai M, Suo Y, Zhang G, Cao X. Matrine inhibited proliferation and increased apoptosis in human breast cancer MCF-7 cells via upregulation of Bax and downregulation of Bcl-2. *Int J Clin Exp Pathol*. 2015;8:14793–14799.
71. Xiao X, Ao M, Xu F, et al. Effect of matrine against breast cancer by downregulating the vascular endothelial growth factor via the Wnt/ β -catenin pathway. *Oncol Lett*. 2018;15:1691–1697. doi:10.3892/ol.2017.7519
72. Shao H, Yang B, Hu R, Wang Y. Matrine effectively inhibits the proliferation of breast cancer cells through a mechanism related to the NF- κ B signaling pathway. *Oncol Lett*. 2013;6:517–520. doi:10.3892/ol.2013.1399
73. Xiao Y, Ma D, Wang H, et al. Matrine suppresses the ER-positive MCF cells by regulating energy metabolism and endoplasmic reticulum stress signaling pathway. *Phytother Res*. 2017;31:671–679. doi:10.1002/ptr.v31.4
74. Gu MR, Li JB, Zhang XH, Yin YM. Analysis of induced apoptosis effect of matrine on human breast cancer MCF-7 cell and its effect on mitochondrial transmembrane potential. *Chin J Biochem Pharm*. 2015;35:39–41.
75. Li HJ, Zhao XX, Bai ML, Zhang LX, Li YZ, Liu H. The effect of matrine on apoptosis and mitochondrial transmembrane potential in MCF-7 cells. *Lishizhen Med Mater Med Res*. 2011;22:2042–2043.
76. Shi WD, Li DX, Hu JL, Wang Y, Yang N, Xiao X. Matrine inhibits proliferation of breast cancer 4T1 cells by regulating expression of annexin A3. *Ningxia Med J*. 2019;9:967–969.
77. Li LQ, Li XL, Wang L, et al. Matrine inhibits breast cancer growth via miR-21/PTEN/Akt pathway in MCF-7 cells. *Cell Physiol Biochem*. 2012;30:631–641. doi:10.1159/000341444
78. Xiao X, Man A, Shi WD, et al. Effects of matrine on proliferation and apoptosis of breast cancer SK-BR-3 cells. *Shandong Med J*. 2018;58:24–27.
79. Yu M, Cao F, Zhu R, Ding HZ. Effect of ZIC1 associated with matrine on proliferation, migration and apoptosis in MDAMB-231 human breast cancer cell line. *Mod Oncol*. 2016;24:1528–1533.
80. Zhou BG, Wei CS, Zhang S, Zhang Z, Wang J. The matrine reverse multidrug resistance on breast cancer MCF-7/ADR cell line and have an influence on downstream factors of PI3K/AKT signal pathway. *Mod Oncol*. 2017;25:9–13.
81. Wei CS, Shen YJ, Zhang Z, Wang J, Zhou BG. Matrine reverses multidrug resistance in breast cancer drug-resistant cell line MCF-7/ADR through inhibiting PI3K/AKT signal pathway. *J Third Mil Med Univ*. 2014;36:2254–2258.
82. Li HY, Chen Y, He QY. Mechanism of combination of matrine and tetrandrine for reversal of multidrug resistance of breast carcinoma MCF-7 cells. *Chin J Exp Tradit Med Formulae*. 2013;19:275–278.
83. Lao YQ. Effect of matrine injection on preventing liver function damage for breast cancer with chemotherapy. *J Chin Med Mater*. 2005;28:735–737.
84. Zhou YJ, Guo YJ, Yang XL, Ou ZL. Anti-cervical cancer role of matrine, oxymatrine and sophora flavescens alkaloid gels and its mechanism. *J Cancer*. 2018;9:1357–1364. doi:10.7150/jca.22427
85. Halim CE, Xinjing SL, Fan L, et al. Anti-cancer effects of oxymatrine are mediated through multiple molecular mechanism(s) in tumor models. *Pharmacol Res*. 2019;147:104327. doi:10.1016/j.phrs.2019.104327
86. Zhou G, Sun J, Fan YZ, Su G. Oxymatrine induces Apoptosis in MCF-7 breast cancer cells. *Chin Pharmacol Bull*. 2002;11:689–691.
87. Cai JQ, Wei XX, Huang XX, Zhuang J, Sun H. Oxymatrine inhibits invasion and metastasis of human breast cancer cells in vitro through regulating epithelial-mesenchymal transition. *Chin J Clin Pharmacol Ther*. 2018;23:13–17.
88. Wu J, Cai Y, Li M, Zhang Y, Li H, Tan Z. Oxymatrine promotes S-Phase arrest and inhibits cell proliferation of human breast cancer cells in vitro through mitochondria-mediated apoptosis. *Biol Pharm Bull*. 2017;40:1232–1239. doi:10.1248/bpb.b17-00010
89. Lin B, Li D, Zhang L. Oxymatrine mediates Bax and Bcl-2 expression in human breast cancer MCF-7 cells. *Pharmazie*. 2016;71:154–157.
90. Zhang Y, Piao B, Zhang Y, et al. Oxymatrine diminishes the side population and inhibits the expression of β -catenin in MCF-7 breast cancer cells. *Med Oncol*. 2011;28(Suppl 1):S99–S107. doi:10.1007/s12032-010-9721-y

91. Zhang Y, Zhu XY, Xu WR, Pei YX, Lin HS. The research of Oxymatrine inhibits the proliferation of human breast cancer MCF-7 cells. *Mod Oncol*. 2014;22:494–497.
92. Zhang Y, Zhu XY, Xu WR, Pei YX, Lin HS. Oxymatrine diminished the side population and inhibited Wnt/ β -catenin signaling pathway in MCF-7 breast cancer cells. *Chin J Integr Med*. 2016;36:1504–1509.
93. Lv JY, Zhao Y. Oxymatrine reverses multidrug resistance on breast cancer MCF-7/ADR cells. *China Mod Doctor*. 2010;48:86–87.
94. Chen DL, Wang Q, Li Z. Oxymatrine enhances sensibility of MCF-7 cells to cytotoxicity of NK-92MI cells. *Chin J Immunol*. 2019;35:680–685.
95. Albin A, Dell'Eva R, Vene R, et al. Mechanisms of the antiangiogenic activity by the hop flavonoid xanthohumol: NF- κ B and Akt as targets. *FASEB J*. 2006;20:527–529. doi:10.1096/fj.05-5128fje
96. Luo H, Rankin GO, Liu L, Daddysman MK, Jiang BH, Chen YC. Kaempferol inhibits angiogenesis and VEGF expression through both HIF dependent and independent pathways in human ovarian cancer cells. *Nutr Cancer*. 2009;61:554–563. doi:10.1080/016355580802666281
97. Priyadarsini RV, Vinothini G, Murugan RS, Manikandan P, Nagini S. The flavonoid quercetin modulates the hallmark capabilities of hamster buccal pouch tumors. *Nutr Cancer*. 2011;63:218–226. doi:10.1080/016355581.2011.523503
98. Sun X, Zhuo XB, Hu YP, Zheng X, Zhao QJ. A novel matrine derivative WM622 inhibits hepatocellular carcinoma by inhibiting PI3K/AKT signaling pathways. *Mol Cell Biochem*. 2018;449:47–54. doi:10.1007/s11010-018-3341-9
99. Wu L, Wang G, Liu S, et al. Synthesis and biological evaluation of matrine derivatives containing benzo- α -pyrone structure as potent anti-lung cancer agents. *Sci Rep*. 2016;6:35918. doi:10.1038/srep35918
100. Liu Y, Qi Y, Bai ZH, et al. A novel matrine derivate inhibits differentiated human hepatoma cells and hepatic cancer stem-like cells by suppressing PI3K/AKT signaling pathways. *Acta Pharmacol Sin*. 2017;38:120–132. doi:10.1038/aps.2016.104
101. Yin H, Que R, Liu C, et al. Survivin-targeted drug screening platform identifies a matrine derivative WM-127 as a potential therapeutics against hepatocellular carcinoma. *Cancer Lett*. 2018;425:54–64. doi:10.1016/j.canlet.2018.03.044
102. Sun M, Han J, Duan J, et al. Novel antitumor activities of Kushen flavonoids in vitro and in vivo. *Phytother Res*. 2007;21:269–277. doi:10.1002/ptr.2066
103. Li X, Zhao WL, Jiang JD, et al. Synthesis, structure-activity relationship and biological evaluation of anticancer activity for novel N-substituted sophoridinic acid derivatives. *Bioorg Med Chem Lett*. 2011;21:5251–5254. doi:10.1016/j.bmcl.2011.07.038
104. Zhang XL, Cao MA, Pu LP, et al. A novel flavonoid isolated from *Sophora flavescens* exhibited anti-angiogenesis activity, decreased VEGF expression and caused G0/G1 cell cycle arrest in vitro. *Pharmazie*. 2013;68:369–375.
105. Bi C, Zhang C, Li Y, et al. Synthesis and biological evaluation of sophoridinol derivatives as a novel family of potential anticancer agents. *ACS Med Chem Lett*. 2014;5:1225–1229. doi:10.1021/ml500289h
106. Bi C, Ye C, Li Y, Zhao W, Shao R, Song D. Synthesis and biological evaluation of 12-N-p-chlorobenzyl sophoridinol derivatives as a novel family of anticancer agents. *Acta Pharmaceutica Sinica B*. 2016;6:222–228. doi:10.1016/j.apsb.2016.03.004
107. Jiang L, Wu L, Yang F, et al. Synthesis, biological evaluation and mechanism studies of matrine derivatives as anticancer agents. *Oncol Lett*. 2017;14:3057–3064. doi:10.3892/ol.2017.6475
108. Li ZY, Huang WC, Tu RS, Gu RY, Lin CF, Liou CJ. Sophoraflavanone G induces apoptosis in human leukemia cells and blocks MAPK activation. *Am J Chin Med (Gard City N Y)*. 2016;44:165–176. doi:10.1142/S0192415X16500117

Cancer Management and Research

Publish your work in this journal

Cancer Management and Research is an international, peer-reviewed open access journal focusing on cancer research and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient.

Submit your manuscript here: <https://www.dovepress.com/cancer-management-and-research-journal>

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Dovepress