

# Traditional Chinese Medicine for Breast Cancer: A Review

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**Abstract:** A total of 18% of global breast cancer (BC) deaths are attributed to BC in China, making it one of the five most common cancers there. There has been a steady rise in BC morbidity and mortality in women in the last few years and it is now a leading cancer among Chinese women. Conventional treatments for BC are currently effective but have several limitations and disadvantages, and Traditional Chinese medicine (TCM) plays a vital role in the overall process of cancer prevention and therapy. It is known that TCM can treat a variety of conditions at a variety of sites and targets. In recent years, increasingly, research has been conducted on TCM's ability to treat BC. TCM has shown positive results in the treatment of breast cancer and the adverse effects of radiotherapy and chemotherapy. This review describes the progress of clinical observation and mechanism research of TCM in the treatment of breast cancer in recent years. It provides some ideas and theoretical basis for the treatment of BC with TCM.

**Keywords:** formulas, acupuncture, mechanism of action, therapy

## Introduction

Among all cancer types, breast cancer (BC) is the fifth leading cause of cancer worldwide, with the highest incidence among Chinese women.<sup>1</sup> Surgery and chemotherapy, targeted therapy, and endocrine therapy are currently used as an anti-cancer therapy for Western medicine.<sup>2</sup> However, there are many disadvantages and limitations: postoperative complications, recurrences and metastases, and many different kinds of side effects.<sup>3</sup> Despite this, TCM plays an important role in cancer treatment due to its multiple sites and targets.<sup>4,5</sup>

The main clinical manifestations of BC are breast nodules, nipple and areola abnormalities, nipple discharge, and breast skin changes including skin infiltration, ulcers, satellite nodules, and eczema-like changes.<sup>6</sup> The cause of BC is still unclear, but the development of BC is closely linked to a number of conditions, like race, ethnicity, family history of cancer, genetic variants, excessive estrogen, high intake of high-fat, high-protein diet, chronic alcohol consumption and younger age of menarche and older age of first full-term pregnancy, which is related to female reproductive factors.<sup>7,8</sup>

TCM has a rich theoretical foundation and clinical application in the treatment of breast cancer and has been widely used in clinical practice. Breast cancer is among the 95 illnesses that TCM considers effective for treatment and recommends. These conditions are acknowledged by the State Administration of Chinese Medicines.<sup>9</sup> Due to TCM's consideration of individual differences and the relationship between a person and his or her environment, it has some unique advantages when it comes to treating tumors.<sup>4</sup> The advantages of Chinese medicine in the treatment of breast cancer also lie in its wide applicability, which is applicable to all types of breast cancer and all clinical stages, with no obvious toxic side effects.<sup>10</sup> The clinical observation and experimental studies of a large number of drug targets and mechanisms of drugs have shown that some classic Chinese medicine prescriptions and chemical compounds isolated from TCM are effective in the management and prophylactic of BC. Acupuncture, in conjunction with TCM, constitutes a fundamental element of traditional Chinese medicine, and there is growing evidence that acupuncture can be a safe and effective treatment for BC, as well as for associated concomitant symptoms such as chronic pain, hot flushes, fatigue,

neuropathy, nausea and vomiting, dry mouth and difficulty swallowing.<sup>10,11</sup> This reviews the progress of research in recent years on the treatment of BC and its adverse effects.

# Pattern Identification of BC in TCM

The diagnosis of BC is based on a mixture of pathology identification and differentiation in TCM. The main characteristics of disease identification can be divided into lumps, nipple discharge, skin changes, and nipple areola changes. In traditional Chinese medicine, BC disease is closely associated with the liver, spleen, stomach and kidneys. TCM believes that BC is mainly caused by the internal invasion of external pathogens and the deficiency of vital qi, resulting in an imbalance of viscera, meridians, qi, blood, body fluid, and yin and yang, leading to abnormal physiological functions of the breast.<sup>12</sup>

The etiology can be summarized as follows:<sup>13</sup> six exogenous factors which cause diseases and pathogenic toxin; deficiency of healthy qi and deficiency of both qi and blood; internal injury by the seven emotions; improper diet; toxic heat accumulation; congenital endowment. Patients are generally classified into the following types based on their pathological changes in yin and yang, qi and blood, viscera, meridians, and other aspects:<sup>14–16</sup> liver qi stagnation, toxic heat accumulation, deficiency of qi and blood, imbalance of Chong and Ren (Table 1).<sup>17,18</sup>

# TCM in the Therapy of BC

## TCM Formulas in the Therapy of BC

BC has different treatment purposes according to different disease stages. The treatment purpose of stage 0, stage I, stage II and stage III is to cure as much as possible, and stage IV is palliative treatment.<sup>8</sup> In clinical practice, many classic Chinese herbal decoctions or improved decoctions have obvious effects on the treatment of BC. Xiang Bei Yang Rong Tang (XBYRT),<sup>19</sup> Ruyiping,<sup>20</sup> Buqi YangXue decoction,<sup>21</sup> Shu Gan Jian Pi Granules,<sup>22</sup> Wuling San,<sup>23</sup> Huangqi Sijunzi

**Table 1** Pattern Identification of BC in TCM

Pattern	Liver Qi Stagnation	Toxic Heat Accumulation	Deficiency of Qi and Blood	Imbalance of Chong and Ren
<b>Pathology</b>	Long-term emotional discomfort, stagnation of liver qi, the liver meridian is lost in catharsis, qi and blood are blocked, breast collaterals are blocked	Improper diet and dereliction of duty in the transportation of the spleen and stomach lead to endogenous phlegm; stagnation of qi leads to blood stasis, fire turns into poison, phlegm, and blood stasis, Qi, fire, phlegm, and heat gather in the liver and stomach meridians	Qi and blood are faint, or qi and blood are damaged after surgery, radiotherapy, and chemotherapy, or the disease is delayed to the late stage, and the spleen and stomach are weak, leading to qi and blood deficiency	Insufficiency of the liver and kidney, or liver and kidney damage after surgery, radiotherapy, and chemotherapy, or the disease has lasted for a long time, deficiency of the liver and kidney leads to imbalance of Chong and Ren
<b>Clinical manifestations</b>	Breast lump distension and pain, hypochondriac chest and abdomen distension and pain or little abdominal distension and pain, frequent sighing	The breast is red, swollen, and painful, the skin becomes purple and uneven, or the skin is ulcerated, nipple discharge, erosive ulcer, or even fever, and the ribs and chest are painful, sometimes like burning	Emaciated, sallow or pale complexion, short of breath and fatigue, sweating when moving, dizziness, loss of appetite, palpitations, and insomnia	Breast lumps, hard as stone, and the surface is not smooth, drawn and haggard face, dizziness, hot flash and night sweats, sore waist and knees, palpitations and insomnia, tinnitus, five upset hearts, dry mouth and throat
<b>Tongue</b>	Tongue red coating thin white or thin yellow	The tongue is crimson with ecchymosis, and the fur is yellow with thin or thick moss	Light and tender tongue, the fur is thin and white	Reddish tongue with little fur
<b>Pulse</b>	Wiry pulse	Wiry and rapid pulse	Thin and weak pulse	Thready and weak pulse

decoction,<sup>24</sup> Xiaoi Jiedu Recipe,<sup>25</sup> Shenqi FuZheng injection,<sup>26</sup> Sini San,<sup>27</sup> Xiaochaihutang,<sup>28</sup> Kangai Injection,<sup>29</sup> Taohong Siwu Decoction,<sup>30</sup> Yanghe Tang,<sup>31</sup> and so on, are widely used in clinical practice.

## Relieve Cancer Fatigue

A very prevalent symptom of BC is cancer-related fatigue, for which many TCM decoctions have been proved to be effective. XBYRT can cure cancer-related fatigue caused by qi and blood deficiency.<sup>19</sup> Shu Gan Jian Pi Granules can treat BC-related fatigue caused by stagnation of liver qi and weakness of spleen qi.<sup>22</sup> Huangqi Sijunzi decoction can treat cancer fatigue in the form of spleen and stomach qi deficiency after chemotherapy for BC.<sup>24</sup>

## Suppressing the Progression of BC

Xihuang pill as a Chinese patent medicine, it has unique efficacy for treating BC, can inhibit the atypical hyperplasia of BC, and shows a marked cytotoxic activity on MDA-MB-231 and MCF-7 human BC cells. Li believes that Xihuang pill can be used alone as a treatment drug for BC.<sup>32,33</sup> Li and his research partners noted that Ruyiping may have an inhibitory effect on BC growth and metastasis by regulating cell cycle termination.<sup>20</sup> Xiaoi Jiedu decoction can effectively suppress BC cell proliferation and trigger cancer cell apoptosis.<sup>25</sup> Sini San can help prevent BC from stemness and spreading.<sup>27</sup> Yanghe Huayan decoction significantly restrained BC cell invasion and angiogenesis.<sup>34</sup> Xiao tan Jieyu Decoction discovered that this recipe can block the development of tumors and decrease the occurrence of BC and can also inhibit PI3K/AKT signal transduction pathway to effectively reduce the development of BC lesions.<sup>35</sup>

## Treatment Complications

As a frequent consequence of mastectomy, upper extremity lymphoedema may lead to bodily discomfort, emotional distress, disfigurement and loss of function. Wuling San can effectively treat upper limb lymphedema after mastectomy.<sup>23</sup> Cancer-related fatigue (CRF) has been identified as among the most distressing symptoms of breast cancer patients. ShuGan JianPi granules and Bu Zhong YiQi Decoction may contribute to the identification of an effective intervention for CRF.<sup>36</sup> Some studies have indicated that breast cancer patients are more prone to anxiety and depression.<sup>37</sup> The use of Shuyu pill in the chemotherapy of advanced breast cancer can alleviate anxiety and depression, decrease the occurrence of side effects, the improvement of related symptoms and enhance the quality of life of patients.<sup>38</sup> Wenshen Zhuanggu Recipe found that it can alleviate the pain of bone metastasis of BC and mitigates microenvironment of tumor cells, control the tumor epithelial–mesenchymal transition (EMT) process, reduce the growth and spread of tumor cells, and also reduce leukopenia, nausea, vomiting, gastrointestinal reaction, alopecia, and bone marrow suppression.<sup>30</sup>

## Adjuvant Therapy

TCM decoctions are remarkably useful in the therapy of BC and its complications and can be used as an effective support to radiotherapy and chemotherapy to enhance their curative effects and reduce side effects. Buqi Yangxue decoction can improve the immune function, nutritional status, and TCM symptoms of BC patients after radiotherapy and chemotherapy.<sup>21,39</sup> Shenqi FuZheng injection can improve the therapeutic results of chemotherapy, increase target response rate, enhance immune response and reduce side effects.<sup>26,40</sup> Xiaochaihutang can influence the expression of neurotransmitter-related receptor genes and subsequently affect neuronal invasion in the BC tumor microenvironment to reach the goal of the therapy of BC.<sup>28</sup> Huaier is a TCM, because its anti-cancer properties have attracted the attention of many researchers, and research has proved that it can inhibit the development of low toxic BC, enhance the response of immunity and increase the susceptibility to radiation therapy and chemotherapy, and can significantly inhibit proliferation and induce programmed cell death.<sup>41</sup> It can also reduce levels of tumor markers.<sup>42</sup> Yanghe Tang can enhance the efficacy of chemotherapy and can inhibit inflammation and improve the body's microenvironment and immunity.<sup>43,44</sup>

## The Chemical Compounds Isolated from Chinese Herbs for BC

The chemical components isolated from Chinese herbs also have therapeutic effects on BC, as evidenced by increasing amounts of research. Andrographolide (AD) is a chemical component isolated from *Andrographis paniculata*, which has a huge anti-tumor effect in a variety of tumors. AD can inhibit the proliferation of BC cells by inhibiting ESR1

transcription via the ROS-FOXM1 axis and may suppress BC cell growth by down-regulation of ER-A expression.<sup>45</sup> *Salvia miltiorrhiza* is commonly used in liver cancer and cardiovascular diseases. The effective components extracted from *Salvia miltiorrhiza* I, II, cryptotanshinone, and dihydrotanshinone. Tanshinone can inhibit tumor cell proliferation and tumor growth, and prevent tumor angiogenesis through induction of apoptosis and cell cycle arrest in cancer cells, inhibition of metastatic phenotype, and enhancement of chemical sensitivity and radiosensitivity.<sup>46</sup> *Cimicifuga dahurica Maxim* as TCM has a long history and the history in the treatment of BC can be traced back to the “Sheng-Ge decoction”. In recent years, the extract of *Cimicifuga* can inhibit the proliferation of BC cells and promote the apoptosis of BC cells.<sup>47</sup> Evodiamine, a major bioactive component of *Evodia rutaecarpa*, can inhibit tumorigenesis, migration and vasculogenesis. Evodiamine (EVO) also induces apoptosis in Doxorubicin (DOX)-sensitive and DOX-resisting cells. It can enhance DOX apoptosis through inhibition of IAPs and the Ras/MEK/ERK cascade. It shows that Evodiamine can play a role in the treatment of BC whether used alone or in combination with chemotherapy drugs.<sup>48</sup> G. lucidum spore oil (GLSO) is a TCM *Ganoderma lucidum* extract. GLSO can induce cell apoptosis through mitochondrial apoptosis, thereby inhibits MDA-MB-231 cell and tumor growth. Therefore, GLSO can be used as a new nutraceutical or drug for the prevention and treatment of breakthrough cancer.<sup>49</sup> Icaritin (ICT) is a prenylated flavonoid derivative of the TCM *Epimedium Herba*. It has anti-cancer properties in several types of cancer. ICT derivative IC2 and demonstrate that IC2 is able to induce apoptosis in mitochondrial cells by blocking the function of stearoyl-CoA desaturase-1 (SCD1). IC2 reduces the expression of the anti-apoptotic factor Bcl-2 by disrupting the mitochondrial membrane potential and promotes apoptosis along with the production of ROS. The result of the study is that IC2 might be a drug candidate to combat BC.<sup>50</sup> Matrine (MAT) is an alkaloid that is extracted from the *Sophora Flavescens*, a TCM, which can be used to treat aggressive cancers. MAT has been shown to inhibit the growth of MDA-MB-231 cells and is an effective apoptosis inducer. It may be a new inhibitor of BC.<sup>51</sup> Osthole, as a major extract from *Cnidium monnieri (L.)*, blocks the growth, proliferation, and intrusion of BC cells, and induces apoptosis of BC cells. It also regulates osteoprotegerin/receptor activator of NF- $\kappa$ B ligand (OPG/RANKL) signaling when osteoblasts interact with cancer cells. Inhibition of bone spread in BC through inhibition of the Transforming growth factor beta/Smads (TGF- $\beta$ /Smads) signaling pathway during bone spread in MDA-MB-231 cells.<sup>52</sup> Red ginseng polysaccharide (RGP), one of the red ginseng’s active components, has good anti-tumor activity. RGP may be used as a preventive medicine against BC by targeting glutathione peroxidase 4 (GPX4) to eliminate the protection of cancer cells from ferroptosis.<sup>53</sup> Shikonin, a naphthoquinone derived from the *Lithospermum erythrorhizon*, has a wide range of uses. By reducing T tumor-derived exosomes, shikonin can suppress the proliferation of human BC cells, and can also inhibit tumor proliferation by regulating the release of exosomes to change the tumor microenvironment.<sup>54</sup> Shikonin (SKO) has significant cytotoxicity to MDA-MB-231 cells, which could become a candidate to treat triple-negative BC.<sup>55</sup>

## Acupuncture for BC

There are many adverse effects associated with BC treatment, whether it is surgery, radiotherapy or chemotherapy. Acupuncture, as well as traditional herbal decoction, has an essential function in treating side effects. Acupuncture is a holistic therapy, which is part of TCM. The principle of treatment of TCM is coordinating yin and yang. And acupuncture can operate by stimulating the pathways or meridians that carry the body’s vital energy, which has a regulating and balancing effect on various organs and the body as a whole.<sup>56</sup>

A common symptom for late-stage cancer patients is pain. Safe and effective pain relief can effectively improve quality of life for late-stage patients. Acupuncture can activate the pain modulation system in the body, promote the production and release of endogenous opioids in the body, and thus alleviate pain.<sup>57</sup> Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common side effects in cancer patients during and after chemotherapy. Most CIPN treatments currently used are based on Western medicines, but these can cause side effects such as fatigue, dizziness and insomnia.<sup>58</sup> Acupuncture combined with painkillers can safely and effectively relieve the pain caused by cancer.<sup>59</sup> Insomnia is a prevalent side effect that can occur during and after chemotherapy. Acupuncture may alleviate the over-activated sympathetic nerves of the patients.<sup>60</sup> And that’s why acupuncture and moxibustion can effectively alleviate insomnia caused by cancer.<sup>61,62</sup> BC complicated with upper limb edema often uses western medicine in clinical practice. Studies have demonstrated that acupuncture in affected limbs can unblock occluded lymphatic vessels, enhance the

phagocytosis of leukocytes and reduce the inflammatory response. At the same time, acupuncture could release lymphatic fluid and relieve the load of the lymphatic system in the affected area, which is conducive to local tissue oedema and inflammation absorption.<sup>63</sup> Taking Chinese herbal recipe in conjunction with acupuncture could better enhance the symptoms of affected limbs and relieve pain, improve clinical efficacy, and promote the recovery of limb function.<sup>64,65</sup> Patients often have nausea and vomiting after chemotherapy. So, a lot of antiemetic drugs are clinically used to prevent the chemotherapy-induced nausea and vomiting (CINV), but these antiemetic drugs may cause a variety of adverse effects. Acupuncture as an additional treatment not only mitigates the adverse effects but is also safer and more tolerable. Wang concluded that acupuncture can effectively improve nausea and vomiting after chemotherapy, and its effect is no less than taking western medicine.<sup>65</sup> The mechanism of acupuncture could be to stimulate and induce alterations in the levels of hormones and neurotransmitters related to regulating appetite controlling, such as the monoamine neurotransmitters 5-HT, gastrointestinal hormones, and NTS cells.<sup>66</sup> Summarize the mechanism of action of acupuncture above (Table 2).

## Pharmacological Mechanism of Chinese Medicine Against BC

According to clinical observations and experimental research results, the pharmacological effects of Chinese herbal medicine in the prevention and treatment of BC can be divided into several categories: affecting cell proliferation and apoptosis, regulating autophagy, inhibiting EMT, and improving the microenvironment. The relevant mechanisms for affecting cell proliferation and apoptosis include affecting relevant signaling pathways, proto-oncogenes and tumor suppressor genes, or acting directly on BC cells (Figure 1) (Table 3).

## Cell Proliferation and Apoptosis

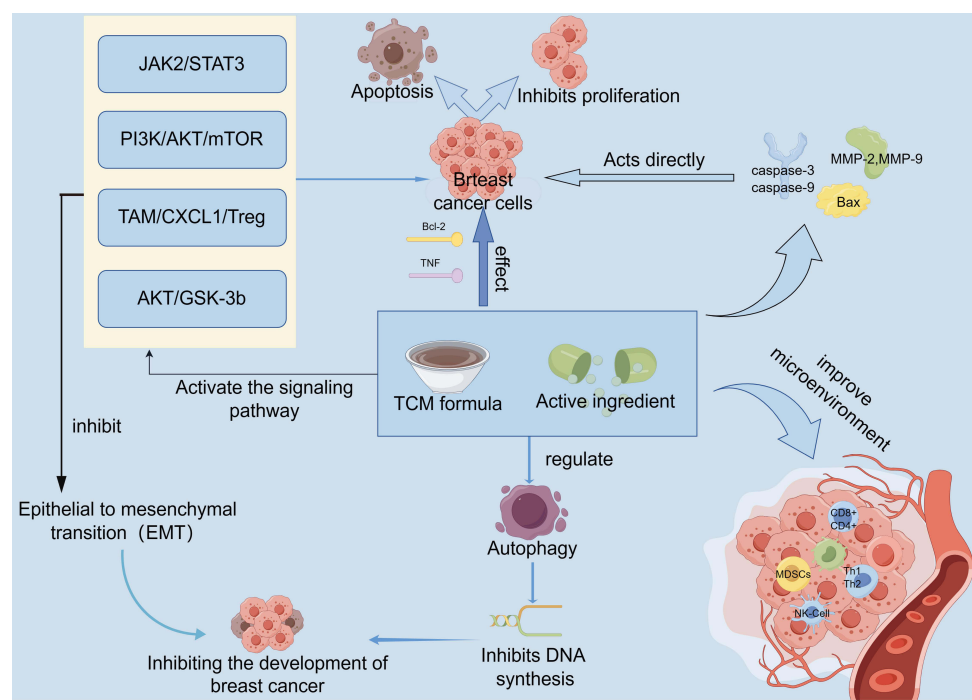
### Relevant Signal Pathway

One critical mechanism by which BC cells proliferate and undergo apoptosis is by interfering with the signaling pathways involved.

AC Roots is the root of *Actinidia chinensis Planch.* Its extract suppressed BC cell growth, proliferation, invasion and increased apoptosis of BC cells via the AKT/GSK-3b pathway.<sup>71</sup> Ai du Qing formula can inhibit TAM/CXCL1/Treg pathway and inhibit immune escape and lung metastasis of BC.<sup>72</sup> Mammalian target of rapamycin (mTOR) was

**Table 2** Mechanism of Action of Acupuncture

BC Complications and Adverse Reactions	Acupoint Selection	Mechanism
Cancer pain	Hegu (LI4), Taichong (LR3), Ashi-point, Zusanli (ST36), Sanyinjiao (SP6), Yanglingquan (GB34).	Activating the pain modulation system in the body, promoting the production and release of endogenous opioids in the body
Chemotherapy-induced peripheral neuropathy (CIPN)	Qiduan (Ex-LE12), Bafeng (Ex-LE10), Baxie (Extra27), Waiguan, (TW5), Taichong (LR3), Quchi (LI11), Zusanli (ST36), Yinlingquan (SP9), Sanyinjiao (SP6), Taixi (K3), Yintang (Extra2)	Stimulate the peripheral and central nervous system to improve nerve conduction
Insomnia	Yintang (Extra2), Zusanli (ST36), Hegu (LI4), Guanyuan (RN4), Taixi (K3), Taichong (LR3), Tianshu (ST25)	Alleviate the over-activated sympathetic nerves
Upper limb edema	Jiquan (HT1), Hegu (LI4), Zusanli (ST36), Sanyinjiao (SP6), Zhongwan (RN12), Qihai (RN6), Guanyuan (RN4)	Unblock occluded lymphatic vessels, enhance the phagocytosis of leukocytes and reduce the inflammatory response.
Chemotherapy-induced nausea and vomiting (CINV)	Neiguan (PC6), Zusanli (ST36), Zhongwan (RN12), Gongsun (SP4), Pishu (BL20), Weishu (BL21)	Stimulating and inducing changes in the levels of hormones and neurotransmitters related to the regulation of appetite



**Figure 1** Pharmacological mechanisms of TCM for treating BC. By Figdraw (ID ROTRubb55b).

identified as the key molecule of multiple signal transduction pathways, and its upstream PI3K/AKT constitutes the PI3K/Akt/mTOR signal pathway. This pathway is highly expressed in BC, regulating cell proliferation, apoptosis, transcription, translation, metabolism, and so on. It is a crucial cell biological procedure in the developing organism and progression of BC. Xihuang Pill can inhibit BC cell development, ingression and migration and suppress tumor angiogenesis through this pathway found that Xihuang Pill can down-regulate NF- κ B protein expression, thus

**Table 3** Mechanism of Action of TCM

Function	The Chemical Compounds Isolated from Chinese Herbs/TCM Formulas	Molecular Mechanism
Signaling pathway	Alkali ethanol <sup>67</sup> Baicalein, <sup>68</sup> Goushecao, <sup>69</sup> Guizhi Fuling Decoction, <sup>70</sup> Xiao ai Jie du decoction <sup>25</sup>	PI3K/AKT relevant pathway
	Tengligen <sup>71</sup>	AKT/GSK-3b pathway
	Ai du Qing formula <sup>72</sup>	TAM/CXCL1/Treg pathway
	Berberine <sup>73</sup>	Ephrin-B2 signaling pathway
	Xihuang Pill, <sup>74,75</sup> Ethyl gallate <sup>76</sup>	NF-κB signaling pathway
	Jin'gan capsules, <sup>77</sup> Yang he decoction <sup>78</sup>	JAK2/STAT3 signaling pathway
	Taohong Siwu Decoction <sup>79</sup>	KRAS signaling
Proto-oncogene and tumor suppressor gene	Yu zhu, <sup>80</sup>	BAX/Bcl-2
	Ruanjian Sanjie decoction, <sup>81</sup>	Caspase 3/7 and caspase 9
	SANT <sup>82</sup>	TMEM74 and TNF
	Rupifang <sup>83</sup>	HER2

(Continued)



Table 3 (Continued).

Function	The Chemical Compounds Isolated from Chinese Herbs/TCM Formulas	Molecular Mechanism
Direct inhibition of human BC cells	Arctigenin, <sup>84</sup> <i>G. lucidum</i> spore oil <sup>49</sup>	MDA-MB-231
	Berberine and Evodiamine, <sup>85</sup> Oxymatrine, <sup>86</sup> Fructus Psoraleae, <sup>87</sup> Dahuang <sup>88</sup>	MCF-7
	Cantharidin, <sup>89</sup> Luteolin <sup>90</sup>	MDA-MB-231 and MCF-7
Regulation of autophagy	Alisol A <sup>91</sup>	Induce reactive oxygen species and DNA injury
	Ai Du Qing formulation <sup>92</sup>	GRP78/ $\beta$ -catenin ABCG2 regulating axis of autophagy
Suppress EMT	HNK <sup>93</sup>	Reduce the expression of Snail and Slug genes
	Wenshen Zhuanggu formula <sup>94</sup>	Inhibit BMSCs
Improve the microenvironment	Xihuang Pill <sup>95</sup>	PI3K/AKT and PD-1/PD-L1 pathway
	Xihuang Pill, <sup>96</sup> Saikosaponin A (SSA) <sup>97</sup>	Th1/Th2
	Xihuang Pill <sup>98,99</sup>	IFN- $\gamma$ , IL-2, IL-4, IL-10
	Saikosaponin A (SSA) <sup>97</sup>	CD8 <sup>+</sup> T, CD4 <sup>+</sup> T cells
	Sanhuang Decoction <sup>100</sup>	Improve chronic oxidative stress within the body
	Yanghe Tang <sup>78</sup>	Reduce the number of MDSCs

blocking BC from developing and progressing.<sup>74,75</sup> Alkali ethanol as the extract of *A. raddeana*. The extract was called total secondary saponin (TSS) and found that TSS can block the triggering of the PI3K/AKT/mTOR signal pathway, thereby promoting the expression of the mitochondria cell death pathway, and can markedly attenuate the growth of MCF-7 cells.<sup>67</sup> As a bioactive ingredient derived from the roots of *Scutellaria baicalensis*, baicalein can inhibit the PI3K/AKT pathway in and ex vivo to cause apoptosis and autophagy in BC cells.<sup>68</sup> *Astragalus membranaceus* extract inhibits the growth of BC cells through the PI3K/AKT/mTOR signaling pathway.<sup>101</sup> Ephrin-B2 contributes to cancer cell survival, invasion and migration. Berberine significantly inhibited tumor cell growth and migration through the Ephrin-B2 signaling pathway.<sup>73</sup> As the major constituent from the roots of *Euphorbia Fischeriana* Steud, ethyl gallate can inhibit BC metastasis through a signal pathway.<sup>76</sup> Eight flavonoids and three flavonoids are extracted from *Turcz. ex DC.*, which can induce apoptosis and autophagy of human BC cells, found that flavonoids can also suppress cell proliferation and trigger apoptosis and autophagy via the PI3K/AKT/mTOR/p70S6K/ULK pathway.<sup>69</sup> Guizhi Fuling Decoction has the function of anti-proliferation, promoting apoptosis and anti-angiogenic, which mainly inhibits BC cells achieved by modulating the PI3K and MAPK signaling pathways.<sup>70</sup> Jin'gan capsules (JGCs) suppress BC cell proliferation and induce cell cycle arrest and apoptosis partly by inhibiting the JAK2/STAT3 signaling pathway.<sup>77</sup> The effective ingredients of Xiao ai Jie du decoction: quercetin and ursolic acid, through the combination of both, the mitochondrial membrane potential is notably reduced and the activity of PI3K Akt signaling pathway is inhibited, which induces cancer cell death.<sup>25</sup> Taohong Siwu Decoction (TSD) can significantly inhibit KRAS signaling in cancer and activation of the apoptosis pathway, p53 pathway, and hypoxia pathways inhibits the growth and spread of cancer cells, induction of G1 arrest and apoptosis of MDA-MB-231 cells can regulate the expression of MYC, BIRC5, EGF and PIK3R1.<sup>79</sup> Yang he decoction, which inhibits 4T1 breast tumor growth, is mainly through negative regulation of JAK/STAT3 pathway.<sup>78</sup>

## Proto-Oncogene and Tumor Suppressor Gene

*Polygonatum odoratum* (*P. odoratum*) is widely used in TCM, and *P. odoratum* extract may have an inhibitory effect on the growth of MDA-MB-231 human BC cells and induce their apoptosis by upregulating Bax expression and inhibiting Bcl-2 expression.<sup>80</sup> Ruanjian Sanjie decoction shows potent cytotoxicity in vitro against BC cells by suppressing the antiapoptotic proteins B-cell lymphoma 2 and survival, which leads to the caspase 3/7 and caspase 9 activation and the apoptotic process.<sup>81</sup> A new combination of Chinese herbs known as SANT. SANT promotes autophagic flux and inhibits tumor angiogenesis by regulating the production of related genes and proteins, increasing the production of ATG16L1, ATG9B and ATG4D genetic factors and decreasing the production of TMEM74 (new autophagy-related genes) and TNF (tumor necrosis factor) genes.<sup>82</sup> Rupifang extract in rat models of breast hyperplasia found that Rupifang can increase the expression of tumor inhibitor P16 by inhibiting the expression of the pro-oncogene HER2, which can efficiently prevent the onset and progression of BC.<sup>83</sup>

## Direct Inhibition of Human BC Cells

Arctigenin is a bioactive lignan which has been extracted from the *Arctium lappa* L. Arctigenin downregulates MMP-2, MMP-9 and heparanase to inhibit infiltration and metastasis of MDA-MB-231 cancer cells.<sup>84</sup> Berberine and Evodiamine acted synergistically to increase BAX protein levels, upregulate the expression on caspase-9 and caspase-7, and subsequently induce cell cycle exit and promote apoptosis in the MCF-7 human BC cellular line.<sup>85</sup> Cantharidin, the active compound of the beetle *Mylabris*, which is widely used in traditional Chinese medicine, is a powerful and specific blocker of the protein phosphatase 2A (PP2A), playing a key role in cell cycle development, division and cell differentiation. Lin and colleagues discovered that DT, a pure substance found in BC, suppressed the development of MCF-7 and MDA-MB-231 cells in vivo and in vitro, and inhibited expression of apoptosis and ferrogenesis in these BC cells.<sup>89</sup> Luteolin, the main bioactive compound of *T. officinale*, effectively suppressed MDA-MB-231 and MCF-7 cell multiplication and migration.<sup>90</sup> *G. lucidum* spore oil (GLSO) is a lipophilic compound which is derived from the sporophyll of *G. lucidum* spores. GLSO may upregulate caspase-3 and caspase-9, exhibit mitochondrial apoptosis-induced inhibited growth in MDA-MB-231 cells, and induce tumor cell apoptosis in vivo.<sup>49</sup> Oxymatrine, a major active and toxic alkaloidal ingredient from the roots of *Sophora japonica*, may have an important role in inhibiting oncogenic BC cells by promoting MCF-7 apoptosis through modulating the expression levels of Bax and bcl-2.<sup>86</sup> There are two phases in the cell cycle. Intermediate phase includes G1, S and G2 stages. Bakuchiol, an effective substance in the TCM *Fructus Psoraleae*, can inhibit BC through the induction of S phase apoptosis and inhibition.<sup>87</sup> The water extract of *Da Huang* has potential anti-cancer properties by inhibiting proliferation and apoptotic effects in MCF-7 and A549 cell line analysis.<sup>88</sup>

## Regulation of Autophagy

As a main protostane triterpene from *Alismatis Rhizoma*, Alisol A significantly inhibited cell viability. Induction of apoptosis in MDA-MB-231 cells exits from the G1 phase of the cell cycle, the activity of autophagy and the generation of inter-cellular reactive oxygen species (ROS) in MDA-MB-231 cells. Treatment with Alisol A induces autophagy-dependent apoptosis in mammary normal cancer cells through the induction of reactive oxygen species and DNA injury.<sup>91</sup> Ai Du Qing formulation can pass through the GRP78/ $\beta$ -catenin ABCG2 regulating axis of autophagy to prevent the development of BC.<sup>92</sup>

## Suppress EMT

EMT participates in tumor infiltration and metastases by generating more motile and invasive cells. The control of EMT can be a potential target for preventive care and management of metastatic tumor.<sup>102</sup> Honokiol (HNK) reduces the expression of Snail and Slug genes at the level of mRNA translation, inhibiting EMT in BC cells.<sup>93</sup> Bone marrow induced mesenchymal stem cells (BMSCs) aggravate the formation and progress of tumors. Inside the tumor micro-environment, BMSC can directly or indirectly influence the behavior of neighboring tumor cells through paracrine secretion and increase tumor cell capacity through motility, tumorigenicity, and metastasis. The Wenshen Zhuanggu formula inhibits EMT and bone metastasis in BMSC-induced BC.<sup>94</sup>



## Improving the Microenvironment

Tumor microenvironment offers a friendly environment for cancer cell development. Tumor microenvironment components are affected by tumor cell gene composition and patients may also be at increased risk of invasive tumors and faster disease progression due to other non-oncological factors, leading to early onset, to adversely affect the survival of patients.<sup>103</sup> Cancer cells and other cells in the cancer microenvironment are involved in metastatic spread (for instance stromal cells, immune cells). These cells secrete a variety of regulatory cytokines and/or growth agents, which in reverse have an impact on the progression of BC through a number of different mechanisms. Inflammation, by establishing a favorable immune microenvironment, may affect the development, metastases and prognosis of BC. Xihuang Pill significantly suppresses BC development by targeting multiple carbohydrate and inflammatory microenvironment signaling pathways.<sup>95</sup> Th1 and Th2 are mainly involved in a cellular immune response. The Th1/Th2 ratio of tumor patients changes, which leads to inhibition of anti-tumor immune response, so that cancerous cells can survive and improve the appearance and progress of malignant tumors. Li and other researchers consider that the immune microenvironment has an essential part in the development and growth of BC,<sup>104</sup> closely associated with the PI3K/AKT and PD-1/PD-L1 signal transduction pathway and inhibits the progression of lymphoma.<sup>96</sup> They found that Xihuang pill can serially enhance IFN- $\gamma$  and IL-2, inhibit IL-4 and IL-10, and modulate Th1/Th2 cell balance, improving the immune microenvironment.<sup>98,99</sup> Saikosaponin A (SSA) is separated from the dried radical of *Radix Bupleuri*. SSA suppresses BC by increasing penetration of CD8<sup>+</sup> T cells and CD4<sup>+</sup> T cells into the microenvironment of the tumor and promoting a Th1/Th2 bias towards a Th1 immunity.<sup>97</sup> Sanhuang Decoction improves tumor microenvironment by regulating pressure-related factors, inflammation, hemorheology, blood lipids, immunity, and angiogenesis factors; all of these functions can help tumors grow or become resistant to drugs. Sanhuang Decoction can effectively relieve chronic stress state and control the tumor microenvironment by improving chronic oxidative stress within the body.<sup>100</sup> As immunosuppressors, MDSCs enhance T-cell apoptosis and inhibit natural killer cell antioxidant activity. Yanghe Tang is able to reduce the development of 4T1 lymphoma cells through a reduction in the number of MDSCs in the tumor microenvironment.<sup>78</sup>

## Conclusions and Perspectives

There is an urgent need for more effective treatments for BC, which is one of the most frequent cancers in women. For the treatment in BC, TCM shows distinct benefits. Traditional decoctions, traditional herbal medicines and traditional herbal extracts are all important for treating BC. This finding could have important implications for treating BC. At present, the use of TCM-supported radiotherapy and chemotherapy for the treatment of BC is more common in clinical practice, to enhance effectiveness and decrease side effects and drug resistance. Many studies have demonstrated that TCM works well against BC. It has a positive impact on the prevention and treatment of anti-tumor therapy-related side effects, and plays an important role in promoting the recovery of patients' physical fitness after anti-tumor therapy, reducing recurrence and metastasis, and improving the quality of survival.

However, the current clinical trials supporting the theoretical basis are insufficient, and the specific mechanisms of action and adverse effects of some TCM are still unclear. At the same time, due to the characteristics of Chinese medicine treatment, there is a lack of standardized symptomatology and uniform evaluation of the efficacy of TCM. Further extensive and in-depth research and development are necessary for some traditional medicines, as well as the rational standardization of these medicines in order to facilitate their clinical promotion and application.

In the future, we can further clarify the mechanism of action of TCM in the treatment of BC, on the basis of which we can improve the efficacy of TCM, standardise the diagnosis and treatment of BC in TCM, and provide more precise clinical guidance.

## Acknowledgments

This research was supported by the National Natural Science Foundation of China (Grant no. 81603412); Health Commission of Hebei Province (Grant no. 20220962); Scientific Research Project of Hebei Administration of Traditional Chinese Medicine (Grant no. 2023045; Grant no. 2024023); General Projects for Improving Scientific

Research Capacity of Hebei College of Traditional Chinese Medicine (Grant no. KTY2019009); Hebei Province “Three Three Three Talent Project” funded project (Grant no. A202002008); and Hebei Graduate Innovation Funding Project (Grant nos. XCXZZSS2023017 and XCXZZSS2023027). We also thank Figdraw platform for visualization.

## Disclosure

The authors declare that they have no conflicts of interest for this work.

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