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REVIEW

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

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**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

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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 flavescens*), 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 anticancer 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<br>In vitro: 50–100 μg/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 μg/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 μg/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 μg/mL | Enhance antitumor activities of taxol, suppress cell proliferation | Unclear | 452.55g/mol |
| Sophoridine | $C_{15}H_{24}N_2O$ | MCF-7 | 30μg/mL | Antiproliferative activity | Unclear | 248.37g/mol |
| Sophoridine+$COCH_2Br$ | $C_{17}H_{26}N_2O_2Br$ | MCF-7 | 20μg/mL | Antiproliferative activity, suspend the cell cycle | Unclear | 370.31g/mol |
| 9-methylanthracene +$CH_2OH$ | $C_{16}H_2O$ | MCF-7/AMD | 1.25–5.0μg/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 | 1.25–5.0μg/mL | Block cell cycle | Unclear | 485.50 g/mol |
| −4′-4′-diethyl sophoridinene bihydrochloride | $C_{26}H_{39}N_2Cl{\cdot}2HCl$ | MCF-7/AMD | 1.25–5.0μg/mL | Block cell cycle | Unclear | 486.98g/mol |
| Matrine+ methyl 6-bromo-2-naphthoate | $C_{26}H_9N_2O_2Br$ | BT-20, MCF-7 | 12.5, 25, 50 μM | Induce apoptosis and oxidative stress | Unclear | 461.27 g/mol |
| 5,7,D, 2′,4′-tetrahydroxy-8-lavandulylflavano | $C_{25}H_{28}O6$ | MDA-MB-231 | 0-30μM | 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 $CD3^+$, $CD4^+$, $CD4^+/C8^+$ 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-κB 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-κB, 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 κB (IκB) kinase β (IKKβ), which is one of the activation of IkB kinases (IKKs) and results in the phosphorylation of IkB.[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 $PIP_3$, 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-3β, 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: $C_{15}H_{24}N_2O_2$) 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, antivirus 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 μg/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-κB 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 S*ophora 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′-methoxy-kurarinone (MeO-Kur,5%), sophoraflavanone G (SFG, 2%) and other flavonoid species. The nonflavonoid compounds consist of alkylxanthones, 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, $COCH_2Br$ 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 μM.[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; IκB, inhibitor of κB; IKKs, IkB kinases; UPR, unfolded protein response; SG, sophoraflavanone G.

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## Disclosure

The authors report no conflicts of interest in this work.

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