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Traditional Chinese medicine in the treatment of breast Cancer

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Abstract

Breast cancer (BC) is the most commonly diagnosed malignancy among women globally. While treatments such as chemotherapy and endocrine therapy have contributed to improving survival rates, there remains a critical need for more effective therapeutic options. Traditional Chinese Medicine (TCM), with a history spanning thousands of years, has long been utilized in the management of BC. This includes a wide range of practices, such as the use of traditional compound prescriptions, Chinese medicine monomers and extracts, acupuncture, moxibustion, and mind-body therapies. This review summarizes the brief history and experience of TCM in treating BC refer to numerous ancient Chinese medical texts, and explores the role of various TCM approaches in the treatment of BC, providing an in-depth analysis of their potential benefits. Additionally, it addresses the current limitations and challenges in researching TCM's effectiveness for BC. Through this review, we aim to offer valuable insights into how TCM can complement conventional therapies and enhance outcomes for patients with BC.

Keywords Traditional Chinese medicine, Breast cancer, Combination therapy, Clinical application, Mechanisms of bioactive ingredients

Introduction

Breast cancer (BC) is the second most commonly diagnosed cancer, surpassed only by lung cancer. Each year, more than 230,897 new cases of BC are diagnosed worldwide, accounting for approximately 11.6% of all new cancer diagnoses. This underscores the significant public health burden that BC represents and highlights the ongoing need for effective prevention, early detection, and treatment strategies. Moreover, the global BC statistics report indicated that in 2022, there were 665,684 deaths globally, accounting for an estimated 6.9% of all cancer-related deaths [1]. Despite advancements in modern therapy using surgery, radiotherapy, and Western medicines (WM), including chemotherapy, endocrine therapy, and the human epidermal growth factor receptor 2 (HER2) targeted monoclonal antibody, trastuzumab, the incidence and mortality of BC remain high, with five-year survival rates of less than 30% in metastatic BC [2].

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WM is commonly used as the first-line treatment for BC. Nevertheless, some WM types can damage healthy cells due to the lack of specificity for cancer cells, leading to severe side effects. These side effects represent significant obstacles for clinicians and are crucial to late recurrence [3, 4]. Therefore, there is a critical need to investigate more effective and less toxic treatment options for BC.

Recently, TCM, including formula, single components, acupuncture, and moxibustion, with anti-tumor effects, has received considerable attention because of its significantly lower toxicity and therapeutic potential [5, 6]. TCM, as a complementary therapy for WM, has achieved extraordinary clinical results in the field of BC treatment. In this review, we will examine the efficacy and underlying mechanisms of TCM in the treatment of BC. We will systematically review the latest advancements in TCM-based therapies for BC, highlighting both clinical outcomes and the scientific rationale behind their use. By analyzing recent research and trends in this field, we aim to provide new perspectives and valuable insights into the potential role of TCM in the management of BC. This review will also outline the critical pathways forward, identifying key areas for further investigation and development to optimize the integration of TCM with conventional treatment approaches.

The current treatment strategy and limitations of BC

BC is recognized as a heterogeneous disease consisting of various subtypes that exhibit distinct morphological and biological characteristics. These differences contribute to variations in clinical behavior and are key factors in the development of precision therapies for individual patients [7]. There are several histopathologic types of BC, each with its unique features. BC is commonly classified into three major categories based on the extent of cancer cell invasion into surrounding tissues and the likelihood of distant metastasis: invasive lobular carcinoma (ILC), invasive ductal carcinoma (IDC), and non-invasive ductal carcinoma in situ (DCIS). This classification plays a crucial role in determining treatment strategies and predicting clinical outcomes, as the behavior of each subtype can differ significantly in terms of growth patterns, spread, and response to therapies [8]. In addition to histological subtypes, tumors exhibit different protein expressions depending on their molecular subtypes. The status of estrogen receptor (ER), progesterone receptor (PR), and HER2 is routinely assessed in BC treatment. Gene expression profiling of BC has defined four intrinsic molecular subtypes based on the expression of ER, PR, HER2 receptors, and the nuclear antigen Ki-67: Luminal A, Luminal B, HER2-positive, and Basal-like [9]. Therefore, the complex molecular characteristics aim to provide accurate treatment for each patient.

Currently, the standard WM treatment of BC ranges from surgery, radiotherapy, chemotherapy, targeted therapy, and endocrine therapy. These methods focus on eliminating tumor and blocking a specific transfer in a particular process [8], however, there are some limitations in treating BC with WM due to the complexities of tumor biology, adverse reactions of therapy, individual differences of patients and so on. Many studies have indicated that tumor tissue is a constantly evolving 'ecosystem' contained a wide variety of cells with different phenotypes and mutations, such as cancer cells, tumor-associated fibroblasts, immune cells, cells related to blood vessels and so on, the gene mutations and epigenetic regulation of which caused by WM treatment could synergistically promote drug resistance and immune escape of cancer cells by rebuilding tumor microenvironment (TME). Despite the advances in BC treatment, chemotherapy-induced nausea and vomiting (CINV), bone marrow suppression, and cardiotoxicity, etc. caused by conventional WM can directly limit the intensity and duration of treatment, and the applicable population because of the specific organ toxicity, which are major challenges for patients on the quality of life and curative effect with long-term treatment [10–12]. The available protocols of treating BC could be limited in some special populations due to the individual differences of patients, which are determined by gene, physiology, pathology, and society. In addition, the treatment response, drug-toxicity, and prognosis are different using the same therapy. The severe side effects and inevitable drug resistance associated with WM often cause incomplete therapy and unsatisfied outcomes for patients, prompting many of them to seek alternative treatments. In China, the United States, and Canada, the use of TCM is common. A recent study performed in the United States showed that up to 75% of cancer patients had been treated with TCM [13].

Brief history and experience of TCM in the treatment of BC

The earliest writing of breast disease were found on oracle bone inscriptions in 1400 – 1100 B.C. (Before Christ), which had recorded that a king of the Shang Dynasty in China was diagnosed with breast disease, and attempted to recuperate by holding sacrifice, because they believe that the breast diseases are caused by demon [14]. The therapeutic method for breast diseases is firstly recorded in the "Fifty-two Disease Prescriptions (Wu Shi Er Bing Fang)," which is the earliest ancient medical book before 160s B.C. The foundational book of TCM theory from 425 to 221 B.C., "Yellow Emperor's Internal Classic (Huang Di Nei Jing)," recorded BC-like symptoms, which were described as "Ju" (swelling, tissue induration, and ulceration). The word "breast cancer" does not appear in any ancient medical books, however, the words such as

"Ru Yong, Ru Yan, Ru Ju, Ru Pi, Ru Jie" had been taken for BC according to its description of clinical characteristics. The comprehensive theories and therapeutic methods of TCM in treating BC have been gradually perfected by numerous medical professionals over thousands of years, which can be clearly divided into five stages (Fig. 1).

In the origin stage (2000 B.C. – 220 A.D. [Anno Domini]) [14], the primitive experience of treating breast diseases, including external applications and oral herbs were recorded, and the symptoms and characteristics of "Ru Yong" were simply described in several ancient medical book. In the formation stage (220 A.D. – 907 A.D.), a theoretical framework of treating breast diseases had been gradually established according to the scattered experience, pathogenesis, symptoms, characteristics, and therapeutic methods of different breast diseases, including "Ru Yong, Ru Yan, Ru Ju, Ru Pi, Ru Jie" had been summarized. In the development stage (960 A.D. – 1368 A.D.), the pathological mechanisms of various breast diseases including BC had been systematically explained, besides, the breast diseases had been divided into TCM surgery, and the progression of breast diseases could be controlled by combining external applications and oral herbs in different pathological stages and syndrome types, which had established a complete system of TCM formulas and prescriptions. In the mature stage (1368 A.D. – 1840 A.D.), there were many records on the etiology, pathogenesis, diagnosis, treatment, and prognosis of breast diseases in the field of TCM surgery, especially, on the etiology, pathogenesis, clinical symptoms, and malignant degree of BC, and the importance of early diagnosis and treatment was emphasized, which had provided a large number of clinical references in treating BC based on syndrome differentiation. In the innovation stage (1949 A.D. – Present), the concept of integrating TCM and WM had been proposed following the spread

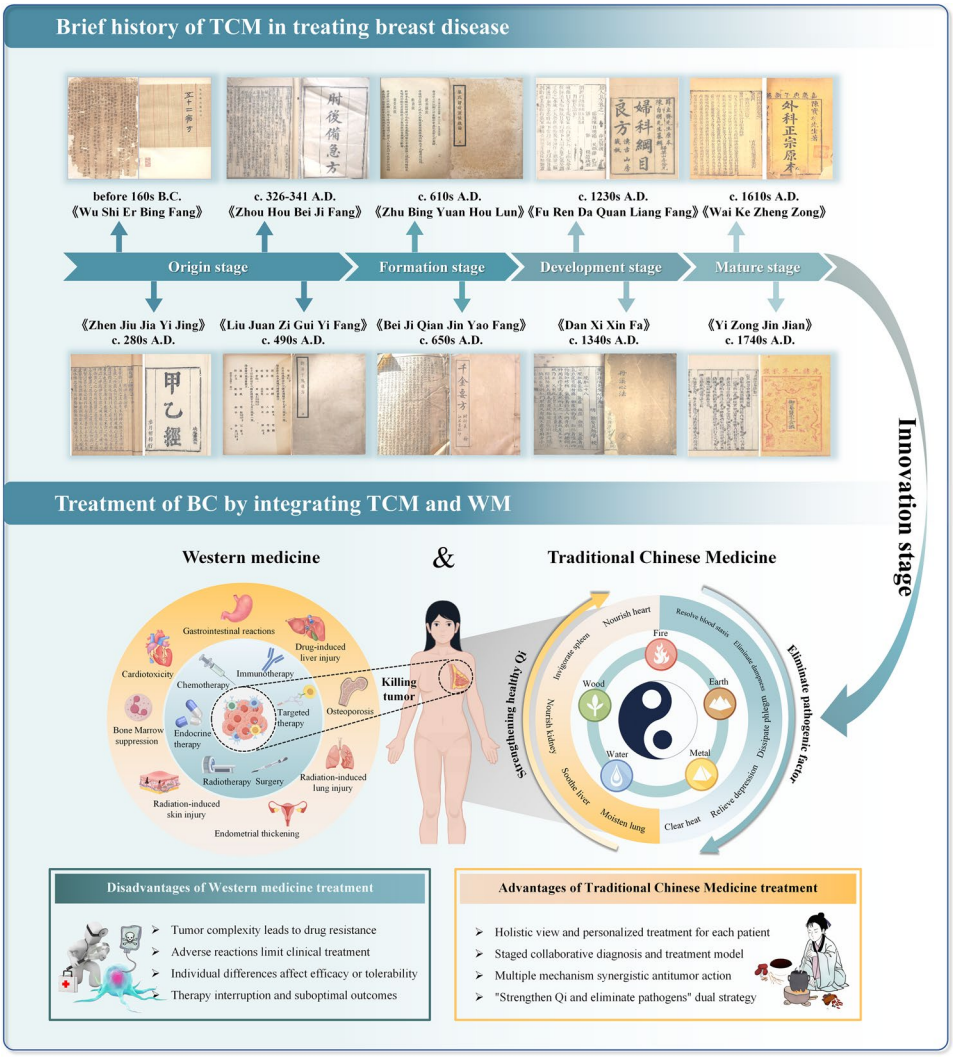

Fig. 1 A brief history of TCM and the comparison of the Western medicine and Traditional Chinese medicine in the treatment of BC

of WM in China, and a complementary integrated medical model has been formed by integrating modern WM treatments such as surgery, radiotherapy, and chemotherapy from with featured treatment of TCM such as syndrome differentiation and treatment, TCM regulation, and acupuncture therapy, and the combination of TCM and WM will demonstrate greater synergistic effects in the prevention and treatment of breast diseases with the development of precision medicine concepts around the world.

The treatment strategies of BC have been gradually standardized and continuously inherited and developed with the development of TCM, and there are many TCM formulas with reliable therapeutic effects in treating breast diseases (Table 1). We synthesized the ancient discussions and found that during the progression of BC, patients typically present with complex syndromes characterized by Qi stagnation, blood stasis, dual deficiency of liver and spleen, and thoroughfare vessel and conception vessel disharmony. Consequently, TCM therapeutic strategies emphasize a comprehensive approach involving boosting Qi, breaking stasis to dissipate masses, removing toxin, and strengthening liver-spleen to restore systemic homeostasis. The TCM treatment paradigm for BC integrates two complementary principles: "Fu-Zheng" (reinforcing healthy Qi) and "Qu-Xie" (eliminating pathogenic factors) (Fig. 1) [15]. This dual approach remarkably parallels the modern oncology's combination of chemotherapy and immunotherapy. The "Qu-Xie" strategy focuses on inducing multiple programmed cell death pathways in cancer cells, including apoptosis, ferroptosis, and autophagy, while simultaneously inhibiting BC cell proliferation and metastasis through modulation of specific signaling pathways. Conversely, the "Fu-Zheng" approach enhances the body's healthy Qi (Zheng-Qi) to boost immune surveillance and effector functions, thereby facilitating the identification and elimination of malignant cells.

TCM is a comprehensive medical system developed through ancient Chinese philosophy and millennia of clinical observation. While WM tends to isolate and treat specific disease entities, TCM emphasizes the dynamic equilibrium and interconnectedness of the body, mind, and environment with the unique theoretical framework and diagnostic methodologies. The core of TCM has been constructed through three foundational theories: Yin-Yang theory (complementary dualistic forces), Wu-Xing theory (Five Phases of systemic interactions), and Qi-Xue theory (the circulation of vital energy and blood via meridians) [16, 17]. The diagnostic and therapeutic approaches of TCM are personalized treatments for each patient, which is called syndrome differentiation (Bian Zheng Lun Zhi). Specifically, the doctors comprehensively collect the information of each patient through the *Four Diagnostic Methods*: observation (examination of the tongue and face), auscultation-olfaction (assessment of the voice and breath), inquiry (investigation of the symptoms and history), and palpation (evaluation of the pulse and abdomen), and identify the specific syndromes of each patient through the theoretical frameworks of TCM [18]. Ultimately, the doctors can formulate the personalized TCM formulas or non-drug therapies based on the patient's clinical manifestations, physical differences, disease stage and symptom pattern [19].

As suggested by "Standards of the Chinese Society of Chinese Medicine" [20], TCM offers unique perspectives in BC treatment, emphasizing stage-specific and syndrome-based therapeutic approaches. Notably, the clinical manifestations and syndrome patterns evolve dynamically as the disease progresses. During the early acute phase, when patients are first diagnosed with BC, surgery, radiotherapy, and chemotherapy are generally the principal treatment modalities. TCM works synergistically to support healthy Qi, reduce toxicity and the enhance efficacy of WM, thereby ensuring treatment completion. In the middle consolidation stage, TCM primarily focuses on regulating the patient's constitution, reinforcing healthy Qi and eliminating pathogenic factors. By modulating immune function and improving the TME, TCM helps reduce the risk of BC recurrence and metastasis. During the advanced palliative phase, when patients live with tumors, TCM aims to control disease progression, alleviate symptoms (such as pain and metastasis-related issues), prolong survival, and improve quality of life. The essence of TCM's staged treatment for BC is the "integration of syndrome differentiation and disease differentiation" utilizing tailored combinations of herbal medicines, external therapies, and acupuncture at each phase.

The clinical application of TCM in the treatment of BC

It is widely recognized that BC is a complex and heterogeneous disease that requires a personalized and comprehensive treatment approach. In contrast to WM, which often follows a "one-size-fits-all" model, TCM takes a more holistic approach, targeting multiple levels, pathways, and targets to produce complementary and synergistic effects [21]. Some classical TCM prescriptions with anti-BC properties have been applied for several thousand years and are still used in current. Furthermore, as adjunct therapies in BC, non-pharmacological TCM modalities such as acupuncture and therapeutic massage have demonstrated notable advantages, including high safety profiles, strong patient acceptance, and growing international recognition. Since the introduction of evidence-based medicine into TCM research, the researchers have emphasized improving the quality of evidence

Table 1 Ancient TCM formulas with reliable efficacy in the treatment of breast diseases [14]

Formula name	Major composition	Administration	Indications	Original source	Time	Author
Huangshu Gao	Rhei Radix et Rhizoma et al.	top.	Ru Yong	***Zhou Hou Bei Ji Fang***	326–341 A.D.	Hong Ge
Duru Formula	Scutellariae Radix, Ampelopsis Radix, Paeoniae Radix Alba	p.o., top.	Ru Yong	***Xiao Pin Fang***	454–473 A.D.	Yanzhi Chen
Danzhuye Tang	Lophatheri Herba, Ophiopogonis Radix, Astragali Radix, Paeoniae Radix Alba et al.	p.o.	Ru Yong	***Liu Juan Zi Gui Yi Fang***	499 A.D.	Juanzi Liu
Zhiruyong Formula	Ophiopogonis Radix, Scutellariae Radix, Paeoniae Radix Alba, Poria et al.	p.o.	Ru Yong	***Qian Jin Yao Fang***	652 A.D.	Simiao Sun
Zhirujian Formula	Angelicae Sinensis Radix, Paeoniae Radix Alba, Astragali Radix, Tribuli Fructus et al.	p.o.	Ru Yan	***Qian Jin Yi Fang***	682 A.D.	Simiao Sun
Siwu Jiaofutie Formula	Asini Corii Colla, Rhei Radix et Rhizoma, Asari Radix et Rhizoma et al.	top.	Ru Yong	***Wai Tai Mi Yao***	752 A.D.	Dao Wang
Fuzi San	Aconiti Lateralis Radix Praeparata, Radix et rhizoma Veratri Nigri..	top.	Ru Ju	***Tai Ping Sheng Hui Fang***	992 A.D.	Huaiyin Wang et al.
Neixiao San	Rhei Radix et Rhizoma, Scutellariae Radix, Coptidis Rhizoma, Pheretima et al.	top.	Ru Yong, Ru Jie He	***Tai Ping Sheng Hui Fang***	992 A.D.	Huaiyin Wang et al.
Gualou San	Trichosanthis Fructus, Olibanum	p.o.	Ru Yong	***Wei Ji Bao Shu***	1170 A.D.	Dong Xuan Ju Shi
Loulu San	Rhapontici Radix, Serpentis Periostracum, Trichosanthis Fructus	p.o.	Ru Yong	***San Yin Ji Yi Bing Zheng Fang Lun***	1174 A.D.	Wuze Chen
Zhike San	Aurantii Fructus, Paeoniae Radix Alba, Ginseng Radix et Rhizoma, Astragali Radix et al.	p.o.	Ru Yong	***Fu Ren Da Quan Liang Fang***	1237 A.D.	Ziming Chen
Zhiruyongxiaohe Formula	Arisaematis Rhizoma, Trichosanthis Fructus, Forsythiae Fructus, Citri Reticulatae Pericarpium Viride	p.o., top.	Ru He	***Dan Xi Zhi Fa Xin Yao***	1279–1368 A.D.	Zhenheng Zhu
Ruyongyou Formula	Aconiti Kusnezoffii Radix, Vignae Semen, Hibisci Mutabilis Folium	top.	Ru Yong	***Shi Yi De Xiao Fang***	1345 A.D.	Yilin Wei
Neituo Shengma Tang	Cimicifugae Rhizoma, Puerariae Lobatae Radix, Forsythiae Fructus, Astragali Radix et al.	p.o.	Ru Yong	***Wai Ke Li Li***	1531 A.D.	Ji Wang
Zaojiao San	Gleditsiae Sinensis Fructus, Olibanum et al.	p.o.	Ru Yong	***Chuang Yang Quan Shu***	1569 A.D.	Hanqing Dou
Furu Formula	Arisaematis Rhizoma, Pinelliae Rhizoma, Gleditsiae Spina, Angelicae Dahuricae Radix et al.	top.	Ru Yong	***Zheng Zhi Zhun Sheng***	1602 A.D.	Kentang Wang
Qinggan Jieyu Tang	Ginseng Radix et Rhizoma, Poria, Rehmanniae Radix Praeparata, Paeoniae Radix Alba et al.	p.o.	Ru He	***Ji Yin Gang Mu***	1602 A.D.	Zhiwang Wu
Shiliuwei Liuqi Yin	Angelicae Sinensis Radix, Chuanxiong Rhizoma, Paeoniae Radix Alba, Ginseng Radix et Rhizoma et al.	p.o.	Ru Yan	***Shou Shi Bao Yuan***	1615 A.D.	Tingxian Gong
Awei Huapi San	Ferulae Resina, Angelicae Sinensis Radix, Atractylodis Macrocephalae Rhizoma, Chuanxiong Rhizoma et al.	p.o..	Ru Jie He	***Wai Ke Zheng Zong***	1617 A.D.	Shigong Chen
Yiqi Yangrong Tang	Ginseng Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, Poria, Citri Reticulatae Pericarpium et al.	p.o.	Ru Yan	***Ji Yin Gang Mu***	1620 A.D.	Zhiwang Wu
Xiangbei Yangrong Tang	Atractylodis Macrocephalae Rhizoma, Ginseng Radix et Rhizoma, Poria, Citri Reticulatae Pericarpium et al.	p.o.	Ru Yan	***Nv Ke Zheng Zong***	1664 A.D.	Songan He, Tianqiu Pu
Huayan Tang	Ginseng Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, Astragali Radix, Angelicae Sinensis Radix et al.	p.o.	Ru Yan	***Dong Tian Ao Zhi***	1694 A.D.	Shiduo Chen
Xiaodu Yin	Citri Reticulatae Pericarpium Viride, Angelicae Dahuricae Radix, Angelicae Sinensis Radix, Bupleuri Radix et al.	p.o.	Ru Yong	***Yi Zong Jin Jian***	1742 A.D.	Qian Wu et al.
Shiquandabu Yinhua Tang	Ginseng Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, Rehmanniae Radix Praeparata, Astragali Radix et al.	p.o.	Ru Yong	***Tai Chan Xin Shu***	1771 A.D.	Guang Jing

Table 1 (continued)

Formula name	Major composition	Administration	Indications	Original source	Time	Author
Jiawei Xiaoyao San	Bupleuri Radix, Poria, Angelicae Sinensis Radix, Atractylodis Macrocephalae Rhizoma et al.	p.o.	Ru Yan	***Nv Ke Yao Zhi***	1803 A.D.	Xiuyuan Chen
Kaijie San	Angelicae Dahuricae Radix, Olibanum, Myrrha, Fritillariae Thunbergii Bulbus et al.	p.o.	Ru Yong	***Wai Ke Zheng Zhi Quan Shu***	1831 A.D.	Kechang Xu, Fa Bi
Ruchui Formula	Amomi Fructu, Abutilisemmen	p.o.	Ru Yan	***Qian Zhai Yi Hua***	1853 A.D.	Shixiong Wang
Rujufu Formula	Codonopsis Radix, Astragali Radix, Rehmanniae Radix Praeparata, Chuanxiong Rhizoma et al.	top.	Ru Ju	***Li Yue Pian Wen***	1864 A.D.	Shangxian Wu
Xiaoru Tang	Anemarrhenae Rhizoma, Forsythiae Fructus, Lonicerae Japonicae Flos, Trichosanthis Fructus et al.	p.o.	Ru Yong	***Yi Xue Zhong Zhong Can Xi Lu***	1909 A.D.	Xichun Zhang

Note: A.D.: Anno Domini; p.o.: per os; top.: topical

and accumulating appropriate evaluation data. High-quality clinical trials have demonstrated the efficacy of some TCM formulas and acupuncture in the treatment of BC (Tables 2 and 3). Here, we summarize the clinical evidence for nine extensively researched TCM herbal formulations and four major non-pharmacological TCM therapies used in BC management [20].

TCM formulas in the treatment of BC

Xiaoyao San is first mentioned in the Tai Ping Hui Min He Ji Ju Fang (formulas of the Bureau of the Taiping Huimin Pharmacy) in ancient China (960 A.D.-1279 A.D.) with the function of soothing liver, relieving depression, fortifying spleen, and nourishing the blood. Many clinical studies have shown that Xiaoyao San combined with chemotherapy can effectively alleviate the toxic reactions caused by chemotherapy, significantly reduce cancer-related fatigue in BC patients, and enhance the immune function of the body [22]. A systematic meta-analysis of 17 randomized controlled clinical trials (RCTs) involving 1,207 patients reported that Modified Xiaoyao San combined with chemotherapy showed multiple significant advantages in the treatment of BC compared with chemotherapy alone. Modified Xiaoyao San combined with chemotherapy significantly improved the short-term outcome of BC patients with solid tumors (odds ratio [OR] = 1.74; 95% confidence interval [CI]: [1.27, 2.39], $P = 0.0006$), substantially improved patients' quality of life (OR = 3.75, 95% CI: [2.58, 5.44], $P < 0.00001$), and prolonged the survival time of BC patients (OR = 2.19, 95% CI: [1.03, 4.66], $P = 0.04$). Specifically, the therapy was found to be effective in alleviating depression (mean differences [MD] = −12.96, 95% CI: [−16.09, −9.83], $P < 0.00001$), gastrointestinal adverse effects (OR = 0.26, 95% CI: [0.15, 0.44], $P < 0.00001$), myelosuppression increased white blood cells (OR = 0.32, 95% CI: [0.20, 0.50], $P < 0.00001$) platelets, (OR = 0.37, 95% CI: [0.2, 0.67], $P = 0.001$) and cardiotoxicity (OR = 0.16, 95% CI: [0.07, 0.36], $P < 0.00001$). However, there was no statistically significant difference between the combination therapy group and the chemotherapy-only group in terms of liver and kidney injuries induced by chemotherapy, the overall efficacy of Xiaoyao San in the treatment of BC is still remarkable [23].

Fuzheng Xiaoliu Tang is a kind of TCM decoction and its main effects are tonifying Qi and nourishing Yin, strengthening the spleen and stomach, and activating blood to dissipate masses. In the adjuvant treatment of BC patients following chemotherapy, this formulation has demonstrated significant and broad clinical value [24]. A systematic review of 15 studies involving a total of 1,258 participants showed that compared with patients who received standard treatment of WM, combination with Fuzheng Xiaoliu Tang significantly improved the clinical remission rate of BC patients (relative risk [RR] = 1.32, 95% CI: [1.17, 1.49]). In addition, Fuzheng Xiaoliu Tang was effective in enhancing patients' immune function, as evidenced by an increase in $CD4^+$ cell counts (MD = 4.57, 95% CI: [3.61, 5.54]), a rise in $CD4^+/CD8^+$ (MD = 0.20, 95% CI: [0.08, 0.33]), as well as a decrease in $CD8^+$ cell counts (MD = −1.85, 95% CI: [−2.64, −1.06]). More importantly, the formula was also effective in reducing the levels of the tumor markers cancer associated antigens 153 (CA153) and carcinoembryonic antigen (CEA) [25]. Fuzheng Xiaoliu Tang demonstrated a multifaceted and positive effect as adjuvant treatment after standard treatment of WM for BC patients.

Bazhen Tang was first mentioned in Ruizhutang Experienced Formula of the Yuan Dynasty, which has the effect of tonifying Qi and blood. Previous studies have shown that Bazhen tang combined with chemotherapy can effectively alleviate fatigue symptoms, reduce inflammatory responses, and significantly enhance immune function in BC patients [26]. The results of a meta-analysis that included 14 papers involving 922 BC patients showed that compared with chemoradiotherapy alone, Bazhen Tang combined with chemoradiotherapy could significantly improve the treatment efficacy (OR = 2.14, 95% CI: [1.33, 3.43], $P = 0.002$) and reduce the incidence of myelosuppression (OR = 0.31, 95% CI: [0.23, 0.43],

Table 2 Clinical application of TCM formulas in the treatment of BC

TCM	Medicinal Constituent	Patient Information	Study Details	Key Findings	Ref.
Sanhuang Plaster	Phellodendri Chinensis Cortex, Scutellariae Radix, Coptidis Rhizoma, Gardeniae Fructus	**Participants**: 80 cases of BC patients receiving radiotherapy	**Type of trial**: RCT **Intervention group**: Sanhuang Plaster combined with honey for local application on the radiation field **Control group**: Magnesium sulfate ointment for local application on the radiation field	1. Incidence of radiation-induced skin symptoms (edema, pruritus, etc.) significantly lower than control group ($P<0.05$). 2. Improved skin injury grading (higher proportion of grade ≤ II, lower proportion of grade ≥ III) ($P<0.05$).	[45]
Shirun Shaoshang Gao	Coptidis Rhizoma, Phellodendri Chinensis Cortex, Scutellariae Radix, Pheretima, Papaveris Pericarpium	**Participants**: 140 cases of BC patients receiving radiotherapy **Tumor stage**: 43 cases of stage I, 80 cases of stage II, 17 cases of stage IIIA	**Type of trial**: RCT **Intervention group**: ShiRun Shaoshang Gao after radiotherapy **Control group**: Biafine cream after radiotherapy	1. Higher quality-of-life score ($P<0.05$). 2. Lower incidence of radiation-induced skin injury ($P<0.05$). 3. Lower adverse reaction rate (1.43% versus 11.43%, $P<0.05$).	[46]
Tanreqing Injection	Scutellariae Radix, Pulvis Fellis Ursi, The bone of *Naemorhedus goral* (Hardwicke), Lonicerae Japonicae Flos, Forsythiae Fructus	**Participants**: 68 cases of BC patients complicated with acute radiation **Pathological type**: 3 cases of ductal carcinoma in situ, 50 cases of invasive ductal carcinoma, 7 cases of invasive lobular carcinoma, 8 cases of others	**Type of trial**: RCT **Intervention group**: Tanreqing Injection combined with Prednisolone **Control group**: Prednisolone	1. Higher total remission rate ($P<0.05$). 2. Improved radiation pneumonitis grading, KPS/FACT-B scores ($P<0.05$). 3. The levels of LN, PICP, and PCIII in both groups decreased, with those in the intervention group being lower ($P<0.05$).	[47]
Bailing Capsule	Fermented powder of Cordyceps	**Participants**: 60 cases of BC patients scheduled for surgical treatment **Tumor stage**: 19 cases of stage I, 27 cases of stage IIA, 14 cases of stage IIB	**Type of trial**: RCT **Intervention group**: Bailing Capsule + conventional treatment **Control group**: Conventional treatment	1. At 1 and 2 weeks post-surgery, the intervention group had higher $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ levels ($P<0.05$) and alleviated decreases in IgM, IgG, and IgA. 2. At 2 weeks post-surgery, the intervention group showed a better grading of TCM Qi-Yin deficiency syndrome ($P<0.05$).	[48]
Kangfuxin Liquid	Extracts of Dried Periplanetae	**Participants**: 50 cases of patients with BC whose drainage volume was still > 20 mL/d at 1 week after operation invasive **Tumor stage**: 21 cases of stage IIA, 25 cases of stage IIB, 4 cases of stage IIIA	**Type of trial**: RCT **Intervention group**: Kangfuxin Liquid combined with pressure bandaging and negative pressure drainage **Control group**: Pressure bandaging and negative pressure drainage	Postoperative drainage volume (10.48 ± 10.70 versus 18.24 ± 11.19 mL) and healing time (7.96 ± 2.49 versus 11.16 ± 3.99 days) significantly lower than control group ($P<0.05$).	[49]
Shengji Yuhong Plaster	Angelicae Sinensis Radix, Arnebiae Radix, Angelicae Dahuricae Radix, Calomelas, Draconis Sanguis, Rosin, Rhei Radix et Rhizoma	**Participants**: 80 cases of patients with flap necrosis and unhealed wound after radical **Pathological type**: 38 cases of invasive ductal carcinoma, 29 cases of ductal carcinoma, 13 cases of invasive lobular carcinoma	**Type of trial**: RCT **Intervention group**: Kangfuxin Liquid combined with Shengji Yuhong Plaster **Control group**: Kangfuxin Liquid	1. Necrosis sloughing time, wound healing time significantly shortened ($P<0.05$). 2. Inflammatory factors (IL-6, TNF-α) significantly reduced ($P<0.05$).	[50]
Pingxiao Capsule	Curcumae Radix, Strychni Semen Pulveratum, Agrimoniae Herba, Faeces Trogopterori, Alumen, Nitrum, Resina, Toxicodendri, Aurantii Fructus	15 RCTs involving 1402 BC patients	**Type of trial**: Meta-analysis **Intervention group**: Pingxiao Capsule combined with conventional treatment **Control group**: Conventional treatment	Improved objective remission rate (RR = 1.21, 95% CI: [1.09, 1.35], $P=0.0004$), disease control rate (RR = 1.15, 95% CI: [1.01, 1.31], $P=0.03$), TCM syndrome efficacy (RR = 1.27, 95% CI: [1.06, 1.53], $P=0.01$), quality of life (MD = 11.03, 95% CI: [0.90, 21.16], $P=0.03$), and $CD4^+/CD8^+$ (MD = 1.19, 95% CI: [0.28, 2.11], $P=0.01$), and reduced adverse reactions ($P<0.05$).	[51]

Table 2 (continued)

TCM	Medicinal Constituent	Patient Information	Study Details	Key Findings	Ref.
Xianling Gubao Capsule	Epimedii Folium, Dipsaci Radix, Salviae Miltiorrhizae Radix et Rhizoma, Anemarrhenae Rhizoma, Psoraleae Fructus, Rehmanniae Radix	**Participants**: 92 cases of postmenopausal BC patients with osteoporosis after postoperative endocrine therapy **Tumor stage**: 27 cases of stage II, 50 cases of stage III, 5 cases of stage IV	**Type of trial**: RCT **Intervention group**: Calcium carbonate tablets combined with Xianling Gubao Capsule **Control group**: Calcium carbonate tablets	The intervention group had higher lumbar spine and ilium BMD ($P < 0.05$), lower s-CTX, s-PINP ($P < 0.05$), higher BGP, and lower ALP ($P < 0.05$) than the control group.	[52]
Jintiange Capsule	Os Tigris	**Participants**: 61 cases of postmenopausal BC patients **Molecular subtype**: Hormone receptor-positive breast cancer	**Type of trial**: RCT **Intervention group**: Anastrozole + Jintiange Capsule + Caltrate D **Control group: A**nastrozole + Caltrate D	1. The intervention group had a higher total effective rate (74.19% versus 50%, $P < 0.05$). 2. After treatment, the lumbar bone mineral density, lumbar T-score, and serum alkaline phosphatase in the intervention group were all superior to those in the control group, with statistically significant differences (all $P < 0.05$).	[53]
Xiaobanxia Decoction	Pinelliae Rhizoma Praeparatum Cum Zingibere et Alumine, Zingiberis Rhizoma Recens	**Participants**: 128 cases of BC patients receiving postoperative chemotherapy	**Type of trial**: RCT **Intervention group**: Granisetron + Dexamethasone + Xiaobanxia Decoction **Control group**: Granisetron + Dexamethasone	1. Severity of nausea/vomiting significantly reduced in acute/delayed phases ($P < 0.05$). 2. Higher complete control rate over entire course (15.6% versus 7.8%, $P < 0.05$).	[54]
Xuanfu Daizhe Decoction	Inulae Flos, Aurantii Fructus Immaturus, Pinelliae Rhizoma Praeparatum Cum Zingibere et Alumine, Codonopsis Radix, Zingiberis Rhizoma Recens, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Jujubae Fructus	**Participants**: 60 cases of BC patients with nausea and vomiting after chemotherapy **Pathological type**: 35 cases of invasive ductal carcinoma, 18 cases of invasive lobular carcinoma, 5 cases of simple carcinoma, 2 cases of mucinous carcinoma	**Type of trial**: RCT **Intervention group**: Ondansetron combined with modified Xuanfu Daizhe Decoction **Control group**: Ondansetron intravenous drip 30 min before chemotherapy	The antiemetic effective rate in the intervention group significantly increased (93.3% versus 70.0%, $P < 0.05$), compared with the control group.	[55]
Bazhen Decoction	Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Poria, Angelicae Sinensis Radix, Chuanxiong Rhizoma, Paeoniae Radix Alba, Rehmanniae Radix Praeparata, Glycyrrhizae Radix et Rhizoma	**Participants**: 82 cases of BC patients after operation **Pathological type**: 55 cases of invasive ductal carcinoma, 20 cases of invasive lobular carcinoma, 6 cases of medullary carcinoma, 1 case of simple carcinoma	**Type of trial**: RCT **Intervention group**: Modified Bazhen Decoction **Control group**: Vitamin C intravenous drip Both groups were first given conventional perioperative antibiotic treatment	1. The total incidence of unhealed wound events in the intervention group was lower than that in the control group (12.2% versus 90.2%, $P < 0.05$). 2. The indwelling time of the drainage tube in the intervention group was shorter than that in the control group ($P < 0.05$).	[56]
		Participants: 79 cases of BC patients	**Type of trial**: RCT **Intervention group**: Bazhen Decoction combined with EC-T chemotherapy regimen **Control group**: EC-T chemotherapy regimen	1. The scores of TCM syndromes and CRF in the intervention group were lower than those in the control group ($P < 0.05$).2. The levels of TNF-α, IFN-γ, IL-6, and IL-10 in the intervention group were lower than those in the control group ($P < 0.05$).3. In the intervention group, the levels of $CD4^+$ and NK cells increased, while the level of $CD8^+$ decreased ($P < 0.05$).	[26]

Table 2 (continued)

TCM	Medicinal Constituent	Patient Information	Study Details	Key Findings	Ref.
Shenfu Injection	Ginseng Radix et Rhizoma Rubra, Aconiti Lateralis Radix Praeparata	**Participants**: 150 cases of BC patients receiving postoperative chemotherapy **Pathological type**: 80 cases of invasive ductal carcinoma, 10 cases of invasive lobular carcinoma, 12 cases of medullary carcinoma, 48 cases of simple carcinoma **Tumor stage**: 9 cases of stage IB, 32 cases of stage II, 40 cases of stage IIIA, 40 cases of stage IIIB, 23 cases of stage IV	**Type of trial**: RCT **Intervention group**: Chemotherapy combined with Shenfu Injection treatment **Control group**: Conventional chemotherapy	The intervention group had a higher total effective rate (96.00% versus 86.67%, $P < 0.05$), higher $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ and NK cell levels, and lower adverse reaction rate (4.00% versus 14.67%, $P < 0.05$), compared with the control group.	[57]
Qijiao Shengbai Capsule	Jujubae Fructus, Asini Corii Colla, Ginseng Radix et Rhizoma, Epimedii Folium, Sophorae Flavescentis Radix, Astragali Radix, Angelicae Sinensis Radix	**Participants**: 312 cases of lung cancer and BC patients with qi and blood deficienc syndrome scheduled for chemotherapy **Pathological type**: 83 cases of non-specific invasive carcinoma, 36 cases of specific invasive carcinoma, 4 cases of non-invasive carcinoma	**Type of trial**: Randomized double-blind, positive drug controlled, multi-center clinical trial **Intervention group**: Qijiao Shengbai Capsule **Control group**: Andolin Capsule	The improvement rate of palpitations and insomnia in the intervention group was better than that in the control group ($P < 0.05$).	[58]
Compound Danshen Dripping Pill	Salviae Miltiorrhizae Radix et Rhizoma, Notoginseng Radix et Rhizoma, Borneolum Syntheticum	**Participants**: 110 cases of BC patients receiving chemotherapy after surgery	**Type of trial**: RCT **Intervention group**: CAF regimen + Compound Danshen Dripping Pills **Control group**: CAF regimen	The intervention group had a lower abnormal electrocardiogram incidence (27.27% versus 61.82%, $P < 0.05$), higher SOD and LVEF, and lower MDA, CK-MB, and cTnI levels ($P < 0.05$).	[59]
Qili Qiangxin Capsule	Astragali Radix, Ginseng Radix et Rhizoma, Aconiti Lateralis Radix Praeparata, Salviae Miltiorrhizae Radix et Rhizoma, Descurainiae Semen Lepidii Semen, Alismatis Rhizoma, Polygonati Odorati Rhizoma, Cinnamomi Ramulus, Carthami Flos, Periplocae Cortex, Citri Reticulatae Pericarpium	**Participants**: 88 cases of BC patients receiving 8 courses of postoperative chemotherapy	**Type of trial**: RCT **Intervention group**: Adjuvant chemotherapy + Qili Qiangxin Capsules **Control group**: Adjuvant chemotherapy + symptomatic supportive treatment	After 4 and 8 chemotherapy courses, the intervention group had lower NT-proBNP, higher LVEF and 6MWD ($P < 0.05$), and lower heart failure incidence ($P < 0.05$).	[60]
Wuling Capsule	Bupleuri Radix, Ganoderma, Salviae Miltiorrhizae Radix et Rhizoma, Schisandrae Chinensis Fructus	**Participants**: 120 cases of BC patients with chemotherapy-induced liver injury **Tumor stage**: 72 cases of stage III, 48 cases of stage IV	**Type of trial**: RCT **Intervention group**: Wuling Capsules **Control group**: Compound Glycyrrhizin Tablets	The intervention group had lower ALP, ALT, AST, and TBIL levels ($P < 0.05$) and a lower total adverse reaction rate ($P < 0.05$).	[61]

Table 2 (continued)

TCM	Medicinal Constituent	Patient Information	Study Details	Key Findings	Ref.
Chaihu Guizhi Decoction	Cinnamomi Ramulus, Scutellariae Radix, Ginseng Radix et Rhizoma, Glycyrrhizae Radix et Rhizoma, Pinelliae Rhizoma, Paeoniae Radix Alba, Jujubae Fructus Zingiberis Rhizoma Recens, Bupleuri Radix	**Participants**: 78 cases of patients with advanced BC **Tumor stage**: 36 cases of stage III, 42 cases of stage IV	**Type of trial**: RCT **Intervention group**: Zhenqi Fuzheng Capsules + Chaihu Guizhi Decoction **Control group**: Zhenqi Fuzheng Capsules	The intervention group had a higher total effective rate (78.05% versus 54.05%, $P < 0.05$); decreased CA125, TSGF, CEA, etc., and increased physical status score, $CD4^+$, $CD4^+/CD8^+$ (all $P < 0.05$) compared with the control group.	[62]
Zaoren Ningxin Capsule	Ziziphi Spinosae Semen, Platycladi Semen, Albiziae Cortex, Panacis Quinquefolii Radix, Salviae Miltiorrhizae Radix et Rhizoma, Rehmanniae Radix, Chuanxiong Rhizoma	**Participants**: 90 cases of BC patients with CRF	**Type of trial**: RCT **Intervention group**: Zaoren Ningxin Capsules **Control group**: Placebo Formula Capsules	1. In the intervention group, the scores of behavior, emotion, sensation, total score of PFS-R, and TCM syndrome scores were all lower than those in the control group ($P < 0.05$). 2. The scores of sleep onset latency, sleep duration, sleep disturbance, daytime dysfunction, and sleep quality in the intervention group were all lower than those in the control group ($P < 0.05$).	[63]
Shenqi Fuzheng Injection	Codonopsis Radix, Astragali Radix	**Participants**: 20 RCTs involving 2,095 BC patients receiving chemotherapy	**Type of trial**: Meta-analysis **Intervention group**: conventional chemotherapy + Shenqi Fuzheng Injection **Control group**: Conventional Chemotherapy	Improve the treatment response rate (RR = 1.41, 95% CI: [1.26, 1.58], $P < 0.00001$), inhibit the decrease of Th lymphocytes (MD = 215.03, 95% CI: [207.68, 222.39], $P < 0.00001$).	[64]
Kanglaite Injection	The oil of Semen Coicis, Soya Lecithin, Glycerol	**Participants**: 120 cases of BC patients scheduled to undergo modified radical mastectomy **Pathological type**: 91 cases of invasive lobular carcinoma, 22 cases of invasive ductal carcinoma, 7 cases of small duct carcinoma **Tumor stage**:84 cases of stage I, 36 cases of stage II	**Type of trial**: RCT **Intervention group**: Neoadjuvant chemotherapy + Kanglaite Injection **Control group**: Neoadjuvant chemotherapy before modified radical mastectomy	After chemotherapy, the intervention group had decreased $CD8^+$ and increased $CD4^+$, $CD3^+$ ($P < 0.05$); greater reduction in VEGF ($P < 0.05$); lower incidences of granulocytopenia, nausea and vomiting, fever and thrombocytopenia ($P < 0.05$).	[65]
Yangzheng Mixture	Ginseng Radix et Rhizoma Rubra, Astragali Radix, Lycii Fructus, Ligustri Lucidi Fructus, Polyporus, Poria	**Participants**: 120 cases of BC patients receiving chemotherapy after surgery **Tumor stage**: 51 cases of stage II, 58 cases of stage III, 11 cases of stage IV	**Type of trial**: RCT **Intervention group**: General Supportive Treatment + Kang'ai Injection **Control group**: General Supportive Treatment + Yangzheng Mixture	1. The intervention group had a lower score of discomfort symptoms than the control group ($P < 0.05$). 2. After chemotherapy, the intervention group showed a higher WBC count, and lower levels of TNF-α and IL-6 compared with the control group ($P < 0.05$). 3. The intervention group had a higher level of FEER and lower levels of FEIR and RBC-ICR than the control group ($P < 0.05$).	[66]

Table 2 (continued)

TCM	Medicinal Constituent	Patient Information	Study Details	Key Findings	Ref.
Fuzheng Hewei Liquid	Codonopsis Radix, Ophiopogonis Radix, Schisandrae Chinensis Fructus, Atractylodis Macrocephalae Rhizoma, Poria, Poria cum Radix Pini, Eriobotryae Folium, Pinelliae Rhizoma Praeparatum Cum Zingibere et Alumine, Perillae Caulis, Coicis Semen, Aurantii Fructus, Raphani Semen, Setariae Fructus Germinatus, Hordei Fructus Germinatus, Glycyrrhizae Radix et Rhizoma	**Participants**: 60 cases of female BC patients receiving highly emetogenic chemotherapy regimens **Molecular subtype**: 27 cases of Luminal type, 16 cases of triple-negative type, 27 cases of HER2-positive type **Tumor stage**: 10 cases of Stage I, 31 cases of Stage II, 19 cases of stage III and above	**Type of trial**: RCT **Intervention group**: Ondansetron + Dexamethasone + Fuzheng Hewei Mixture **Control group**: Ondansetron + Dexamethasone	1. The intervention group had a higher effective rate of delayed nausea and vomiting than the control group ($P < 0.05$). 2. During the acute vomiting phase, the difference in serum 5-HT concentration in the experimental group was greater than that in the control group ($P < 0.01$). 3. After chemotherapy, serum albumin levels in the intervention group were higher than that in the control group ($P < 0.05$).	[67]
Zishui Qinggan Yin	Rehmanniae Radix Praeparata, Dioscoreae Rhizoma, Corni Fructus, Moutan Cortex, Poria, Alismatis Rhizoma, Bupleuri Radix, Paeoniae Radix Alba, Gardeniae Fructus, Angelicae Sinensis Radix, Ziziphi Spinosae Semen	**Participants**: 100 cases of BC patients with insomnia after surgery	**Type of trial**: RCT **Intervention group**: Postoperative Basic Treatment + Estazolam Tablets + Zishui Qinggan Decoction **Control group**: Postoperative Basic Treatment + Estazolam Tablets	The intervention group had higher N2/N3 sleep stages, REM sleep, total sleep time, and sleep efficiency ($P < 0.05$); lower WASO, sleep latency ($P < 0.05$); lower HAMA score, and higher WHO-QOL-BREF scores ($P < 0.05$).	[68]
Liuwei Dihuang Pills	Rehmanniae Radix Praeparata, Corni Fructus, Moutan Cortex, Dioscoreae Rhizoma, Poria, Alismatis Rhizoma	**Participants**:72 cases of BC patients eligible for endocrine therapy with AIs	**Type of trial**: RCT **Intervention group**: AIs + Vitamin D + Calcium Supplements + Liuwei Dihuang Pills **Control group**: AIs + Vitamin D + Calcium Supplements	1.After 12 months of treatment, the BMD of the 2nd to 4th lumbar vertebrae in the intervention group increased significantly ($P < 0.001$). 2.The BMD of the Ward's triangle in both femurs rebounded compared with that at 6 months of treatment and increased significantly compared with that before treatment ($P = 0.005$).	[69]
Compound Cantharis Capsule	Mylabris, Ginseng Radix et Rhizoma, Astragali Radix, Acanthopanacis Senticosi Radix et Rhizoma Seu Caulis, Sparganii Rhizoma, Scutellariae Barbatae Herba, Curcumae Rhizoma, Corni Fructus, Ligustri Lucidi Fructus, Pulvis Fellis Ursi, Glycyrrhizae Radix et Rhizoma	**Participants**: 78 cases of BC patients receiving chemotherapy after surgery **Pathological types**: 11 cases of medullary carcinoma, 9 cases of adenocarcinoma, 27 cases of invasive lobular carcinoma, and 31 cases of invasive ductal carcinoma	**Type of trial**: RCT **Intervention group**: Chemotherapy (CEF) + Compound Banmao Capsules **Control group**: Chemotherapy (CEF)	The intervention group had a higher total effective rate (87.18% versus 66.66%, $P < 0.05$); lower symptom scores at 6 and 9 weeks ($P < 0.01$); higher IgA, IgM, and lower $CD4^+/CD8^+$, $CD8^+$, etc. ($P < 0.01$).	[70]

Table 2 (continued)

TCM	Medicinal Constituent	Patient Information	Study Details	Key Findings	Ref.
Zhenqi Fuzheng Granules	Astragali Radix, Ligustri Lucidi Fructus	**Participants**: 112 cases of BC patients **Tumor stage**: 43 cases of Stage I, 37 cases of Stage II, 32 cases of Stage III **Pathological type**: 95 cases of invasive ductal carcinoma, 14 cases of invasive lobular carcinoma, and 3 cases of special-type breast cancer	**Type of trial**: Observational study **Intervention group**: Chemotherapy (CAF) + Granisetron + Zhenqi Fuzheng Granules **Control group**: Chemotherapy (CAF) + Granisetron	1. Compared with the control group, the objective response rate in the intervention group was increased ($P < 0.01$), while the local tumor recurrence rate, distant metastasis rate, and incidence of adverse reactions were all decreased ($P < 0.05$). 2. After treatment, the $CD8^+$ level in both groups were decreased, and the levels of $CD4^+$and $CD4^+/CD8^+$ were increased ($P < 0.05$); moreover, the intervention group was superior to the control group ($P < 0.05$).	[71]
Shenyi Capsule	Ginsenoside Rg3	**Participants**: 56 female patients with BC who relapsed after multiple courses of chemotherapy following surgery **Tumor stage**: Stage IV	**Type of trial**: RCT **Intervention group**: Shenyi Capsule + Capecitabine **Control group**: Capecitabine	1. Compared with the control group, the incidence rates of leukopenia and fatigue in the intervention group were reduced (42.9% versus 17.9%, 32.1% versus 7.1%, $P < 0.05$). 2. The serum VEGF level in the intervention group decreased ($P < 0.05$).	[72]
Aiyu Capsule	Cremastrae Pseudobulbus Pleiones Pseudobulbus, Solani Lyrati Herba, Epimedii Folium, Sophorae Flavescentis Radix, Angelicae Sinensis Radix, Atractylodis Macrocephalae Rhizoma, Ginseng Radix et Rhizoma	**Participants**: 136 cases of postmenopausal HR positive BC patients **Tumor stage**: Stage IV	**Type of trial**: RCT **Intervention group**: Anastrozole Tablets + Aiyu Capsules **Control group**: Anastrozole Tablets	The intervention group had a higher clinical efficacy rate (76.5% versus 60.3%, $P < 0.05$); reduced tumor diameter, TCM symptom scores, and tumor markers (CA15-3, CEA, etc.) ($P < 0.05$), and increased FACT-B score ($P < 0.05$).	[73]

Note: 6MWD: 6-Minute Walk Distance; AC-T: Doxorubicin and Cyclophosphamide followed by Taxane; AIs: aromatase inhibitors; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BGP: bone gla protein; BMD: bone mineral density; CAF: Cyclophosphamide + Doxorubicin + Fluorouracil; CEF: cyclophosphamide epirubicin fluorouracil; CK-MB: creatine kinase-mb; cTnI: cardiac troponin I; FACT-B: functional assessment of cancer therapy-breast; HAMA: hamilton anxiety scale; KPS: Karnofsky performance status; LN: Laminin; LVEF: left ventricular ejection fraction; MDA: malondialdehyde; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PICP: Procollagen type I carboxy-terminal propeptide; PCIII: Procollagen type III; REM: rapid eye movement; s-CTX: Serum C-terminal telopeptide of type I collagen; SOD: superoxide dismutase; s-PINP: serum N-terminal propeptide of type I procollagen; TBIL: total bilirubin; TSGF: tumor specific growth factor; VEGF: vascular endothelial growth factor; WASO: wake after sleep onset; WHOQOL-BREF: World Health Organization Quality of Life-BREF

$P < 0.00001$), and patients' white blood cells, neutrophils, and platelets were significantly higher than those of patients treated with chemoradiotherapy alone. In addition, the counts of T-lymphocyte subpopulations $CD3^+$ (MD = 8.90, 95% CI: [4.26, 13.54], $P = 0.0002$) and $CD4^+$ (MD = 9.47, 95% CI: [3.34, 15.61], $P = 0.002$) were also significantly higher in patients with Bazhen Tang combined with chemoradiotherapy than in patients with chemoradiotherapy alone, which further confirmed its positive role in regulating immune function [27].

Huaier Granule is a modern Chinese medicine preparation prepared by the Chinese medicine Sophora Fructus mycelium using modern pharmaceutical technology. Huaier Granule has the functions of activating blood to dissipate masses, and is widely used in the adjuvant treatment of various malignant tumors, such as BC, liver cancer, and lung cancer. Zhang et al. conducted a retrospective study on 284 BC patients treated with or without Huaier Granule, and the results showed that the patients treated with Huaier Granule had a longer disease-free survival (DFS). Serum tumor marker levels were reduced to the normal range after treatment with Huaier Granule, and Karnofsky performance status (KPS) scores were increased in BC patients [28]. Another study found that locust ear granules improved DFS and overall survival (OS) in patients with early-stage invasive BC, suggesting that locust ear granules have potential benefit in this population [29]. A meta-analysis that included 27 trials involving 2,562 BC patients showed that Huaier Granule in combination with conventional therapy significantly improved overall response and quality of life, prolonging OS and DFS at 2 and 5 years, in addition to a significant enhancement of immune function in patients following the combined intervention, with the percentage of $CD3^+$, $CD4^+$, and natural killer cells and the $CD4^+/CD8^+$ ratio were significantly higher. In addition, the incidence of myelosuppression and hepatotoxicity was lower in patients treated with Huaier Granule in combination

Table 3 Clinical application of TCM non-drug interventions in the treatment of BC

Cancer complication	Intervention	Acupoints	Safety Assessment	Outcome	Ref.
Insomnia	**Participant Characteristics**: BC patients with chemotherapy-associated insomnia **Intervention Group**: Electroacupuncture on body acupoints and auricular acupressure ($n=69$) **Control Group**: Sham Electroacupuncture, Sham Auricular Acupressure ($n=69$)	**Body acupoints**: EX-HN1, GV 20, GV 24, PC 6, KI 3, SP 6 **Auricular Acupressure**: Heart, Shenmen, Sympathetic	Treatment-related AEs were mild. The most common AE was bruising. No participants discontinued treatments due to AEs.	1. The ISI-measured severity of insomnia reduced in 2 groups (all $P<0.001$). 2. Acupuncture is improving sleep onset latency, total sleep time and sleep efficiency.	[94]
	Participant Characteristics: BC survivors with insomnia **Intervention Group**: 10 treatments of auricular acupuncture within 5 weeks ($n=26$) **Control Group**: A single session of psychoeducation plus an insomnia advice booklet ($n=26$)	Postantitragal Belt, Helix Channel, and Shenmen	A total of 55 AEs occurred in the auricular acupuncture group. Bruising, pain pressure sensitivity, hot flushes, insatiable hunger, fatigue were judged to be intervention-related by the researchers	Auricular acupuncture group showed a stronger increase in sleep quality ($P=0.031$, $\eta^2_p=0.094$), improved stress ($P=0.030$, $\eta^2_p=0.094$), anxiety ($P=0.001$, $\eta^2_p=0.192$), and fatigue ($P=0.006$, $\eta^2_p=0.148$)	[95]
Chemotherapy-induced Peripheral Neuropathy (CIPN)	**Participant Characteristics**: BC survivors with CIPN **Intervention Group**: 18 sessions of acupuncture over 8 weeks ($n=20$) **Control Group**: Usual care over 8 weeks, followed by nine sessions of acupuncture over 8 weeks ($n=20$)	Ex-LE12, Ex-LE10, Extra 27, TE 5 (TW 5), LR 3, LI 11, ST 36, SP 9, SP 6, K 3, Extra 2	2 participants (1 in each group) reported mild reactions: grade 1 pruritis in the feet, grade 2 joint pain.	1. Acupuncture improvements in PNQ sensory score (-1.0 ± 0.9 versus -0.3 ± 0.6, $P=0.01$), FACT-NTX summary score (8.7 ± 8.9 versus 1.2 ± 5.4, $P=0.002$), and BPI-SF pain severity score (-1.1 ± 1.7 versus 0.3 ± 1.5, $P=0.03$) 2. Improvements in neuropathic symptoms from an 8-week acupuncture treatment regimen.	[77]
	Participant Characteristics: BC patients with CIPN **Real Acupuncture Group**: 8 weeks of electroacupuncture **Sham Acupuncture Group: R**eceived a noninsertion procedure on nonacupoints **Usual Care Group**: not received any interventions throughout the study period	LI 4, PC 6, SI 3, LR 3, GB 42, ST 40, Bafeng 2, Bafeng 3	Adverse events were few and mild.	1. Compared with usual care, NRS-measured pain, tingling, and numbness significantly decreased in real acupuncture. 2. Mean absolute reduction in CIPN pain was greatest in real acupuncture (– 1.75, 95% CI: [– 2.69, – 0.81]).	[96]
	Participant Characteristics: survivors of solid tumors with persistent moderate-to-severe CIPN **Real Acupuncture Group**: 10 treatments of acupuncture within 8 weeks ($n=27$) **Sham Acupuncture Group**: 10 treatments of sham acupuncture within 8 weeks ($n=24$) **Usual Care Group**: Received no acupuncture treatments or any other interventions ($n=24$)	**Auricular Acupuncture**: Shenmen, Point Zero, and a Third Electrodermal Active Point **Bilateral Body**: LI 4, PC 6, SI 3, LR 3, GB 43, ST 40, Bafeng 2, Bafeng 3	6 patients in the real acupuncture group reported grade 1 AEs such as pain at the needling site, bruising, and feeling claustrophobic with the eye mask on.	1. Compared with baseline, FACT/GOG-NTX, HADS anxiety, and ISI scores improved in acupuncture group. 2. Compared with usual care group, at week 8, FACT/GOG-NTX scores increased in acupuncture group. 3. Acupuncture may improve CIPN-related symptoms and quality of life in cancer survivors with persistent CIPN.	[97]

Table 3 (continued)

Cancer complication	Intervention	Acupoints	Safety Assessment	Outcome	Ref.
Pain Related to AIs	**Participant Characteristics**: postmenopausal women with early-stage BC who were taking an aromatase inhibitor and scored at least 3 on the BPI-WP **True Acupuncture Group**: 12 acupuncture sessions over 6 weeks (2 sessions per week), followed by 1 session per week for 6 weeks ($n=110$) **Sham Acupuncture Group**: In keeping with true acupuncture ($n=59$) **Waitlist Control Group**: Not receive any intervention ($n=57$)	**Body acupoints**: SJ 5, GB 41, GB 34, LI 4, LI 4, KD 3 **Auriculara-cupressure**: Shenmen, Kidney, Liver, Upper Lung, Sympathetic	In the true acupuncture group experienced grade 1 bruising (47%) than in the sham acupuncture group (25%, $P=0.01$) There was 1 episode of grade 2 presyncope in the true acupuncture group and 1 episode in the sham acupuncture group.	1. From baseline to 6 weeks, the mean observed BPI-WP score decreased by 2.05 points (reduced pain) in the true acupuncture group. 2. True acupuncture resulted in a statistically significant reduction in joint pain at 6 weeks.	[78]
Pain among Cancer Survivors with Insomnia	**Participant Characteristics**: Cancer survivors with comorbid pain and insomnia **Acupuncture Group**: Received acupuncture twice weekly for 2 weeks, then weekly for 6 more weeks, for a total of 10 treatments for 8 weeks ($n=80$) **CBT-I Group**: Received five weekly sessions of CBT-I followed by two biweekly sessions, for seven total sessions over 8 weeks ($n=80$)	**Body acupoints**: H.T.7, Sp. 6, GV 20, GV 24 **Auricular acupoints**: Shenmen Sympathetic	9 reported AEs. Most were related to the needling site and included soreness, itchiness, and pain.	1. Acupuncture significantly reduced average pain severity (mean = −1.4 points, 95% CI: [−2.0, −0.8], $P<0.001$). 2. Acupuncture produced more rapid and sustained reduction in pain severity compared with CBT-I, which contributed to a clinically meaningful insomnia response to acupuncture.	[98]
Chronic Pain after Mastectomy	**Participant Characteristics**: Patients were women scheduled for radical mastectomy under general anesthesia **Sham-operated Group**: Received electrode attachment but without stimulation ($n=188$) **Single Acupoint Group**: TEAS was applied for 30 min before anesthesia induction ($n=198$) **Combined Acupoint Group**: TEAS was applied for 30 min before anesthesia induction ($n=190$)	PC 6, CV 17	1 patient in the single acupoint group reported discomfort in the skin area attached to the electrodes.	1. Study found a lower incidence of chronic pain at 6 months after mastectomy in the combined-acupoint TEAS group (22.1%) than that in the sham (34.6%) and single-acupoint TEAS groups (36.4%). 2. Remifentanil consumption during surgery and postoperative nausea and vomiting at 24 h after surgery were lower in the combined acupoint group than that in the sham-operated group.	[99]
Climacteric-like Symptoms in BC	**Participant Characteristics**: Female gender, diagnosed with BC, receiving tamoxifen treatment for at least 6 months, and experiencing climacteric-like symptoms **Acupuncture Group**: 10 weekly sessions of manual acupuncture ($n=20$) **Sham Acupuncture Group**: 10 weekly sessions of sham acupuncture ($n=20$) **Waitlist Control Group**: 10 weeks on a wait-list ($n=20$)	GV 16, GV 20, BL 23, CV 6	Minor local bruises from needling. No participants discontinued treatments due to AEs.	1. Acupuncture group improved BDI-II ($P<0.001$), PSQI ($P<0.002$), and MRS ($P<0.004$). 2. Acupuncture improved sleep, and mental and emotional distress symptoms.	[100]

Table 3 (continued)

Cancer complication	Intervention	Acupoints	Safety Assessment	Outcome	Ref.
Hot Flashes in Hormone Receptor-positive BC	**Participant Characteristics**: BC patients were receiving endocrine therapy and experiencing hot flashes **Acupuncture Group**: 20 acupuncture sessions over 10 weeks included manual acupuncture and electroacupuncture ($n=79$) **Delayed Acupuncture Control Group**: Received usual care, then crossed over to acupuncture with a reduced intensity ($n=79$)	**Core acupuncture points**: SP 6, LI 11, Yintang, GV 20, and Shenmen/ear **optional points**: LR 3, ST 36, K 3, PC 7, CV 6, Heart/ear	There were no serious AEs reported from the three trial sites in response to the acupuncture intervention in both group.	1. Acupuncture statistical improvements in the endocrine symptom subscale score (5.1 ± 0.9 versus 0.2 ± 1.0, $P=0.0003$), the hot flash score (-5.3 ± 0.9 versus -1.4 ± 0.9, $P<0.003$), and the FACT-Breast total score (8.0 ± 1.6 versus -0.01 ± 1.6, $P=0.0005$). 2. Acupuncture led to statistically and clinically meaningful improvements in hot flashes, endocrine symptoms, and BC-specific quality.	[101]
Hot flushes and Night Sweats (HFNS)	**Participant Characteristics**: Early BC patients who received adjuvant hormonal treatments (tamoxifen or AIs) for ≥ 6 months experienced symptoms such as HFNS. Data were analyzed from 415 referrals to a service offering women eight standardized treatments using the National Acupuncture Detoxification Association (NADA) protocol	Sympathetic, Shenmen, Kidney Point, Liver Point, Lung Point	Two AEs were reported, that is dizziness and nausea, neither were serious.	1. Median daily frequency of HFNS reduced from 9.6 (IQR 7.3) to 5.7 (IQR 5.8) at EOT and 6.3 (IQR 6.5) 18 weeks after EOT. 2. HFRS problem rating showed a clinically meaningful reduction of ≥ 2 points at all measurement points. 3. Improvements in several symptoms associated with the menopause.	[102]
	Participant Characteristics: BC patients experiencing at least moderate-level hot flashes **Acupuncture Group**: Acupuncture + Enhanced Self-care ($n=85$) **Control Group**: Enhanced Self-care ($n=105$)	A TCM evaluation of the tongue and radial pulses was performed to identify the prevailing syndrome and consequently choose appropriate acupoints in addition to 3 common acupoints (i.e. SP 6, LI 11, CV 4)	12 patients in the acupuncture arm experienced mild AEs (muscle pain, headache, and one menstrual bleed). No serious AEs were reported.	1. Acupuncture group was associated with a lower hot flash score than enhanced self-care at EOT ($P<0.001$) and at 3- and 6-month post-treatment follow-up visits ($P=0.0028$ and 0.001, respectively). 2. Acupuncture was also associated with fewer climacteric symptoms and higher quality of life in the vasomotor, physical, and psychosocial dimensions ($P<0.05$).	[75]

Table 3 (continued)

Cancer complication	Intervention	Acupoints	Safety Assessment	Outcome	Ref.
Chemotherapy-induced Nausea and Vomiting	**Participant Characteristics**: BC patients who received the AC (Anthracyclines and Cyclophosphamide) chemotherapy regimen **Acupuncture Group**: Combined acupuncture with antiemetic regimens **Control Group**: A triple antiemetic regimen	PC 6, ST 36, CV 12, SP 4, BL 20, BL 21	The major AEs in the two groups were headache, diarrhea and constipation. all of them were grades 1 to 2 and had no serious impact on patients.	1. Acupuncture group decreased the frequency of nausea and vomiting ($P=0.034$). 2. ECOG-PS score in the acupuncture group was significantly improved ($P=0.004$). 3. Reduce the incidence of adverse side effects of antiemetic drugs.	[103]
	Participant Characteristics: BC patients undergoing highly emetogenic chemotherapy **True Electroacupuncture Group**: Standard Triple Antiemetic Therapy + True Electroacupuncture ($n=120$) **Sham Electroacupuncture Group**: Standard Triple Antiemetic Therapy + Sham Electroacupuncture ($n=119$)	ST 36 (bilateral), PC 6, LI 4	Bruising is the most common AE (18.5% versus 8.5%, $P=0.026$). Only 1 patient in the true electroacupuncture group discontinued treatment because of an AE.	True electroacupuncture enhanced total control (4.3% versus 13.4%, $P=0.014$), no significant nausea (37.9% versus 58.8%, $P=0.001$), no nausea (4.3% versus 13.4%, $P=0.014$), and nausea VAS score = 0 mm (4.3% versus 12.6%, $P=0.023$).	[104]
Chemotherapy-induced Constipation	**Participant Characteristics**: BC patients receiving chemotherapy **Experimental Group**: Auricular acupressure was applied to 7 auricular acupoints for 6 weeks using vaccaria seeds ($n=28$) **Control Group**: Received the usual care ($n=28$)	Rectum, Large Intestine Spleen, Lung, San Jiao, Subcortex, Sympathesis	Auricular acupressure carries no side effects.	1. The experimental group reduced constipation-assessment scores ($P<0.001$). 2. The experimental group improved stool-form scores ($P=0.003$). 3. The experimental group reduced patient assessment of constipation–quality of life scores ($P<0.001$).	[105]
Chemotherapy-related Gastrointestinal Discomfort Symptoms	**Participant Characteristics**: BC patients undergoing chemotherapy **Observation Group**: Intravenous infusion of tropisetron hydrochloride (5 mg), once a day for 3 days + mild moxibustion and salt-separated moxibustion, 15 min per treatment, once a day for 7 days ($n=24$) **Control Group**: Intravenous infusion of tropisetron hydrochloride (5 mg), once a day for 3 days ($n=24$)	ST 36, CV 12, CV 4, CV 6, and salt-separated moxibustion at CV 8	No adverse symptom events occurred	Mild moxibustion combined with salt-separated moxibustion reduced the total scores of nausea, vomiting and constipation during chemotherapy (all $P<0.05$).	[106]
Chemotherapy-induced Myelosuppressio-n	**Participant Characteristics**: BC patients with indication for ANT chemotherapy **Acupuncture Group**: Acupuncture + G-CSF ($n=10$) **Control Group**: G-CSF ($n=16$)	GV 14, CV 6, ST 36, SP 6, KI 3, GB 39, ST 36, SP 6	In this study, no adverse effects such as bruising, dizziness, or discomfort were observed in the acupuncture group.	1. Acupuncture promoted a myeloprotective effect in women with BC undergoing chemotherapy with anthracycline. 2. Acupuncture improved quality of life.	[107]
	Participant Characteristics: BC patients with chemotherapy-induced myelosuppression during adjuvant chemotherapy **Moxibustion Group**: Routine Adjuvant Chemotherapy + Moxibustion Treatment (once daily after each cycle of chemotherapy) ($n=48$) **Control Group**: Routine Adjuvant Chemotherapy ($n=44$)	CV 8, ST 36 (bilateral), SP 6 (bilateral)	No moxibustion-related toxic side effects including skin reactions, burns, and heat syndrome were observed	moxibustion can reduce the incidence of myelosuppression-related serious AEs and improve the compliance and safety of chemotherapy in BC.	[108]

Table 3 (continued)

Cancer complication	Intervention	Acupoints	Safety Assessment	Outcome	Ref.
Chemotherapy-induced Fatigue	**Participant Characteristics**: BC patients with chemotherapy-induced fatigue **ATAS Group**: Time-Acupoints-Space Acupuncture ($n=30$) **Sham Acupuncture Group**: Non-penetrating sham acupuncture at locations away from traditional acupoints ($n=30$) **Waitlist Control Group**: Not any acupuncture treatment ($n=30$)	SP 4, PC 6, LU 7, LI 6, BL 62, SI 3, GB 41, TE 5	Reported a total of 9 AEs. These AEs included hematoma, bleeding, or pain around the acupuncture sites.	1. ATAS treatment is superior to sham acupuncture and the waitlist control in improving fatigue (mean difference 4.98, 95% CI: [3.96, 6.00], $P<0.05$). 2. Secondary outcome analysis shows that the ATAS group has positive effects on ISI, HADS, and inflammatory factors.	[109]
Cancer-related Fatigue	**Participant Characteristics**: Female BC survivors with moderate to severe fatigue **Infrared Laser Moxibustion Group**: Received real infrared laser moxibustion treatment, 2 sessions per week for 6 weeks, for a total of 12 sessions ($n=56$) **Sham Infrared Laser Moxibustion Group**: Received sham infrared laser moxibustion treatment, 2 sessions per week for 6 weeks, for a total of 12sessions ($n=56$) **Waitlist Control Group**: Not provide ILM or SILM treatment ($n=28$)	ST 36 (bilateral), CV 4, CV 6	4 patients in the ILM group exhibited localized erythema ~ 5 mm in diameter below the laser probe. No serious AEs were reported in any groups.	1. Compared with waitlist control group, infrared laser moxibustion group reduced the average BFI score by 0.9 points (95% CI: [0.3, 1.6], $P=0.007$). 2. Compared with sham group, infrared laser moxibustion group treatment resulted in a non-significant reduction in the BFI score (0.4, 95% CI: [− 0.2, 0.9], $P=0.206$).	[110]
	Participant Characteristics: BC patients with CRF **Thunder-fire Moxibustion Group**: Moxibustion + health education and conventional nursing care for 14 days ($n=30$) **Conventional Nursing Group**: Health education and conventional nursing care for 14 days ($n=30$)	BL 20 to BL 24, CV 12 to CV 4	Not mentioned.	Thunder-fire moxibustion can effectively relieve the degree of fatigue and the symptoms of Qi deficiency in BC patients undergoing chemotherapy.	[111]
BC-related Chronic Lymphedema (BCRL)	**Participant Characteristics**: BC patients with chronic lymphedema **Intervention Group**: Received 30 min of acupuncture, with 3 of the needles each being topped by a 3-cm moxa stick **Control Groups**: Diosmin 900 mg 3 times daily	LI 10, LI 11, LI 14, LI 15, SJ 5, SJ 14	No AEs were reported during treatment, and no local burns, bleeding, ecchymosis, or inflammation events occurred.	1. BCRL improved by 51.46% in the experimental group and by 26.27% in the control group ($P<0.00001$). 2.Warm acupuncture can reduce the degree of BCRL at the specific acupoints treated and can promote quality of life.	[76]
	Participant Characteristics: BC patients with upper limb lymphedema **Treatment Group**: TEAS combined with warm acupuncture based on the control group methods for 4 weeks ($n=25$) **Control Group**: Lymphedema comprehensive detumescence treatment (CDT) for 4 weeks ($n=27$)	HT 1, PC 2, SJ 13, HT 3, PC 3, LU 5, LI 10, SJ 5, PC 6, LI 4, SJ 2	There were subcutaneous hematomas at individual acupoints and a slight aggravation of edema in the affected limbs. No serious AEs occurred in either group.	1. Treatment group significantly reduced the swelling degree of the affected limbs ($P<0.01$). 2. The total effective rate was 72% in the treatment group, higher than that in the control group (55.56%, $P<0.05$).	[112]
	Participant Characteristics: BC patients with surgical treatment **Treatment Group**: Moxibustion for 4 consecutive weeks ($n=24$). **Control Group**: pneumatic circulation with compression garments worn every day for 4 consecutive weeks ($n=24$).	LI 14, LI 13, SJ 5, SI 9, BL 23	No AEs such as local burns, bleeding, ecchymosis, or inflammatory reactions occurred during treatment.	1. Moxibustion significantly reduced the affected-side arm circumference and the VAS score. 2. The Revised Piper Fatigue total scores were improved in both the moxibustion and control group ($P>0.05$).	[113]

Table 3 (continued)

Cancer complication	Intervention	Acupoints	Safety Assessment	Outcome	Ref.
Chemotherapy-related Cognitive Impairment (CRCI)	**Participant Characteristics**: Early BC patients (stage 0–II) with chemotherapy-related cognitive impairment **Treatment Group**: Conventional Chemotherapy + Acupuncture ($n=40$) **Control Group**: Conventional Chemotherapy	DU 24, ST 36, KI 3, KI 4, GB 39, EX-HN1, DU 20	No serious AEs were reported in any groups	1. The scores on FACT-COG, AVLT-recognition and CDT assessments all significantly increased in the treatment group ($P<0.05$ in all cases). 2. Serum BDNF levels after acupuncture treatment were significantly higher than before treatment ($t=3.242$, $P<0.01$). 3. Acupuncture therapy is effective in the treatment of CRCI in BC patients through a mechanism that may be related to an increase of BDNF.	[114]
Perioperative Parameters and Postoperative Quality of Life	**Participant Characteristics**: BC patients undergoing surgery **Group A**: No acupuncture treatment ($n=36$) **Group B**: Acupuncture treatment given 1 day before surgery ($n=36$) **Group C**: Acupuncture treatment given on the day of surgery ($n=36$) **Group D**: A combination of preoperative and intraoperative acupuncture ($n=36$)	HT 7, PC 6, EX-HN3, DU 20, LI 4, PC 6, ST 34	No adverse reactions occurred with acupuncture.	1. Intraoperative consumption of sufentanil and blood glucose level was significantly decreased in intraoperative acupuncture. 2. The one week postoperative functional assessment of cancer therapy-breast score was most markedly improved in group C compared with other groups.	[115]
Preoperative Anxiety in BC Surgery	**Participant Characteristics**: BC patients undergoing breast conserving surgery **Group A**: No electroacupuncture treatment ($n=34$) **Group B**: Electroacupuncture treatment given 1 day before surgery ($n=36$) **Group C**: Electroacupuncture treatment given on the day of surgery ($n=35$) **Group D**: A combination of preoperative and intraoperative electroacupuncture ($n=36$)	HT 7, PC 6, EX-HN3, DU 20, LI 4, PC 6, ST 34	No participants discontinued treatments due to AEs.	1. Groups B and D self-rating anxiety scale were significantly lower than A and C ($P<0.01$); the sleep quality was significantly better ($P<0.01$). 2. The incidence of nausea at 6 h postoperatively was significantly lower in group D than other groups ($P<0.007$).	[116]

Note: ANT: anthracycline-based chemotherapy; AVLT: auditory-verbal learning test; BD-II: Beck depression inventory-II; BDNF: brain-derived neurotrophic factor; BFI: brief fatigue inventory; BPI: brief pain inventory; BPI-WP: brief pain inventory worst pain; CBT-I: cognitive behavioral therapy for insomnia; CDT: comprehensive decongestive therapy; ECOG-PS: eastern cooperative oncology group performance status; EOT: end of treatment; FACT: functional assessment of cancer therapy; FACT-B: functional assessment of cancer therapy-breast; FACT-COG: functional assessment of cancer therapy - cognitive function; FACT-GOG-Ntx: functional assessment of cancer therapy - gynecologic oncology group-neurotoxicity; GB: gallbladder meridian; HADS: hospital anxiety and depression scale; HT: heart meridian; IQR: interquartile range; ISI: insomnia severity index; K/KD/KI: kidney meridian; LI: large intestine meridian; LR: liver meridian; LU: lung meridian; MRS: menopause rating scale; NRS: numeric rating scale; PC: pericardium meridian; PNQ: patient neurotoxicity questionnaire; PSQI: pittsburgh sleep quality index; SJ/TE: triple energizer/sanjiao meridian; SP: spleen meridian; ST: stomach meridian; TEAS: transcutaneous electrical acupoint stimulation; VAS: visual analog scale

with conventional therapy, whereas there was no significant difference in the incidence of other toxicities [30].

Xihuang Pill/Capsule is derived from the classic work ***Surgery Quan Sheng Jie***, which is effective in clearing heat, removing toxin, dissipating masses, and dispersing swellings [31]. A meta-analysis that included 26 RCTs involving 2,272 patients evaluated the efficacy and safety of Xihuang Pill/Capsule in the adjuvant treatment of BC. Results showed that Xihuang Pill/Capsule combined with either chemotherapy or endocrine therapy could inhibit tumor progression (chemotherapy: RR = 0.59, 95% CI: [0.48, 0.73], $P<0.00001$; endocrine therapy: RR = 0.56. 95% CI: [0.33, 0.96], $P=0.04$), improved patients' quality of life (chemotherapy: RR = 1.73, 95% CI: [1.11, 2.70], $P=0.02$; endocrine therapy: RR = 1.18, 95% CI: [1.01, 1.38], $P=0.03$), and adjusted the ratio of $CD3^+$ and $CD4^+$T cell subsets [32]. Moreover, Xihuang medication combined with chemotherapy could reduce the levels of tumor markers (CA153, CA125, CEA), improve the 5-year survival rate, and reduce the recurrence and metastasis rate of tumors. The combination of Xihuang medication with radiotherapy has been shown to enhance the immune function of patients. While Xihuang medication, when used alongside non-anti-tumor therapies, does not exhibit significant anti-tumor effects, it can effectively reduce the incidence of leukopenia and decrease the reduction of erythrocytes or hemoglobin levels. In terms of safety, Xihuang medication combined with chemotherapy relieved gastrointestinal adverse effects as well as leukopenia and combined with endocrine therapy did not increase adverse events (AEs), indicating a favorable safety profile. The meta-analysis

also revealed that Xihuang medication, when combined with chemotherapy, did not show significant improvements in preventing the decrease in erythrocyte count or hemoglobin levels, thrombocytopenia, or liver damage. Additionally, Xihuang medication was not found to alleviate the cardiac damage or renal insufficiency commonly associated with antineoplastic therapy. Despite these findings, the analysis suggests that Xihuang medication may offer potential benefits in enhancing cellular immune function, highlighting its possible role in supporting the immune system during cancer treatment.

Cinobufagin is a kind of Chinese medicinal preparation extracted from the skin of Chinese giant toad, the main ingredient of which is dried toad skin extract, which has the efficacy of removing toxin and relieving pain. Cinobufagin is often used in combination with chemotherapy for the adjuvant treatment of BC patients, which can significantly improve the lipid level and immune function of BC patients after chemotherapy [33], strengthen the anti-tumor effect, prolong the median OS and median progression-free survival (PFS) of patients [34]. A meta-analysis of 16 RCTs involving 1,331 patients showed that the combination of chemotherapy with Cinobufagin could significantly improve patients' objective response rate (ORR) (RR = 1.35, 95% CI: [1.23, 1.49], $P < 0.00001$), clinical benefit rate (CBR) (RR = 1.14, 95% CI: [1.08, 1.21], $P < 0.00001$), KPS score (RR = 1.98, 95% CI: [1.45, 2.68], $P < 0.0001$), and pain remission rate (RR = 1.34, 95% CI: [1.01, 1.78], $P = 0.04$), and decreased the expression of tumor markers CA125, CA153, and CEA. These data suggest that Cinobufagin combined with chemotherapy can improve the clinical efficacy and quality of life of BC patients [35]. In terms of safety, combination chemotherapy with Cinobufagin was able to reduce the gastrointestinal adverse reactions (RR = 0.58, 95% CI: [0.48, 0.70], $P < 0.00001$), hepatic and renal damage (RR = 0.57, 95% CI: [0.38, 0.84], $P = 0.004$), and alopecia (RR = 0.61, 95% CI: [0.40, 0.92], $P = 0.02$). However, the incidence of peripheral neurotoxicity and myelosuppression did not improved by the combination of Cinobufagin with chemotherapy compared to chemotherapy alone. Current evidence suggests that the efficacy of Cinobufagin in combination with chemotherapy for the treatment of BC is superior to that of chemotherapy alone and does not increase the incidence of associated adverse effects.

Aidi Injection is a TCM approved by the National Medical Products Administration to be used alone or in combination with conventional therapy for the treatment of various cancers. Its indications include clearing heat, removing toxin, activating blood, and resolving stasis [36]. Clinically, Aidi Injection is often used in the treatment of BC as adjuvant chemotherapy, and it has been reported that Aidi Injection can mitigate the toxic side effects of chemotherapy drugs, delay tumor progression time of anthracycline-resistant advanced BC patients [37], regulate immune function of patient, and improve the quality of life. In a meta-analysis incorporating 20 RCTs with 1,449 BC patients, combining Aidi Injection with chemotherapy, could significantly improve response rate (OR = 1.76, 95% CI: [1.32, 2.35], $P < 0.0001$) and KPS improvement rate (OR = 2.68, 95% CI: [1.34, 6.46], $P < 0.007$). Addition of Aidi Injection significantly reduced the rate of myelosuppression, digestive tract reaction, leukocyte decrease, II-IV cardiac function abnormality, atrial dysrhythmia, ventricular arrhythmia, ST segment T wave inversion, and abnormal electrocardiogram (all $P < 0.05$). Based on the existing evidence, treatment with Aidi Injection significantly changed the overall response rate of patients with advanced BC and improved their quality of life with few side effects. More randomized trials involving larger samples should be considered, and detailed mechanisms need to be uncovered [38].

Shenmai Injection is a commonly used TCM preparation in clinical practice. It has the effects of tonifying, producing fluid, activating blood, and resolving stasis [39]. One real-world use and safety evaluation of Shenmai Injection showed that Shenmai Injection was mainly used for the adjuvant treatment of chemotherapy in cancer patients, among which BC was one of the most used tumors [40]. A systematic meta-analysis of 29 RCTs involving 3,039 BC patients reported that Shenmai Injection combined with chemotherapy could reduce the incidence of CINV (OR = 0.31, 95% CI: [0.23, 0.44], $P < 0.01$), and leukopenia (OR = 0.26, 95% CI: [0.19, 0.36], $P < 0.01$), compared to chemotherapy alone. In terms of cardiac toxicity, studies have shown that Shenmai Injection combined with chemotherapy is beneficial for the recovery of the left ventricular ejection fraction (LVEF) (MD = 2.06, 95% CI: [1.81, 2.31], $P < 0.0001$) and significantly improves the levels of cardiac troponin (cTn) after chemotherapy (MD = −4.84, 95% CI: [−6.02, −3.66], $P < 0.0001$). Current evidence indicates that combining Shenmai Injection with chemotherapy for the treatment of BC not only enhances therapeutic efficacy but also helps mitigate chemotherapy-induced gastrointestinal reactions, hematological toxicity, cardiac toxicity, and oxidative stress damage. Additionally, it supports the recovery of T-cell subsets ($CD3^+$, $CD4^+$, $CD8^+$), thereby strengthening the patient's immune system [41].

Compound Kushen Injection (CKI) has been approved by the National Medical Products Administration for the treatment of cancer patients. Its effects include clearing heat and dispelling dampness, cooling the blood and removing toxin, and dissipating masses and relieving pain [42]. A study on the real-world clinical application characteristics of CKI in the treatment of patients with breast malignant tumors showed that CKI combined with

conventional BC therapy is widely used in clinical treatment [43]. It has been reported that CKI can improve the clinical efficacy and reduce the side effects of conventional therapy. One meta-analysis of the adjuvant treatment of BC with CKI, including 30 RCTs with 2,556 BC patients, the results showed that CKI combined with chemotherapy showed significant effects in increasing ORR (RR = 1.30, 95% CI: [1.18, 1.43], $P < 0.00001$), increasing disease control rate (DCR) (RR = 1.21, 95% CI: [1.15, 1.28], $P < 0.00001$) and increasing KPS score(RR = 1.42, 95% CI: [1.26, 1.61], $P < 0.00001$). The results indicated that combining CKI and chemotherapy was associated with a lower risk of adverse drug reactions compared to chemotherapy alone. However, due to insufficient evidence, no definitive conclusions could be made regarding PFS or OS outcomes based on this review. Therefore, these findings must be validated through larger, more rigorous clinical trials to confirm their clinical relevance and effectiveness [44].

TCM non-drug interventions in the treatment of BC

Acupuncture is an ancient treatment method of TCM, which uses specific slender needles to stimulate certain meridians and acupoints, so as to regulate the Qi and blood within the human body and the function of ZangFu organs to achieve the purpose of treating diseases. The needles are stimulated by manual manipulation, electrical stimulation, or heat. Acupuncture is widely used for palliative and supportive care for cancer patients. Based on recommendations made by clinical practice guideline development groups and expert groups from 13 countries, acupuncture has been recommended for chemotherapy-induced nausea and vomiting, cancer pain, cancer-related fatigue, xerostomia, post-surgery pain, post-operative nausea and vomiting, hot flashes, and neuropathy [74–77]. A multicenter randomized clinical trial involving 226 women with early-stage BC, patients in the acupuncture group, compared with those in the sham acupuncture group or the waitlist control group, had significant reductions in changes in joint pain scores from baseline to 6 weeks (between-group difference vs. sham acupuncture, 0.92 points and 0.96 points vs. the waitlist control group [0- to 10-point scale]) [78]. A systematic review and meta-analysis that included 29 studies involving 2,524 patients showed that acupuncture significantly improved quality of life in patients with BC, and the use of acupuncture in BC patients lead to considerable reduction in the scores of all subscales of the Brief Pain Inventory-Short Form (BPI-SF) and the Visual Analog Scale (VAS) measuring pain. Moreover, patients treated with acupuncture were more likely to experience improvements in hot flash scores, fatigue, sleep disturbances, and anxiety compared to those in the control group, while the improvements in depression were comparable across both groups. In general, acupuncture can be used as a safe and effective adjuvant therapy in the comprehensive treatment of BC patients [79].

Tai Chi and Baduanjin, as traditional Chinese mind-body exercise methods, embody thousands of years of health-preserving wisdom and have gained increasing attention in contemporary health management. With their unique movement patterns and integrated concepts of mind-body regulation, these practices have been validated through long-term application, demonstrating their potential in promoting health and assisting in disease rehabilitation, thus becoming important directions in non-pharmacological intervention research. As a traditional Daoyin technique originating from ancient China (960 A.D.-1279 A.D.), Baduanjin regulates bodily functions through a training approach that integrates mind-body coordination and the coordination of breathing with movements. Tai Chi, whose philosophy of guiding bodily functions through consciousness aligns with modern exercise physiology, emphasizes the regulatory role of neural signals in limb control to optimize system functions. A RCT ($n = 68$) [80] conducted on BC patients undergoing postoperative chemotherapy showed that the Baduanjin exercise group for 8 consecutive weeks significantly improved upper limb motor function (28.05 ± 7.052 versus 37.46 ± 6.080), reduced anxiety and depression (6.74 ± 1.653 versus 8.3 ± 1.442), and improved patients' quality of life. Wang et al. found [81] that the combination of Tai Chi and Baduanjin could improve sleep quality (1.56 ± 0.92 versus 1.06 ± 0.80), shorten sleep latency (3.17 ± 2.23 versus 2.39 ± 2.15), and reduce daytime dysfunction dimensions (3.11 ± 1.84 versus 2.06 ± 1.47). A meta-analysis incorporating 16 RCTs involving 1247 patients revealed [82] that compared with conventional treatment methods, sustained functional exercises such as Tai Chi and Baduanjin can significantly improve cognitive function (standard mean difference [SMD] = 1.00, 95% CI: [0.66, 1.35], $P < 0.00001$), increase shoulder joint motor function scores (SMD = 7.34, 95% CI: [6.32, 8.35], $P < 0.00001$), and improve sleep quality (SMD = − 1.44, 95% CI: [−2.57, −0.31], $P = 0.01$) and quality of life indicators (SMD = 6.94, 95% CI: [5.60, 8.27], $P < 0.00001$). Additionally, Tai Chi and Baduanjin can alleviate anxiety (SMD = −2.22, 95% CI: [−3.15, −1.29], $P < 0.00001$), depression (SMD = 1.44, 95% CI: [−2.46, −0.41], $P < 0.006$), and fatigue symptoms (SMD =−1.02, 95% CI: [−1.52, −0.53], $P < 0.0001$) in BC patients. These evidences support Tai Chi and Baduanjin as effective supplementary approaches in the integrative rehabilitation program for BC. Moreover, both Tai Chi and Baduanjin have been verified to have good safety, which can reduce the risk of adverse reactions [83, 84]. Considering the limitations of existing studies, further high-quality research with large sample sizes is required to more

robustly evaluate the effectiveness of Tai Chi and Baduanjin for BC patients.

Chinese massage, a wide range of technical manipulations conducted by a practitioner's finger, hand, elbow, knee, or foot applied to muscle or soft tissues at specific body locations. This therapy is characterized by its simplicity of operation and high safety profile. The society for integrative oncology (SIO) guidelines recommend massage therapy for alleviating mood disorders in BC survivors following active treatments (i.e., surgery, chemotherapy, radiotherapy) [6]. Additionally, clinical guidelines for cancer-related fatigue classify massage therapy as a Class I recommendation [85]. The mechanism of action is mainly reflected in two aspects: on the one hand, it stimulates vasoconstrictor nerves to improve systemic venous and lymphatic return and enhance local microcirculation; on the other hand, it regulates neuroendocrine and immune system functions, thereby producing multifaceted clinical benefits in the short term. Existing research evidence strongly supports the comprehensive efficacy of massage for cancer patients: in relieving cancer-related fatigue. A meta-analysis showed that it significantly improved fatigue symptoms in BC patients (SMD =−1.01, 95% CI: −1.50, −0.51], $P<0.00001$) [86], and another comparative meta-analysis indicated that it had the best efficacy in relieving cancer-related fatigue (surface under the cumulative ranking curve = 82.3%) [87]. In pain management, a meta-analysis including 13 RCTs ($n=1000$) confirmed that this therapy could significantly reduce cancer pain (SMD =−1.16, 95% CI: −1.39, −0.93], $P<0.00001$) [88]. Additionally, studies have found that massage can effectively improve gastrointestinal symptoms such as nausea, vomiting, and constipation caused by conventional treatment and enhance the quality of life of cancer patients [89]. The quality of life of cancer patients is often significantly diminished by cancer-related symptom clusters, adverse reactions from treatments, and anxiety/distress caused by cognitive dysfunction. As a characteristic therapy of TCM, massage can effectively intervene in treatment-related adverse reactions and improve patients' quality of life, providing a unique TCM solution for optimizing tumor treatment tolerance and promoting long-term rehabilitation.

TCM five-element music therapy (FEMT) has a history of over 2,000 years, originating from the Yellow Emperor's Classic of Internal Medicine. The five tones are Jue, Zhi, Gong, Shang and Yu which connect the five internal organs (Liver, Heart, Spleen, Lung, Kidney), and the five emotions (Anger, Joy, Anxiety, Worry/Sorrow, Fear/Fright) [90]. By balancing Yin and Yang, regulating the circulation of Qi and blood in the human body, TCM-FEMT help for both physically and psychologically [91]. Modern research has confirmed that music therapy is one of the most effective psychotherapies for eliminating psychosomatic diseases through non-pharmacological clinical intervention [92]. Music can affect patients' heart rate, blood pressure, respiratory rate, and blood cortisol levels through rhythm and pitch, thereby relieving emotions such as anxiety and depression. A meta-analysis examining the effectiveness of five-element music therapy for cancer patients, including 22 RCTs with a total of 2,053 cancer patients, showed significant differences in relieving depression (SMD =−1.11, 95% CI: −1.41, −0.82], $P<0.00001$), quality of life (SMD = 1.41, 95% CI: [0.58, 2.23], $P=0.0008$), sleep quality (MD =−1.73, 95% CI: [−2.34, − 1.12], $P<0.00001$), and KPS (MD = 4.75, 95% CI: [2.31, 7.18], $P=0.0001$) [93]. And five-element music therapy did not show a positive effect on anxiety. Despite the lack of high-quality research data, as a non-pharmacological and non-invasive intervention, five elements music therapy has significant advantages such as high safety, ease of implementation, relatively low cost, and good patient acceptance. It avoids the side effects and dependency risks that may be brought by drugs, and is very suitable as an important supplement to comprehensive treatment of cancer.

The underlying mechanisms of bioactive ingredients extracted from TCM in the treatment of BC

Bioactive ingredients derived from TCM, including pachymic acid, formononetin, and coptisine, have identified with encouraging anti-cancer activities, which could affect BC cell apoptosis, autophagy, ferroptosis, cell cycle, proliferation, migration, invasion, epithelial–mesenchymal transition (EMT), angiogenesis, and host immunity by regulating multiple signaling pathways. Table 4 highlights and summarizes the research progress related to the mechanisms of these representative bioactive ingredients in BC treatment.

Bioactive ingredients of TCM arresting the cell cycle of BC

The orderly progression of the cell cycle is primarily governed by the sequential activation of cyclin-dependent kinases (CDKs) complexed with their regulatory cyclin partners. At specific stages, distinct cyclin-CDK complexes is activated and phosphorylate key target proteins, thereby advancing the cycle [117]. Consequently, aberrant cell cycle regulation critically underpins the uncontrolled proliferation, enhanced metastatic potential, and frequent recurrence characteristic of BC cells. Promisingly, various bioactive ingredients derived from TCM have been shown to specifically induce tumor cell cycle arrest by targeting crucial regulatory nodes (Fig. 2). These mechanisms include interfering with DNA replication, modulating cyclin stability, inhibiting CDK kinase activity, and potentially disrupting checkpoint pathways, thus

Table 4 Effects and specific mechanisms of TCM's bioactive ingredients for the treatment of BC

TCM	Bioactive Ingredient	Model	Effect	Specific mechanism	Ref.
Poria	Poria Cocos Polysaccharides	In vitro (MCF-7)	Inhibiting the expression of lipid metabolism-related genes (LEP, SREBP1, FASN)	↓LEP/SREBP1/FASN and PI3K/AKT pathways	[197]
		In vitro (MCF-7)	Inhibiting the proliferation of BC cells induced by high glucose and promoting the apoptosis	↓JAK1/STAT3 pathway	[260]
		In vitro (MDA-MB-231)	Inhibiting migration of BC cells	↓SATB-1	[261]
	Pachymic Acid	In vitro (SK-BR-3)	Downregulating glycolysis and inducing mitochondrial apoptosis	↓Hexokinase II ↑Pyruvate Kinase M2, Cyt c	[191]
		In vitro (MDA-MB-231)	Inhibiting metastasis of BC	↓PITPNM 3	[262]
	Hesperidin	In vitro (4T1), In vivo (BALB/c)	Suppressing metastasis, angiogenesis and tumor growth	↑E-cadherin ↓Ki67, VEGF, MMP, VEGFR	[229]
		In vitro (MDA-MB-231, MCF-7)	Suppressing BC cell migration through the inhibition of the expression of PD-L1	↓AKT and NF-κB pathway	[245]
		In vitro (4T1)	Downregulating EMT in highly metastatic BC cells	↓MMP-9, Rac-1	[263]
		In vitro (MCF-7)	Downregulating DNA repair genes in MCF-7 BC cells and augmenting doxorubicin toxicity	↓ERCC1, ATM, OGG1	[264]
		In vitro (MCF-7/Dox)	As a preventive resistance agent in MCF-7 BC cells line resistance to doxorubicin	↓Pgp	[265]
		In vivo (Wistar rats)	Reduceing toxicity of doxorubicin due to the hesperidin's anti-inflammatory and antioxidant activity	↑IFNγ ↓TNF-α, IL-6, Ki67, NF-κB	[266]
	β-glucan	In vitro (T47D, Raw264.7), In vivo (MMTV-PyMT transgenic mice)	Restraining macrophage polarization from M1 to M2 phenotype and promoting autophagic tumor cell death	↓Nur77, p62, AKT/mTOR pathway	[255]
		In vitro (MCF-7, T47D), In vivo (MMTV-PyMT transgenic mice)	Downregulating hypoxia-induced HIF-1α and inhibiting the growth and the metastasize of BC	↓Nur77/HIF-1α axis	[267]
		In vitro (E0771), In vivo (C57BL/6 mice)	Reversing the tumor immunosuppressive microenvironment induced by Gemcitabine	↓PD-L1, IDO1 ↑MHC-II, CD86, TNF-α, IL-6	[239]
		In vitro (MCF-7, T47D, MDA-MB-231, MDA-MB-468), In vivo (BALB/c nude mice)	Suppressing cell proliferation and promoting apoptosis in estrogen receptor positive BCs	↑p53, p-ERK1/2, caspase-3, PARP 1 ↓MDM2, TERT, NF-κB, Bcl-2, ERα, PI3K/AKT/mTOR pathway	[151]
		In vitro (MCF-7)	Inducing cell-cycle arrest and apoptosis	↑Bax/Bcl-2 ratio	[268]

Table 4 (continued)

TCM	Bioactive Ingredient	Model	Effect	Specific mechanism	Ref.
Astragali Radix	Formononetin	In vitro (MDA-MB-231, 4T1)	Inhibiting migration and invasion	↓MMP-2, MMP-9 and PI3K/AKT pathway	[269]
		In vitro (T-47D, SK-BR-3, MCF-7, MDA-MB-231, HCC1937)	Suppressing tumor growth and angiogenesis	↓FGFR2-mediated AKT pathway	[234]
		In vitro (MDA-MB-468, MDA-MB-231), In vivo (BALB/c nude mice)	Inducing ferroptosis	↓xCT, GPX4, mTORC1/SREBP1/SCD1 pathway	[188]
	Astragalus Polysaccharides	In vitro (MCF-7, MDA-MB-231)	Inhibiting cell survival, migration, and invasion	↓CCNB1, CDC6	[270]
		In vitro (RAW 264.7), In vivo (EAC tumor-bearing mice)	Modulating immunity of host organism	↑TLR4-mediated MyD88 pathway	[256]
	Astragaloside IV	In vitro (THP-1)	Suppressing macrophage polarized to M2 phenotype	↓AKT/Foxo1 pathway	[252]
		In vitro (MDA-MB-231), In vivo (BALB/c nude mice)	Inhibiting proliferation, migration, invasion, and metastasis of BC cells	↓ERK1/2 and JNK pathways	[271]
Angelicae Sinensis Radix	Angelica sinensis polysaccharide	In vitro (T47D, HS578T), In vivo (BALB/c nude mice)	Promoting apoptosis of BC cells	↑CREB/Bcl and caspase-3/ROCK1/Mlc pathways	[157]
		In vitro (MCF10A, MDA-MB-231, MCF-7), In vivo (BALB/c nude mice)	Inhibiting the proliferation, migration, invasion, and other malignant biological behaviors of BC cells	↑PCDH10 ↓Wnt/β-catenin pathway	[219]
	Z-ligustilide	In vitro (MDA-MB-231, MDA-MB-453, HS578t)	Restoring tamoxifen sensitivity of ERa negative BC cells	↓MTA1/IFI16/HDACs complexes	[272]
	N-Butylidenephthalide	In vitro (MDA-MB-231, MCF-7)	Enhancing the radio sensitivity and inducing apoptosis of BC cells	↓Homologous recombination repair protein Rad51	[273]
Ginseng Radix et Rhizoma	Ginsenoside Rd	In vitro (4T1), In vivo (BALB/c mice)	Attenuating BC metastasis	↓miR-18a-mediated Smad2 expression regulation	[274]
		In vitro (HUVEC, MDA-MB-231), In vivo (BALB/c nude mice)	Preventing tumor angiogenesis and inducing apoptosis of BC cells	↓HIF-α/VEGF/VEGFR and AKT/mTOR/P70S6 kinase pathways	[230]
	Ginsenoside Rh4	In vitro (EMT-6), In vivo (BALB/c mice)	Inhibiting tumor growth, blocking the PD-L1 immune checkpoint and activating $CD8^+$ T cells	↓JAK/STAT pathway	[246]
		In vitro (MCF-7), In vivo (BALB/c nude mice)	Arresting the cell cycle in S phase and inducing apoptosis of BC cells	↓Bcl-2 ↑Bax, caspase-8, caspase-3, PARP pathway	[158]
	Ginsenoside Rp1	In vitro (MCF-7, T-47D, MDA-MB-231)	Inhibiting the proliferation of BC cells	↓IGF-1R/AKT pathway	[275]
	Ginsenoside Rk1	In vitro (MDA-MB-231)	Inducing cell cycle arrest and apoptosis of BC cells	↓ROS/PI3K/AKT pathway	[276]
	Ginsenoside Rg3	In vitro (MDA-MB-231)	Inducing apoptosis of BC cells	↑Bax/Bcl-2 ratio	[277]
		In vitro (MDA-MB-231, MCF-7, SK-BR-3), In vivo (BALB/c nude mice, C57BL/6J mice)	Decreasing BC stem-like phenotypes	↓ MYC mRNA	[278]
	Ginsenoside Rh2	In vitro (MCF-7), In vivo (BALB/c nude mice)	Inducing apoptosis and G1/S phase arrest of BC cells	↑ERβ, TNFα ↓ERα	[279]
		In vitro (4T1, MDA-MB-231, MCF-7), In vivo (BALB/c nude mice)	Enhancing immune surveillance of natural killer (NK) cells	↓ERp5	[258]

Table 4 (continued)

TCM	Bioactive Ingredient	Model	Effect	Specific mechanism	Ref.
Glycyrrhizae Radix et Rhizoma	Isoliquiritigenin	In vitro (BT474, 4T1, MCF-10 A, MCF-7, MDA-MB-231) In vivo (MMTV-PyMT mice)	Suppressing BC tumorigenesis and metastasis	↓miR-374a/PTEN/AKT axis	[280]
		In vitro (4T1, MDA-MB-231, MDA-MB-436), In vivo (BALB/c nude mice)	Enhancing the anti-tumor immunity	↓PD-L1, Src and ERK	[247]
		In vitro (MCF-7, MDA-MB-231), In vivo (BALB/c nude mice)	Inhibiting BC neoangiogenesis	↓VEGF/VEGFR-2	[231]
		In vitro (MDA-MB-231, MCF-7), In vivo (PyMT mice)	Limiting the activities of BC stem cells	↑WIF1 ↓Wnt/β-catenin	[281]
	Liquiritigenin	In vitro (BT-20, MCF-10 A)	Blocking BC progression by inhibiting connective tissue growth factor expression	↑miR-383-5p	[282]
		In vitro (MCF-7, BT20)	Restraining BC cell invasion and migration	↑E-cadherin ↓HSP90, Snail	[283]
		In vitro (MDA-MB-231, BT549)	Decreasing tumorigenesis	↑BRCA1 ↓DNMT	[284]
	Glycyrrhetinic Acid	In vitro (BT549, HS578T, MDA-MB-231), In vivo (BALB/c nude)	Suppressing BC invasion and metastasis	↓p38 MAPK-AP1 signaling axis	[226]
Alismatis Rhizoma	Alisol A	In vitro (MDA-MB-231, MCF-7, MDA-MB-453)	Suppressing proliferation, migration, and invasion of BC cells	↓MMP-2, MMP-9, NF-κB and PI3K/AKT/mTOR pathways	[223]
		In vitro (MDA-MB-231)	Inducing cell apoptosis, G1 phase cell cycle arrest, autophagy, and ROS generation in MDA-MB-231 cells	↑caspase-3, caspase-9, p-p38 ↓Bcl-2, cyclin A, cyclin D1	[125]
	Alisol B	In vitro (MDA-MB-231, MDA-MB-468, MDA-MB-453, MCF-7)	Inducing cell apoptosis and cell cycle arrest, decreasing mitochondrial membrane potential	↓MMP, p-AKT, p-p65, NF-kB and p-mTOR ↑caspase-3, caspase-9, p-p38	[285]
Bupleuri Radix	Saikosaponin D	In vitro (HCC1937, MDA-MB-468, MDA-MB-231, MCF-7, SUM-159)	Suppressing TNBC cells proliferation	↓Wnt/β-catenin	[286]
		In vitro (MDA-MB-231)	Inhibiting autophagosome-lysosome fusion and inducing autophagy-independent apoptosis of BC cells	↑P38 MAPK	[168]
	Saikosaponin B2	In vitro (MCF-7)	Inhibiting proliferation and migration of BC cells	↓STAT3 pathway	[287]
	Saikosaponin A	In vitro (SUM149, MDA-MB-231); In vivo (BALB/c nude mice)	Inhibiting growth and metastasis of BC	↓CXCR4/SDF-1 axis and AKT/mTOR pathway	[288]
		In vivo (SD rats)	Regulating the balance of Th1/Th2	↑IL-12/STAT4 pathway ↓IL-4, IL-10	[259]

Table 4 (continued)

TCM	Bioactive Ingredient	Model	Effect	Specific mechanism	Ref.
Moutan Cortex	Paeonol	In vitro (EMT6), In vivo (Kunming mice)	Inducing apoptosis of BC cells	↑Bax, caspase-8, caspase-3 ↓Bcl-2	[160]
		In vitro (MDA-MB-231)	Inducing apoptosis of BC cells	↑CXCR3-B ↓CXCL4, Nrf2,HO-1, BACH1	[289]
		In vitro (4T1, MCF-7), In vivo (BALB/c mice)	Enhancing the antitumor activity of epirubicin in a synergistic manner	↑PARP, Bax, caspase-3 ↓p38/JNK/ERK MAPK	[290]
	Gallic acid	In vitro (MDA-MB-231, HS578T)	Inducing G1 phase arrest and apoptosis of TNBC cells	↓cyclin D1/CDK4 and cyclin E/CDK2 ↑p21Cip1and p27Kip1, caspase-9 and caspase-3	[129]
		In vitro (TNBC HCC1806, MDA-MB-468)	Suppress TNBC cells proliferation and promote cells apoptosis through the mitochondrial apoptosis pathway	↓PI3K/AKT/EGFR pathway ↑MAPK pathway	[169]
	Paeoniflorin	In vitro (MCF-7 cells)	Inhibiting proliferation and invasion of BC	↓Notch-1 signaling pathway	[291]
		In vitro (MDA-MB-231, MCF-7)	Preventing hypoxia-induced EMT	↓PI3K/AKT, HIF-1α	[292]
		In vitro (MCF-7)	Enhancing the sensitivity of ER-positive BC cells to tamoxifen	↑Sirtuin 4	[293]
		In vitro (MCF-7)	Inhibiting proliferation and invasion of BC cells	↑p38MAPK pathway ↓Ki67, PCNA, MMP-9, VEGF	[294]
Dioscoreae Rhizoma	Diosgenin	In vitro (MDA-MB-231)	Inhibiting migration of BC cells	↓Vav2, Cdc42	[295]
		In vitro (MCF-7, HS578T)	Inducing G2/M phase arrest to promote apoptosis of BC cells	↑Chk1 kinase, Cdc25C ↓Bcl-2	[139]
		In vitro (MCF-7, MCF-10 A)	Inhibiting the proliferation and migration of BC cells	↑miR-145	[296]
		In vitro (MCF-7, MDA-MB-231), In vivo (BALB/c nude mice)	Inducing apoptosis and inhibiting proliferation of BC cells	↓pAKT, cyclin D1, CDK-2, CDK-4	[297]
		In vitro (MCF-7, MDA-MB-231)	Reducing BC cell viability and inducing apoptosis	↓Skp2	[138]
	Dioscin	In vitro (MDA-MB-231, MDA-MB-453, T47D)	Inducing caspase-independent apoptosis through activation of apoptosis-inducing factor in BC cells	↓Bcl-2, cIAP-1,Mcl-1	[298]
		In vitro (MCF-7, MDA-MB-231)	Inhibiting the invasion of BC	↑GATA 3, DNMT 3 A, E-cadherin ↓Vim, MMP 9	[299]
		In vitro (MDA-MB-231, MCF-7)	Decreasing BC stem-like cell proliferation via cell cycle arrest	↑p53, p21, p-p38 ↓Cdc2, cyclin B1, cyclin D, cyclin E, CDK4, CDK2, AKT/mTOR pathway	[130]
		In vitro (MCF-7, MDA-MB-435 S), In vivo (BALB/c nude mice)	Inhibiting BC by suppressing EMT	↑E-cadherin ↓VEGF, MMP-9, Vim	[300]
		In vitro (MCF-7, MCF-7/ADR)	Strengthen the efficiency of adriamycin through autophagy	↑IκB-α, LC3-II ↓p-PI3K, p-AKT, MDR1, NF-κB	[178]

Table 4 (continued)

TCM	Bioactive Ingredient	Model	Effect	Specific mechanism	Ref.
Atractylodis Macrocephalae Rhizoma	β-eudesmol	In vitro (MDA-MB-468, MDA-MB-231)	Inhibiting BC cell proliferation and inducing ferroptosis	↑caspase-3 ↓MAPK, SLC7A11, GPX4, SLC40A1, Bcl-2	[185]
	Atractylenolide III	In vitro (MCF-10 A), In vivo (SD rats)	Repressing NMU-induced mammary tumor progression	↑Nrf2/ARE pathway	[174]
		In vivo (NOD/SCID mice)	Preventing BC metastasis	↓TGF-β, p-Runx2	[212]
	Atractylenolide II	In vitro (MDA-MB-231, MCF-7, MCF-10 A)	Inducing cell cycle arrest and apoptosis of BC cells	↑ER-β ↓IKK-α, COX-2, NF-κB, TNF-α, ERα	[301]
		In vitro (MCF-10 A), In vivo (SD rats)	Repressing NMU-induced mammary tumor progression	↑JNK/ERK-Nrf2-ARE pathway	[302]
	Atractylenolide I	In vitro (MCF-7, MDA-MB-231, MCF-10 A), In vivo (SD rats)	Inhibiting BC cells proliferation, migration and invasion, and inducing cells apoptosis	↓TLR4/NF-κB pathway	[217]
Scutellariae Radix	Baicalein	In vitro (MDA-MB-231, MCF-7), In vivo (BALB/c nude mice)	Reducing cell viability, inhibiting cell-cycle progression, and inducing apoptosis of BC	↑lncRNAPAX8-AS1-N, miR-17-5p	[303]
		In vitro (MCF-7, MDA-MB-231, 4T1, EO771), In vivo (BALB/c nude mice)	Impeding chronic stress-induced BC metastasis	↓β2-AR, cAMP/PKA/FAK pathway	[304]
		In vitro (MDA-MB-231, MCF-7), In vivo (BALB/c nude mice)	Regulating polarization of M2 macrophages and attenuating TGF-β1 secretion	↓TGF-β1, EMT	[305]
		In vitro (MCF-10 A, MCF-7, MDA-MB-231)	Inhibiting cell viability, migration, and invasion but promoting apoptosis of BC cells	↑miR-338-3p ↓MORC4	[306]
		In vitro (MCF-7)	Inducing apoptosis and inhibiting invasion and migration of BC cells	↓Wnt3α/β-catenin	[220]
		In vitro (MDA-MB-231, BT549, MCF-7, MDA-MB-468, ZR-75-1, T47D, MCF-10 A), In vivo (BALB/c nude mice)	Inhibiting TNBC progression	↑BICD1, KDM4E, caspase-3, E-cadherin ↓Vimentin and SNAI1	[307]
	Oroxylin A	In vitro (MDA-MB-231), In vivo (BALB/c nude mice)	Suppressing BC-induced osteoclastogenesis and osteolysis	↓Acp5, Ctsk, MMP9, Integrin β3 and Src/NFATc1	[308]
	Quercetin	In vitro (MDA-MB-231)	Suppressing BC stem cell proliferation, self-renewal, and invasiveness	↓ALDH1A1, CXCR4, MUC1, EpCAM	[309]

Table 4 (continued)

TCM	Bioactive Ingredient	Model	Effect	Specific mechanism	Ref.
Epimedii Folium	Icariin	In vitro (MDA-MB-231)	Suppressing the proliferation, EMT, and stem cell-like of BC cells	↓lncRNA NEAT1/TGFβ/SMAD2 pathway	[215]
		In vitro (MDA-MB-468, MDA-MB-231, 4T1), In vivo (BALB/c mice)	Exerting anti-tumor activity by inducing autophagy	↑AMPK/mTOR/ULK1	[176]
		In vitro (MDA-MB-231, MDA-MB-453, MCF-10 A, 4T1), In vivo (BALB/c nude mice BALB/c mice)	Triggering apoptosis in BC cells and downregulating expression levels of PD-L1, enhancing the proportion of infiltrating $CD4^+$/$CD8^+$ T cells and reducing the abundance of MDSCs in tumors	↓NF-κB/EMT pathway ↑SIRT6, Bax/Bcl-2 ratio	[241]
	Icariside I	In vitro (4T1), In vivo (BALB/c mice)	Reducing BC proliferation, invasion, and metastasis	↓IL-6/STAT3 pathway	[221]
	Anhydroicaritin	In vitro (MDA-MB-231, 4T1, MCF-7, SK-BR-3), In vivo (BALB/c mice)	Inhibiting tumor growth and lung metastasis	↓HIF-1α, VEGFA	[310]
	Hyperoside	In vitro (MCF-7, 4T1), In vivo (BALB/c mice)	Inhibiting migration and inducing apoptosis of BC cells	↑Bax, caspase-3 ↓Bcl-2, XIAP, NF-κB	[164]
	Baohuoside I	In vitro (MCF-7, MDA-MB-231, SK-BR-3)	Inducing apoptosis of BC cells	↓EGFR, PI3K/AKT and MAPK signaling pathways ↑PARP	[311]
		In vitro (MCF-10 A, HBL100, BT549, 4T1, Raw264.7), In vivo (BALB/c mice)	Suppressing BC metastasis and TAMs/CXCL1 activity	↓CXCL1	[254]
Salviae Miltiorrhizae Radix et Rhizoma	Dihydroisotanshinone I	In vitro (MCF-7, MDA-MB-231), In vivo (BALB/c nude mice)	Inducing apoptosis and ferroptosis of BC cells	↓GPX4	[183]
	Cryptotanshinone	In vitro (SKBR-3)	Inducing apoptosis of BC cells	↑caspase-3 ↓PI3K/AKT pathway	[312]
	Tanshinol	In vitro (ZR-75-1), In vivo (BALB/c nude mice)	Activating NK cells to release multiple killing mediators	↑IFN-γ ↓TGF-β1	[257]
	Total Salvianolic Acid	In vitro (E0771), In vivo (C57BL /6J mice)	Reducing the number of M2-TAM and increasing the number of $CD4^+$T and $CD8^+$T cells	↓IL-6, MCP-1, cxcl1, cxcl2, cxcl3, ccl2, GM-CSF	[251]
	Resveratrol	In vitro (MDA-MB-231, T-47D, THP-1), In vivo (NOD/SCID Mice)	Restraining macrophage polarization from M1 to M2 phenotype	↑CXCL10 ↓IL-6/STAT3	[313]
	Neoprzewaquinone A	In vitro (MDA-MB-231, MCF-7)	Inhibiting BC cell migration	↓ROCK2/STAT3 pathway	[143]
	Dihydrotanshinone I	In vitro (MDA-MB-231, MCF-7, SKBR-3, 4T1), In vivo (BALB/c nude mice)	Inhibiting the lung metastasis of BC by suppressing neutrophil extracellular traps formation	↓TIMP1, neutrophil extracellular traps	[314]

Table 4 (continued)

TCM	Bioactive Ingredient	Model	Effect	Specific mechanism	Ref.
Sophorae Flavescentis Radix	Cardamonin	In vitro (MDA-MB-231), In vivo (BALB/c nude mice)	Inhibiting cancer growth by repressing HIF-1α-dependent metabolic reprogramming	↓HIF-1α, mTOR/p70S6K pathway	[204]
	Matrine	In vitro (MDA-MB-231, MCF-7)	Suppressing metastasis and EMT in BC cells	↑Integrin β1	[315]
		In vitro (MCF-7)	Promoting the occurrence of endoplasmic reticulum stress and downregulating energy metabolism	↑GRP78, p-eIF2α, CHOP ↓hexokinase II	[192]
		In vitro (MCF-7)	Promoting apoptosis and autophagy of BC cells	↓AKT/mTOR pathway	[177]
		In vitro (4T1, MCF-7), In vivo (BALB/c mice)	Inhibiting cell growth, proliferation and invasion, but inducing apoptosis and autophagy of BC cells	↑caspase-3, caspase-9 ↓Wnt/β-catenin	[316]
		In vitro (MDA-MB-231, MDA-MB-468)	Promoting cell apoptosis and autophagy of BC cells	↑LC3-II, caspase-3 ↓PI3K/AKT pathway	[317]
	Oxymatrine	In vitro (MCF-7, MCF-10 A)	Inhibiting proliferation and promoting apoptosis of BC cells	↑miRNA-140-5P	[318]
		In vitro (MDA-MB-231, 4T1)	Reversing EMT	↓αVβ3 integrin/FAK/PI3K/AKT	[319]
		In vitro (MDA-MB-231, MDA-MB-468), In vivo (BALB/c nude mice)	Reversing the EMT phenotype and depleting the subpopulation of TNBC stem cells induced by Bevacizumab	↓Wnt/β-catenin	[320]
		In vitro (MCF-7, MDA-MB-231)	Promating S-phase arrest and inhibiting proliferation through mitochondria-mediated apoptosis	↑caspase-3, caspase-9 ↓Bcl-2/Bax	[321]
Coptidis Rhizoma	Berberine	In vitro (MDA-MB-231)	Inhibiting proliferation and inducing autophagy of BC cells	↑Beclin 1 ↓AKT/mTOR	[322]
		In vitro (ZR-75-30, MCF-7)	Inhibiting BC cells proliferation and migration	↓VEGFR, MMP2, MMP9, AKT, and Erk1/2	[232]
		In vitro (MD-MB-231)	Inhibiting invasion and promoting apoptosis of BC cells	↓JAK2, PI3K, AKT, and NF-κB pathways	[323]
	Coptisine	In vitro (MDA-MB-468, ZE751, BT549, HCC1937, HS578T, MDA-MB-453, MDA-MB-436, MDA-MB-231, MCF-7, SK-BR-3, T47D, 4T1), In vivo (BALB/c nude mice)	Inhibiting mitochondrial functions, reprogramming cellular metabolism, and inducing apoptosis	↓Mitochondrial electron transport chain	[193]
		In vitro (MDA-MB-231)	Suppressing BC metastasis	↓MMP-9 ↑TIMP-1	[324]
		In vitro (MDA-MB-231)	Inhibiting proliferation of BC cells	↑p21 ↓CDK4, CDK6	[124]
	Epiberberine	In vitro (4T1, MDA-MB-231), In vivo (BALB/c nude mice)	Inhibiting bone metastatic	↓AKT/c-Fos signaling pathway	[325]

Table 4 (continued)

TCM	Bioactive Ingredient	Model	Effect	Specific mechanism	Ref.
Rabdosiae Rubescentis Herba	Oridonin	In vitro (MDA-MB-231)	Inducing apoptosis of BC cells	↑ROS, caspase-3 ↓Bcl-2	[148]
		In vitro (MDA-MB-468, MDA-MB-231)	Suppressing growth of BC cells	↓PI3K/AKT	[326]
		In vitro (MDA-MB-231, 4T1), In vivo (BALB/c mice)	Inhibiting VEGF-A-associated angiogenesis and EMT of BC	↓HIF-1α/VEGF	[327]
		In vitro (MCF-7, MDA-MB-231)	Promoting ferroptosis of BC cells	↓JNK/Nrf2/HO-1 axis	[189]
		In vitro (MDA-MB-231, MCA-7)	Inducing apoptosis but inhibiting migration and invasion of BC cells	↓IKKα, IKKβ, NF-κB, p-mTOR ↑Fas, PPARγ	[127]
		In vitro (MDA-MB-468)	Inhibiting proliferation and inducing apoptosis of BC cells	↑p53, PARP, caspase-3, caspasee-9	[128]
		In vitro (MDA-MB-231, 4T1), In vivo (BALB/c mice)	Suppressing Treg differentiation	↓TGF-β	[244]
	Lasiokaurin	In vitro (MDA-MB-231, MDA-MB-468, MCF-7), In vivo (BALB/c nude mice)	Inducing cell cycle arrest, apoptosis, and DNA damage in TNBC cells, while inhibiting cell metastasis	↓PI3K/AKT/mTOR and STAT3 pathways	[328]
		In vitro (SK-BR-3, MDA-MB-231, BT-549, MCF-7, T-47D), In vivo (BALB/c nude mice)	Inducing BC cell G2/M phase block and apoptosis	↓PLK1 pathway	[329]
Rhei Radix et Rhizoma	Chrysophanol	In vitro (MCF-7, MDA-MB-231)	Inhibiting proliferation and inducing apoptosis of BC cells	↓NF-κB pathway	[126]
	Emodin	In vitro (MDA-MB-231, MDA-MB-453)	Inhibiting EMT and metastasis of TNBC	↓CCL 5	[330]
		In vitro (MDA-MB-231), In vivo (BALB/c nude mice)	Inhibiting migration, invasion and metastasis of BC	↓p38 and ERK1/2	[331]
		In vitro (4T1), In vivo (BALB/c mice)	Inhibiting macrophage infiltration and M2-like polarization	↓MCP1, CSF1, STAT6 pathway	[332]
		In vitro (MDA-MB-231), In vivo (NOD/SCID mice)	Inhibiting angiogenesis and metastasis of BC	↓Runx2, MMPs, VEGFR	[333]
	Rhein	In vitro (MCF-10 A)	Inducing apoptosis of BC	↑Bim	[163]
	Melosuavine I	In vitro (BT549)	Inducing apoptosis of BC	↑caspase-3, p53 ↓Bcl-2	[152]
Mylabris	Cantharidin	In vitro (MDA-MB-231), In vivo (BALB/c nude mice)	Suppressing cell growth and migration	↓MAPK signaling pathway	[225]
		In vitro (MCF-7)	Inhibiting cell proliferation	↓E2F1/MCM7miR-106b-93/p21 PTEN signaling axis	[131]
		In vitro (BT474, MDA-MB-231, MCF-10 A, 4T1), In vivo (BALB/C mice)	Inhibiting apoptosis of BC	↓PI3K/AKT/mTOR and ERK/MAPK pathways ↑miR-607	[162]
		In vitro (MDA-MB-231, MDA-MB-468), In vivo (BALB/c nude mice)	Suppressing cell autophagy and inducing apoptosis	↑caspase-3, PARP ↓Beclin-1	[172]
	Sodium Cantharidate	In vitro (MCF-7), In vivo (BALB/c nude mice)	Promoting autophagy in BC cells	↓PI3K/AKT/mTOR pathway	[334]
Bolbostemmatis Rhizoma	Tubeimoside-1	In vitro (MCF-7, T47D, MDA-MB-231)	Inducing cytoprotective autophagy of BC cells	↓AKT/mTOR pathway	[179]
Magnoliae Officinalis Cortex	Honokiol	In vitro (MCF-7, MDA-MB-231, 4T1), In vivo (BALB/c nude mice)	Suppressing invasion and migration of BC	↑E-cadherin ↓Snail, Slug, vimentin, EMT	[335]
Ganoderma	Ganoderiol F	In vitro (MDA-MB-231, MDA-MB-468, SK-BR-3, MCF-7, 4T1), In vivo (BALB/C mice)	Retarding BC cell cycle progression	↓cyclin D1, CDK4, CDK6, cyclin E, CDK2, c-Myc	[136]

Table 4 (continued)

TCM	Bioactive Ingredient	Model	Effect	Specific mechanism	Ref.
Dichroae Radix	Halofuginone	In vitro (MCF-7)	Inhibiting migration and invasion of BC	↓STMN 1, p53	[336]
Puerariae Lobatae Radix	Puerarin	In vitro (HCC38)	Inhibiting cell viability and promoting cell apoptosis	↑microRNA-133a-3p, DUSP1	[337]
		In vitro (MCF-7, MDA-MB-231)	Suppressing BC cell migration, invasion and adhesion	↓p65, NF-κB and Erk pathways	[338]
Arnebiae Radix	Shikonin	In vitro (MCF-7)	Inhibiting BC cell proliferation	↓Exosome	[339]
		In vitro (MCF-7, SK-BR-3)	Inhibiting BC cell proliferation	↓GPER, ERα, EGFR/p-ERK pathway	[340]
Eriobotryae Folium	Oleanolic Acid	In vitro (4T1), In vivo (BALB/c mice)	Inhibiting tumor progression	↑*Lactobacillus* in the intestinal flora	[341]
Ecliptae Herba	Wedelolactone	In vitro (4T1)	Suppressing BC growth and metastasis	↓TGF-β1/Smad signaling pathway	[214]
Caryophylli Flos	Eugenol	In vitro (MCF-10 A)	Reducing ATP production and decreasing oxidative stress	↓c-Myc/PGC-1β/ERRα pathway	[198]
Andrographis Herba	Andrographolide	In vitro (MDA-MB-231, MCF-7, T47D, MDA-MB-361, BT549), In vivo (BALB/c nude mice)	Inhibiting angiogenesis	↓VEGF	[342]
Anemones Raddeanae Rhizoma	Raddeanin A	In vitro (MDA-MB-231, BMMs)	Inhibiting bone metastases and inducing cell apoptosis	↓AKT/mTOR and SRC/AKT pathways	[343]
Euphorbiae Ebracteolatae Radix	Ethyl gallate	In vitro (MDA-MB-231, MCF-7)	Inhibiting cell proliferation and invasion	↓PI3K/AKT/NF-κB pathway	[224]
Viticis Fructus	Casticin	In vitro (MDA-MB-231, 4T1), In vivo (BALB/c mice)	Inhibiting cell proliferation and metastasis	↓PI3K/AKT pathway	[344]
		In vitro (MDA-MB-231, MCF-7)	Inducing BC cell apoptosis	↓Forkhead box protein M1	[345]
Nelumbinis Semen	Neferine	In vitro (MDA-MB-231)	Inhibiting cell proliferation and metastasis	↓miR-374a/FGFR-2	[235]
	Narciclasine	In vitro (HCC-1937, MDA-MB-231), In vivo (BALB/c nude mice)	Promoting autophagic apoptosis	↑4EBP1, Beclin-1, ATG 4B, ATG 8, AMPK-ULK1 axis ↓PRAS 40, p70S6K	[346]
Nardostachyos Radix et Rhizoma	Jatamanvaltrate P	In vitro (MDA-MB-231, MDA-MB-453, MDA-MB-468), In vivo (BALB/c nude mice)	Inducing cell cycle arrest, apoptosis, and autophagy	↓cyclin B1, cyclin D1, Cdc-2 ↑caspase-3, LC3	[144]
Curcumae Radix	Elemene	In vitro (MCF-7, MDAMB-231, 4T1, MDAMB-435 S)	Inhibiting the migration and invasion of BC	↓Heparanase, FGF-2,VEGF, p-ERK, p-AKT	[347]
Notoginseng Radix et Rhizoma	Panax Notoginseng Saponins	In vitro (4T1)	Inhibiting BC metastasis	↑Brms1, Mtss1, Timp2, E-cadherin ↓MMP3, MMP9, vimentin	[348]
Curcumae Longae Rhizoma	Curcumin	In vitro (MCF-7, MDA-MB-231), In vivo (BALB/c nude mice)	Inhibiting self-renewal and proliferation of BC cells	↓ABCG2, ABCC1	[349]
Paridis Rhizoma	Polyphyllin I	In vitro (MDA-MB-231), In vivo (BALB/c nude mice)	Inducing mitophagic and apoptotic cell death of BC cells	↑PINK1	[350]
	Polyphyllin VII	In vitro (MCF-7, MDA-MB-231, MCF-10 A), In vivo (BALB/c nude mice)	Promoting apoptosis of BC cells	↓SOS1, Bcl-2 and MAPK/ERK pathway ↑Bax, caspase-3, caspase-9	[166]
Inulae Radix	Isoalantolactone	In vitro (MDA-MB-231)	Inhibiting migration and invasion of BC cells	↓p38 MAPK/NF-κB pathway	[351]
	Alantolactone	In vitro (MDA-MB-231)	Promoting apoptosis of BC cells	↑cyt-c, Bax/Bcl-2 ratio, caspase-9, caspase-3, p-c-Jun ↓MMP, p-p65, p-STAT3	[161]

Table 4 (continued)

TCM	Bioactive Ingredient	Model	Effect	Specific mechanism	Ref.
Ophiopogonis Radix	Ophiopogonin D	In vitro (MCF-7)	Inhibiting cell proliferation, causing cell cycle arrest at G2/M, and inducing apoptosis of BC cells	↓cyclin B1 ↑caspase-8, caspase-9	[145]
	DT-13	In vitro (MDA-MB-435), In vivo (BALB/c nude mice)	Inhibiting proliferation, migration, adhesion, and metastasis of BC	↓HIF-1α, VEGF, CCR5	[352]
Platycodonis Radix	Platycodin D	In vitro (4T1), In vivo (BALB/c mice)	Inhibiting inflammatory signaling pathway of microenvironment formation of pre-pulmonary metastasis induced by S100A8/A9	↓NF-κB pathway	[353]
Strychni Semen	Brucine	In vitro (MDA-MB-231)	Suppressing vasculogenic mimicry	↓MMP-9, MMP-2	[354]
Cnidii Fructus	Osthole	In vitro (MDA-MB 435)	Inducing BC cell cycle arrest and apoptosis	↑p53, p21, caspase-9, caspase-3 ↓CDK2, cyclin D1, PARP	[355]
		In vitro (MDA-231BO cells), In vivo (BALB/c nude mice)	Inhibiting bone metastasis of BC	↓TGF-β/Smad pathway	[213]
		In vitro (4T1)	Inhibiting cancer cell proliferation and inducing S-phase cell cycle arrest and apoptosis by inhibiting fatty acid metabolism	↓mTOR/SREBP1/FASN pathway	[196]
Chuanxiong Rhizoma	Tetramethylpyrazine	In vitro (MDA-MB-231)	Regulating the viability, migration, invasion and apoptosis of BC	↓AKT pathway ↑caspase-3	[356]
Leonuri Herba	Stachydrine Hydrochloride	In vitro (MCF-7, T47D)	Inhibiting proliferation and inducing apoptosis of BC cells	↓AKT and ERK pathways	[167]
Psoraleae Fructus	Bakuchiol	In vitro (MDA-MB-231, MCF-7), In vivo (zebrafish)	Inducing S phase arrest and apoptosis of BC cells	↑ERβ, cyclin B1, P-Cdc2 (Tyr15), p21, Myt1 and P-Wee1 ↓ERα	[357]
Sappan Lignum	Brazilin	In vitro (4T1)	Actuating ferroptosis in BC cells	↓p53/SLC7A11/GPX4 axis	[182]
Bletillae Rhizoma	Blestriarene C	In vitro (BT549), In vivo (BALB/c nude mice)	Promoting apoptosis and causing S-phase cycle arrest of BC cells	↓Ras/ERK/c-Fos pathway	[140]
Aurantii Fructus Immaturus	Poncirin	In vitro (SKBR3, MCF-10 A), In vivo (BALB/c nude mice)	Inhibiting proliferation and metastasis of BC cells	↓PI3K/AKT/mTOR pathway ↑Bax and caspase-3	[159]
Centellae Herba	Asiaticoside	In vitro (MCF-7, MDA-MB-231), In vivo (BALB/c nude mice)	Inhibiting BC proliferation and angiogenesis	↓Yap1/VEGFA pathway	[358]
		In vitro (MDA-MB-231), In vitro (BALB/c nude mice)	Inhibiting proliferation, migration, invasion, and EMT	↑PPARG ↓TGF-β/Smad pathway	[211]
Bruceae Fructus	Bruceantinol	In vitro (MCF-7, MDA-MB-231, MCF-10 A)	Inhibition the growth of BC cells	↑ ERK pathway	[123]
	Bruceine A	In vitro (MDA-MB-231, MCF-7), In vivo (BALB/c nude mice)	Inhibiting BC proliferation, invasion and migration by inducing autophagy	↑ATG5, LC3I/II ↓P62, PI3K/AKT	[173]
Coriolus	Polysaccharopeptide	In vitro (MDA-MB-231, SUM-159, MCF-7, MCF-10 A), In vivo (BALB/c mice)	Inhibiting growth, proliferation and inducing apoptosis	↓p-JAK2 and p-STAT3	[359]
Acanthopanac-is Senticosi Radix et Rhizoma Seu Caulix	Syringin	In vitro (MDA-MB-231, MCF-7)	Inhibiting proliferation and migration and promoting apoptosis of BC cells	↓PI3K/AKT and EGFR/RAS/RAF/ERK pathways	[360]
Carthami Flos	Hydroxysafflor Yellow B	In vitro (MCF-7)	Inhibiting proliferation of BC cells	↓cyclin D1, cyclin E, CDK2	[135]
Centipeda Herba	Arnicolide D	In vitro (MDA-MB-231, MCF-7)	Inhibiting oxidative stress-induced BC cell growth and invasion through apoptosis, ferroptosis, and parthanatos	↑ROS, PARP, caspase-3 ↓MMP-2, MMP-9, GPX4	[154]

Table 4 (continued)

TCM	Bioactive Ingredient	Model	Effect	Specific mechanism	Ref.
Arctii Fructus	Arctigenin	In vitro (MDA-MB-231)	Inhibiting BC migration and invasion	↓MMP-2, MMP-9, Heparanase	[361]
Melodinus Fusiformis	Melognine	In vitro (BT549)	Inducing apoptosis of BC cell	↑caspase-3, p53 ↓Bcl-2	[153]
Ginseng Radix Rhizoma Rubra	Red Ginseng Polysaccharide	In vitro (MDA-MB-231)	Inducing ferroptosis of BC cell	↓GPX4	[184]
Pulsatillae Radix	Raddeanoside R13	In vitro (ZR75-1, MCF-7, 4T1)	Inhibiting BC cell proliferation, invasion, and metastasis	↑cleaved PARP, caspase-3, E-cadherin, p21 ↓cyclin D1, cyclin A, cyclin E, N-cadherin, vimentin	[362]

Note: ↓:decreased/suppressed; ↑: increased/enhanced

halting malignant progression and presenting potential therapeutic avenues.

The Gap 1 (G1) phase is driven by the CDK4/6-cyclin D complex, which directly phosphorylates the retinoblastoma-associated proteins (Rb) and the transcription factor forkhead box protein M1 (FOXM1). Phosphorylated Rb and FOXM1 induce the transcription of cell-cycle-related genes and ultimately facilitating the transition into the S phase [118, 119]. Compelling evidence identifies CDK4/6 as pivotal drivers of proliferation in BC [120, 121]. CDK4/6 inhibitor can dually inhibit CDK4/6 and ER signaling. This combined action effectively blocks the growth of ER^+ BC cells in the G1 phase, restores cell cycle control, and halts tumor cell proliferation [122]. As an inhibitor of CDK4/6, bruceantinol inhibits the growth of BC cells by promoting the degradation of CDK4/6 via the proteasome pathway and exerting cytotoxic effects through the activation of ERK [123]. Coptisine can inhibit the proliferation of BC cells by blocking the cell cycle at the S and G2/M phases, which may be related to the decrease of CDK4/6 induced by the upregulation of p21 [124]. Alisol A and chrysophanol induce the G1 phase cell cycle arrest by inhibiting cyclin D1 pathways [125, 126]. Furthermore, other natural ingredients induce G1 arrest through complementary pathways. Oridonin causes the accumulation of BC cells in the G1 phase by upregulating p53 [127, 128]. Gallic acid and dioscin attributes to G1 phase arrest via the p38 MAPK/p21/p27 axis [129, 130]. Cantharidin, one of various natural products used in TCM for the treatment of BC, increases the levels of miR-106b-93 while decreasing the expression of the target gene p21 [131].

The S phase encompasses the period from the initiation to the completion of DNA replication. During this critical stage, the cell duplicates its entire genome through semi-conservative DNA replication and synthesizes essential chromosomal proteins (e.g., histones) in preparation for subsequent cell division [132, 133]. This precise duplication ensures the accurate transmission of genetic information to daughter cells during mitosis (M phase), thereby safeguarding the stability of inherited traits. Consequently, the S phase represents one of the most crucial and tightly regulated stages of the cell cycle. The S-phase complex, CDK2-cyclin E, has become a promising therapeutic target for BC treatment and mediates the regulation of the G1/S transition [134]. Hydroxysafflor yellow B, isolated from the Carthami Flos,, downregulates cyclin E and CDK2 to arrest BC cells at the G1-S phase [135]. Dioscin, gallic acid, and ganoderiol F induce cell death through cell cycle arrest in the G1-S phase by down-regulating CDK2-cyclin E complex [129, 130, 136].

The blockade at the Gap 2 (G2) phase primarily targets the CDK1-cyclin A complex, which drives the transition from the S phase to the G2/M phase [133]. Diosgenin, a major steroidal saponin of Dioscoreae Rhizoma, induces G2 phase arrest through a dual mechanism. Diosgenin inhibits the expression of S-phase kinase-associated protein 2 (Skp2), which has been characterized to play a critical role in oncogenesis and tumor progression via ubiquitinating p21, p27, and p57. The deletion of Skp2 by diosgenin has been shown to result in the upregulation of p57 and the downregulation of cell cycle cyclin A and CDK2 [137, 138]. Furthermore, diosgenin activates the DNA damage response (DDR) effectors Chk1 and Chk2 (downstream of ATM/ATR kinase). Activated Chk1/2 then phosphorylate and inhibit the phosphatase CDC25. The inhibition of CDC25 prevents the removal of inhibitory phosphates by CDK1 (Tyr15), thereby preventing its activation and entry into mitosis [139]. Blestriarene C, a dibiphenine ingredient extracted from Bletillae Rhizoma, causes the G2-S phase cycle arrest by inhibiting the Ras/ERK/c-Fos signaling pathway and down-regulating the expression of cyclin A and CDK2 [140].

The central target of M-phase blockers is the CDK1-cyclin B complex, which serves as the master regulator and the molecular engine driving mitotic entry [133]. Among all cyclin-dependent kinases, CDK1 holds a unique and indispensable role in cell cycle progression.

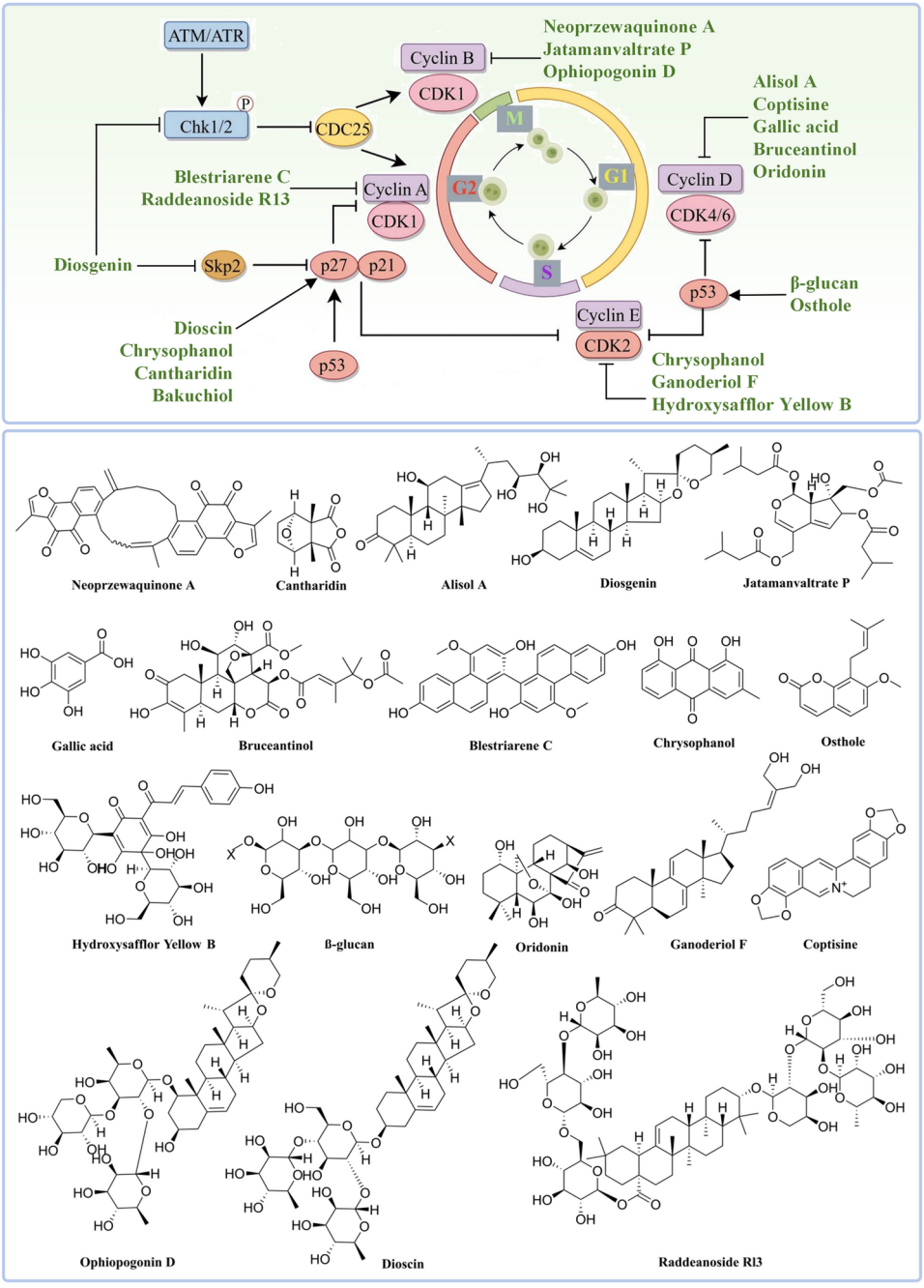

Fig. 2 Bioactive ingredients of TCM arrest the cell cycle of BC. ↑: activation; ⊥: inhibition

It is the only CDK essential for cell cycle progression, functioning as both the initiator of mitosis and a guardian of mitotic fidelity [141]. The CDK1-cyclin B complex ensures that key mitotic events, including nuclear envelope breakdown, chromosome condensation, and spindle assembly, are temporally and precisely sequenced and executed, thereby maintaining the accuracy of cell division [142]. This central role makes the CDK1-cyclin B axis an attractive therapeutic target for cell cycle intervention strategies. Neoprzewaquinone A, an ingredient investigated for decades as a promising therapeutic agent against various cancers due to its low toxicity and minimal side effects, induces cell cycle arrest at the G0/G1 phase and prevents M-phase entry by decreasing cyclin B expression and increasing cyclin D levels [143]. Furthermore, jatamanvaltrate P and ophiopogonin D induce G2/M cell cycle arrest through downregulation of cyclin B1 [144, 145]. This inhibition of cyclin B1/CDK1 activity impairs progression through the spindle assembly checkpoint, ultimately preventing tumor cell division.

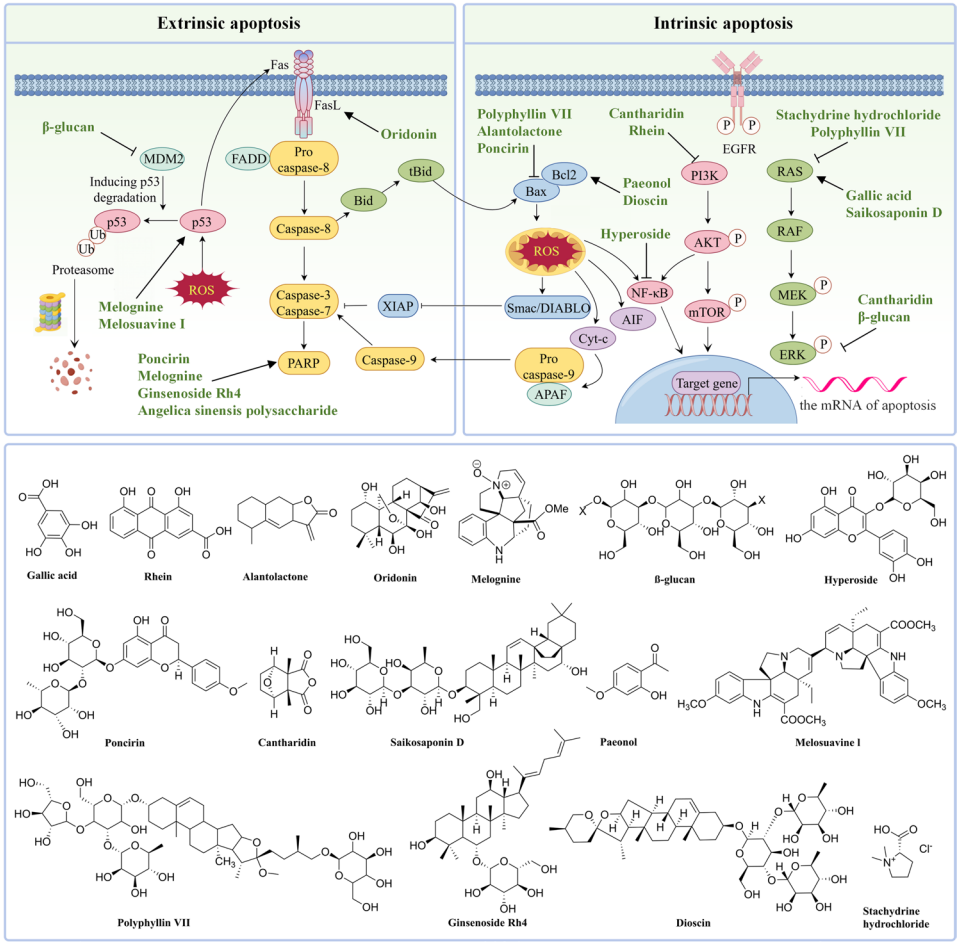

Fig. 3 Bioactive ingredients of TCM promote the apoptosis of BC cells. ↑: activation; ⊥: inhibition

Bioactive ingredients of TCM promoting apoptosis of BC cells

Apoptosis, the programmed cell death, results in the orderly and efficient removal of damaged cells, which can be divided into two primary pathways: the extrinsic death receptor pathway, which is initiated by the binding of ligands (Fas-L), and the intrinsic mitochondrial pathway, which is mediated by intracellular signals. These two pathways are interrelated, cross-regulated, and converged to activate effector apoptotic caspases, ultimately leading to the apoptosis of cancer cells [146] (Fig. 3).

Fas (CD95), a corresponding receptor, is activated by Fas ligand (FasL), which recruits caspase-8 and activates caspase-3/7, thereby initiating apoptosis [147]. Oridonin increases the level of Fas, cleaved PARP, and activated caspase-3. And γH2AX-containing nuclear foci, indicating that the pro-apoptotic ability of oridonin is related to DNA damage and both intrinsic and extrinsic apoptotic pathways [127, 148]. Except inducting cell cycle arrest, p53 is a homotetrameric transcription factor with pro-apoptotic function. In normal cells, p53 is targeted for proteasomal degradation by mouse doubleminute 2 homolog (MDM2), maintaining p53 at low levels [149, 150]. Thereby, β-glucan induces the degradation of MDM2 and causes excess p53 activation, resulting in cancer cells apoptosis [151]. Melosuavine I and melognine are alkaloids derived from TCM, possessing the pro-apoptotic effect by activating p53 and caspase-3 directly and decreasing Bcl-2 [152, 153]. Arnicolide D not only increases the production of reactive oxygen species (ROS) and decreases mitochondrial membrane potential in BC cells, but it also significantly promotes the expression of PARP-1, enhances the nuclear translocation of apoptosis-inducing factor (AIF), and reduces the level of AIF in mitochondria, thereby inducing the occurrence of apoptosis in a ROS-dependent manner [154]. Thioredoxin reductase (TrxR) plays an important role in keeping the intracellular redox balance. Glaucocalyxin A inhibits TrxR activity by primarily targeting the Sect. 498 residue of the protein, eventually induction of oxidative stress mediated apoptosis in TNBC [155, 156]. As suggested before, dysregulation of apoptosis leads to uncontrolled proliferation of cancer cells, which is one of the causes of BC development, progression, and therapeutic

failure. Many natural products, including angelica sinensis polysaccharide, ginsenoside Rh4, poncirin, alantolactone and paeonol are potential apoptosis-inducing drugs as an important strategy for the treatment of BC [157–161].

Abundant studies have revealed that TCM ingredients can induce apoptosis by influencing the signaling pathways involved, including PI3K/AKT, MAPK, and NF-κB. MiRNA-607, a novel EGFR regulator, attenuates the oncogenic effects of EGFR. Cantharidin downregulates miR-607-mediated EGFR to inhibit the phosphorylation of downstream of EGFR, PI3K/AKT/mTOR and ERK, which associated with downregulate pro-apoptotic proteins and upregulate anti-apoptotic protein levels [162]. Rhein, one of the anthraquinone ingredients in the root of rhubarb, inhibits the phosphorylation of PI3K/AKT/FOXO3a, resulting in sustained high levels of Bim expression, which ultimately induces caspase cleavage and apoptosis [163]. Hyperoside (quercetin 3-O-β-D-galactopyranoside) is one of the flavonoid glycosides with anti-cancer effect. Qiu et al. have proved that hyperoside induces ROS-related apoptosis and the mechanisms include activation of the Bax-caspase-3 axis and the inhibition of the NF-κB signaling pathway [164]. RAS/RAF/ERK pathway inhibits apoptosis by promoting anti-apoptotic proteins and inhibiting pro-apoptotic proteins. Therefore, RAS effector signaling cascade kinase inhibitors, including RAF, MEK or ERK inhibitors for cancer therapy, are a potential strategy for cancer treatment [165]. Polyphyllin VII and stachydrine hydrochloride induce apoptosis via the mitochondrial pathway by inhibiting the MAPK/ERK pathway [166, 167]. However, an emerging view sustained MAPK activation can promote apoptosis in BC [165]. The ingredient of saikosaponin D and gallic acid activate the apoptosis by activating MAPK [168, 169].

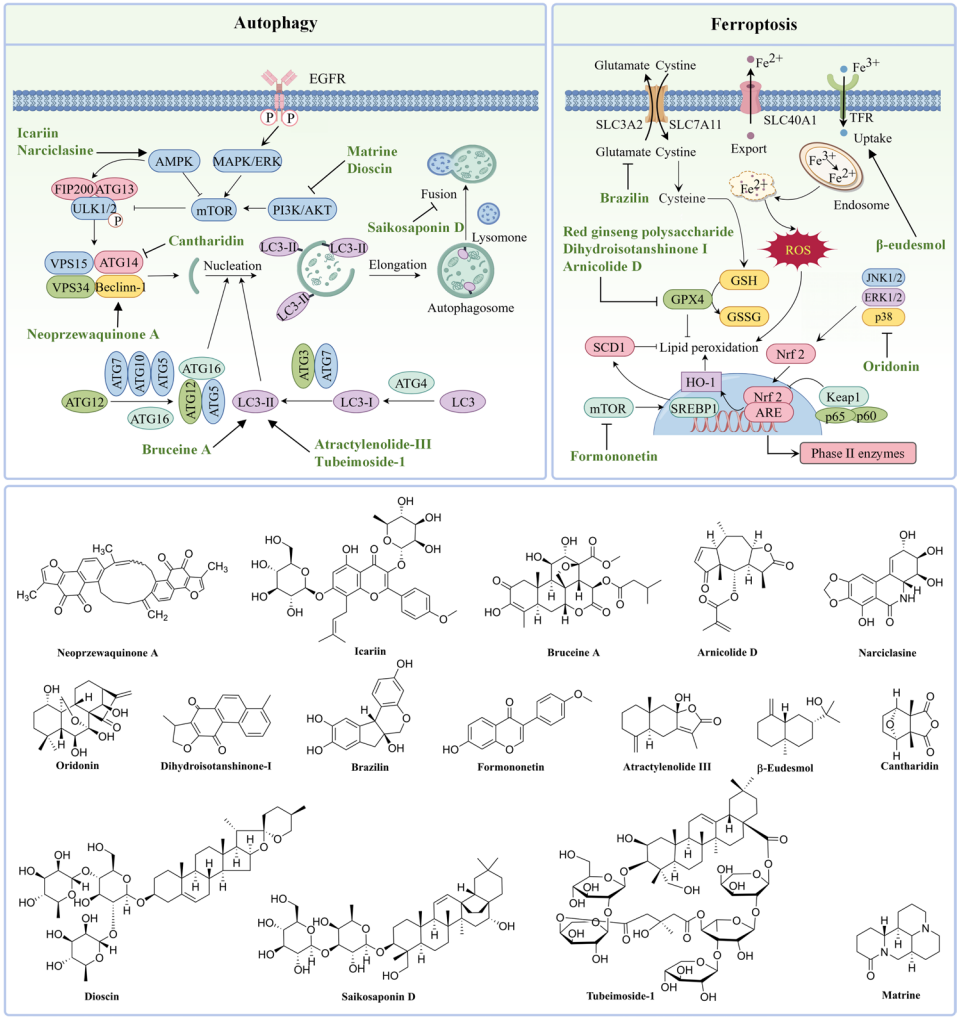

Fig. 4 Bioactive ingredients of TCM affect the autophagy and ferroptosis of BC cells. ↑: activation; ⊥: inhibition

Bioactive ingredients of TCM affecting autophagy of BC cells

Autophagy, as a type II programmed cell death, is a highly conserved cellular catabolic process, which is a multistep pathway involving autophagy initiation, nucleation, elongation, maturation, fusion with lysosome and degradation. The autophagy process is controlled by the autophagy-related (ATG) proteins-Unc-51-like kinase (ULK1/2) kinase core complex, the autophagy-specific class III PI3K complex, the ATG9A trafficking system, and the microtubule-associated protein 1 A/1B-light chain 3 (LC3) systems [170]. In cancer, the dual roles of autophagy depend on the disease stage and mutational background, which can play both tumor-suppressive and tumor-promoting roles [171] (Fig. 4). In addition to blocking the cell cycle, neoprzewaquinone A can induce apoptosis and autophagic death by upregulating the expression of Beclin1 and LC3B while down-regulating the expressions of ATG5 [143]. However, cantharidin suppresses autophagy through inhibiting the conversion of LC3I to LC3II and the formation of autophagosomes. By suppressing the expression of Beclin-1, the efficacy of cantharidin is increased in TNBC cells [172]. Bruceine A, a quassic ester from Bruceae Fructus, initiates autophagy as indicated by the upregulation of LC3I/II and ATG5 through targeting the PI3K-AKT pathway [173]. Saikosaponin D, activating p38/MAPK pathway to induce apoptosis of BC cells, blockades the fusion of autophagosomes and lysosomes, resulting in the inhibition of the autolysosome formation and autophagic flux [168]. Atractylenolide-III palys chemopreventive roles on mammary tumorigenesis. Mechanically, atractylenolide-III promotes the upregulation of the autophagy markers Beclin1, LC3, and ULK1 and autophagic degradation of Keap1, by which activating the Nrf2/ARE pathway and inhibiting inflammation and oxidative stress [174].

mTOR, as a key effector of autophagy, inhibits the activation of ULK1, which is regulated by multiple pathways [175]. Adenosine monophosphate-activated protein kinase (AMPK) directly phosphorylates and activates ULK1 while inactivating mTOR. Icariin is the main flavonoid of the Epimedium, significantly inhibiting BC growth. Zhao et al. treated TNBC cells with icariin, they find that the LC3 II/LC3 I ratio (an indicator of autophagic flux) and BECN1 (a marker of autophagosome formation) increased while p62 (an indicator of autophagic degradation) decreased, indicating the promoting of autophagy through the AMPK/mTOR/ULK1 pathway [176]. Matrine exerts anti-BC activity by promoting protective autophagy via the AKT/mTOR pathway. Higher matrine concentrations induce the upregulation of LC3 II and the downregulation of p62 [177]. Pharmacological research has demonstrated that dioscin attributes to the G1 phase arrest in BC [130]. Several researchers have also proved that, as an inducer of autophagy, dioscin increases adriamycin chemosensitivity by upregulating LC3 II expression through inhibiting PI3K/AKT pathway [178]. Tubeimoside-1 is a natural ingredient isolated from Bolbostemma paniculatum (Maxim.), which has been widely used in numerous Chinese medicine preparations. As a promising antitumor modulator, tubeimoside-1 induces autophagy in BC cells by inhibiting AKT-mTOR-eEF-2 K pathway, evidenced by increased LC3 II level, presence of autophagosomes, and enhanced autophagic flux [179].

Bioactive ingredients of TCM inducing ferroptosis of BC cells

Ferroptosis is a form of programmed cell death that was proposed in 2012. Unlike apoptosis and autophagy, ferroptosis is usually accompanied by iron-dependent ROS accumulation and extra-mitochondrial lipid peroxidation induced by inhibiting system Xc- and preventing cystine import, or by inactivating the phospholipid hydroperoxidase glutathione peroxidase 4 (GPX4), which ultimately leads to oxidative cell death [180, 181]. Recent studies have indicated that ferroptosis is closely linked to the pathophysiological processes of tumors. Consequently, inhibiting BC progression through intervening ferroptosis has become a major research focus. Here, we summarize the novel roles of natural ingredients as ferroptosis inducers in cancer therapy (Fig. 4).

Brazilin, a main active ingredient of Sappan wood, has been proved has antitumor effects by actuating ferroptosis. Specifically, with the treatment of brazilin in BC cells, the levels of Fe^{2+}, ROS, and MDA are increased, while the expression of SLC7A11, GPX4, and glutathione (GSH) are decreased, indicating the occurrence of lipid peroxidation and ferroptosis [182]. The clinical effect of Salvia miltiorrhiza Bunge in the treatment of BC is promising. Its bioactive ingredient, dihydroisotanshinone I, inhibits the proliferation and promotes apoptosis of BC cells by inducing ferroptosis through lipid peroxidation [183]. Furthermore, arnicolide D and red ginseng polysaccharide downregulate GPX4 expression while promoting Fe^{2+} and MDA accumulation, thereby inducing ferroptosis in BC cells [154, 184]. Iron transport proteins, including ferroportin (SLC40A1) and transferrin receptor (TFR), mediate iron release and cellular iron trafficking. A deficiency in SLC40A1 or overexpression of TFR causes iron overload, thereby triggering ferroptosis. β-eudesmol, a sesquiterpene from Atractylodis macrocephalae Rhizoma, elevates Fe^{2+} levels by targeting SLC40A1 and TFR. Simultaneously, β-eudesmol suppresses SLC7A11 and GPX4 to

promote lipid peroxidation. Through the dual action on iron metabolism and antioxidant pathways, β-eudesmol induces ferroptosis in BC cells by inhibiting MAPK signaling [185]. The mTOR signaling pathway also plays an important role in regulating ferroptosis. As an isoflavone derived from Astragali Radix, formononetin inhibits the PI3K/AKT/mTOR signaling pathway to induce ferroptosis. On the one hand, formononetin suppresses cystine uptake via SLC7A11, thereby reducing GSH synthesis, while concurrently inhibiting GPX4 expression to promote lipid peroxidation. On the other hand, formononetin mTOR downstream effectors SREBP1 and SCD1, which regulate lipid synthesis/distribution and modulate cellular sensitivity to ferroptosis [186, 187]. Collectively, these mechanisms enable formononetin to suppress BC proliferation through ferroptosis induction [188]. JNK/Nrf2 pathway plays a critical role in oxidative stress by regulating detoxification and antioxidant substances, such as MDA, GSH, and heme oxygenase-1 (HO-1). Research has demonstrated that oridonin can decrease the nuclear Nrf2 levels by inhibiting JNK to enhance the effect of RAS-selective lethal 3 on accumulation of lipid peroxidation products and iron to induce ferroptosis in BC cells [189].

Bioactive ingredients of TCM affecting metabolism of BC

Metabolic reprogramming, a hallmark of malignancy, drives rapid cancer cell growth and proliferation by modulating energy metabolism (Fig. 5). Glycolysis and lactic acid fermentation have been reported to be the preferred metabolic modes for hypoxic and proliferating cancer cells. Unlike normal cells obtaining energy through oxidative phosphorylation (OXPHOS), cancer cells preferentially convert pyruvate, the end product of glycolysis, into lactate rather than directing it into mitochondrial for O_2-dependent metabolism even in the presence of oxygen, which is the Warburg effect, the most classic example of metabolic reprogramming in cancer [190]. Pachymic acid, a competing activator of pyruvate kinase M2, mimics fructose-1,6-bisphosphate to blockage glycolysis and lactate production. Moreover, pachymic acid inhibits hexokinase II and promotes the detachment of hexokinase II from mitochondria, thereby inhibiting glycolysis and initiating the mitochondrial apoptotic

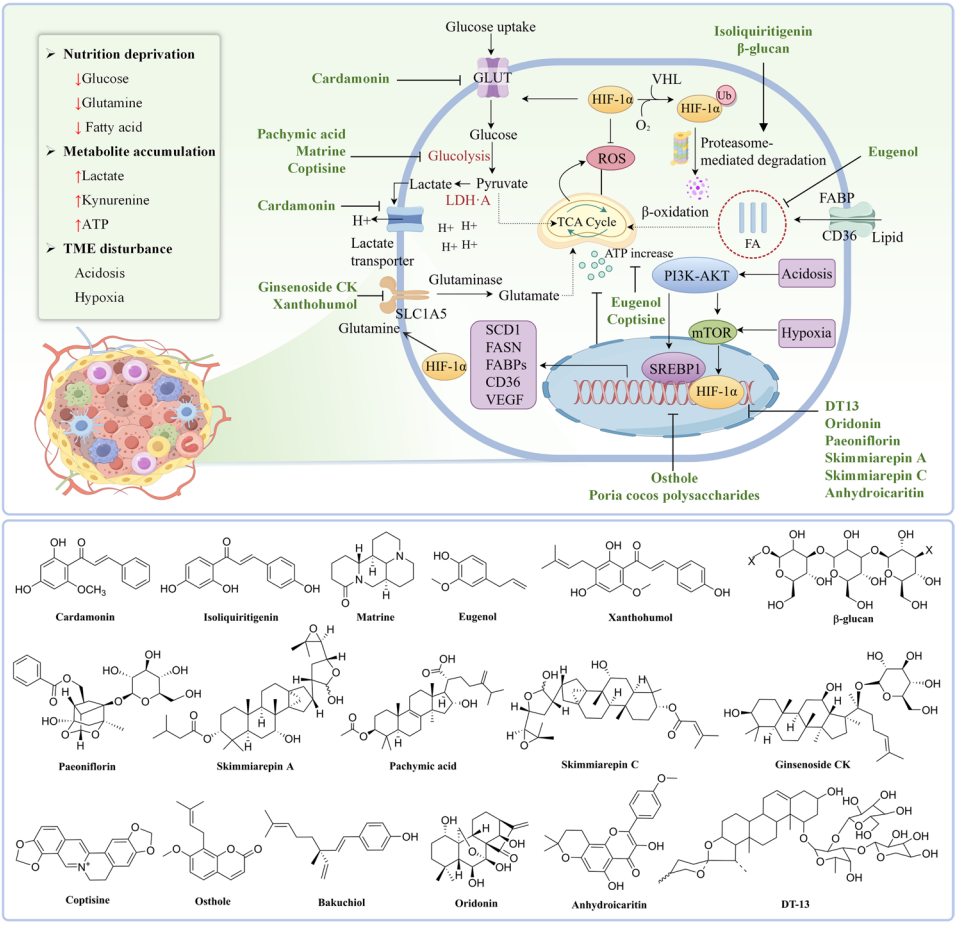

Fig. 5 Bioactive ingredients of TCM inhibit the energy metabolism of BC. ↑: activation; ⊥: inhibition

pathway [191]. Matrine, a key quinolizidine alkaloid isolated from the roots of *Sophora flavescens* Ait., inhibits BC by promoting autophagy [177]. Xiao et al. have also proved that matrine inhibits the expression of hexokinase II to down-regulate energy metabolism, accounting for its cytotoxic effects [192]. In addition to inhibiting glycolysis, certain natural products can directly affect mitochondrial OXPHOS. For example, coptisine inhibits the complex I of mitochondrial electron transport chain, reprograms cellular metabolism, and ultimately inhibits the proliferation of TNBC cells [193].

Lipid metabolism is abnormal in rapidly proliferating cancer cells. For example, tumor cells prefer de novo fatty acid (FA) synthesis compared to normal cells, which is fundamental for the biosynthesis of cell membranes and signaling molecules [194]. Therefore, limiting the supply of FA or inhibiting FA synthesis is one of the means to limit the proliferation of cancer cells. Fatty acid synthase (FASN), a key enzyme involved in endogenous fatty acid synthesis, is upregulated in BC and promotes metastasis [195]. Osthole inhibits FASN expression by suppressing mTOR and downregulating sterol regulatory element-binding protein 1 (SREBP1), a transcription factor consoling fatty acid and cholesterol biosynthesis, which reduces FA synthesis and esterification into phospholipids, limiting their incorporation into cell membranes. Eventually, osthole inhibits cell proliferation, induces cell cycle arrest, and promotes apoptosis [196]. Poria cocos polysaccharides not only inhibits FASN, but also decreases the expression of CD36 to suppress the uptake of lipid through LEP/SREBP1/FASN and PI3K/AKT pathways [197]. At the same time, fatty acid oxidation (FAO) as an important alternative energy source has been used to provide ATP for BC cells survival and proliferation. Eugenol, a phenolic aromatic ingredient derived from clove oil, significantly suppresses intracellular ATP levels in BC cells by reducing OXPHOS complex activity and FAO protein expression (PPARα, MCAD, and CPT1C) through the downregulating c-Myc/PGC-1β/ERRα pathway. Consequently, eugenol shifts energy metabolism away from OXPHOS and FAO, limiting ATP availability for rapid proliferation and suggesting a preventive role in mammary carcinogenesis [198].

Amino acids, particularly glutamine, are important sources of energy in cancer cells. Inhibition of glutamine metabolism decreases energy and nutrient production in cancer cells, ultimately limiting their proliferation. Ginsenoside CK inhibits glutamine metabolism by decreasing glutaminase synthesis in TNBC, decreasing ATP production and amino acid availability, resulting in GSH depletion and ROS accumulation, and ultimately leading to cell growth inhibition and apoptosis. The researchers also found that ginsenoside CK inhibits carbon metabolism, purine metabolism, and the metabolism of numerous amino acids (glycine, serine and threonine metabolism, histidine metabolism, etc.) and downregulates phenylalanine and tyrosine, which are essential amino acids involved in glucose and lipid metabolism [199]. The natural ingredient xanthohumol, the most abundant prenylated flavonoid in hops, has been proved inhibition of BC cell proliferation and migration through different mechanisms [200]. Recently, scientists have found that xanthohumol exerts cytotoxic effects on TNBC cells by inhibiting glutamine uptake. Mechanically, xanthohumol is a non-competitive inhibitor of Na-dependent 3 H-glutamine transport systems and inhibits L-γ-glutamyl-p-nitroanilide (GPNA) sensitization, alanine, serine, and cysteine transporter 2 (ASCT2) mediated and non-ASCT2 mediated 3 H-glutamin uptake [201].

Hypoxia-inducible factor-1α (HIF-1α) is an important regulator of BC cell metabolism. Under hypoxic conditions, HIF-1α increases glycolysis to produce lactate while suppressing mitochondrial OXPHOS [202]. Importantly, HIF-1α contributes to an acidic TME and induces lipid droplet accumulation that can be used for energy production [203]. Abundant studies have proved that natural products target HIF-1α through various mechanisms to inhibit BC progression. Cardamonin, a chalcone isolated from Sophorae Flavescentis Radix, not only inhibits glucose uptake by suppressing the expression of the glucose transporter (GLUT) induced by HIF-1α. At the same time, cardamonin inhibits the expression of lactate transporter proteins, leading to a decrease in lactate efflux and ultimately reducing BC cell activity [204]. Skimmiarepin A and skimmiarepin C are extracted from Bael tree (Aegle marmelos), having the ability of suppressing cellular respiration by selectively inhibiting the mitochondrial electron transport chain at complex I (NADH dehydrogenase) and inhibiting HIF-1 activation by blocking the hypoxia-induced accumulation of HIF-1α protein [205].

Bioactive ingredients of TCM inhibiting BC metastasis

The spread of cancer cells to distant organs and lymph nodes poses a major challenge in the clinical management of BC. Tumorigenesis begins with uncontrolled proliferation of cancer cells at the primary site [206]. Under conditions of hypoxia and acidosis, cancer cells activate EMT programs, acquiring migratory and invasive capabilities [207]. These cells breach the basement membrane and degrade the extracellular matrix (ECM), subsequently intravasating into nearby blood or lymphatic vessels to become circulating tumor cells (CTCs) [208]. Within the circulatory system, CTCs face significant challenges, including detrimental shear stress and immune attacks, yet a subset survives through cluster formation or entry into dormancy. Upon reaching the

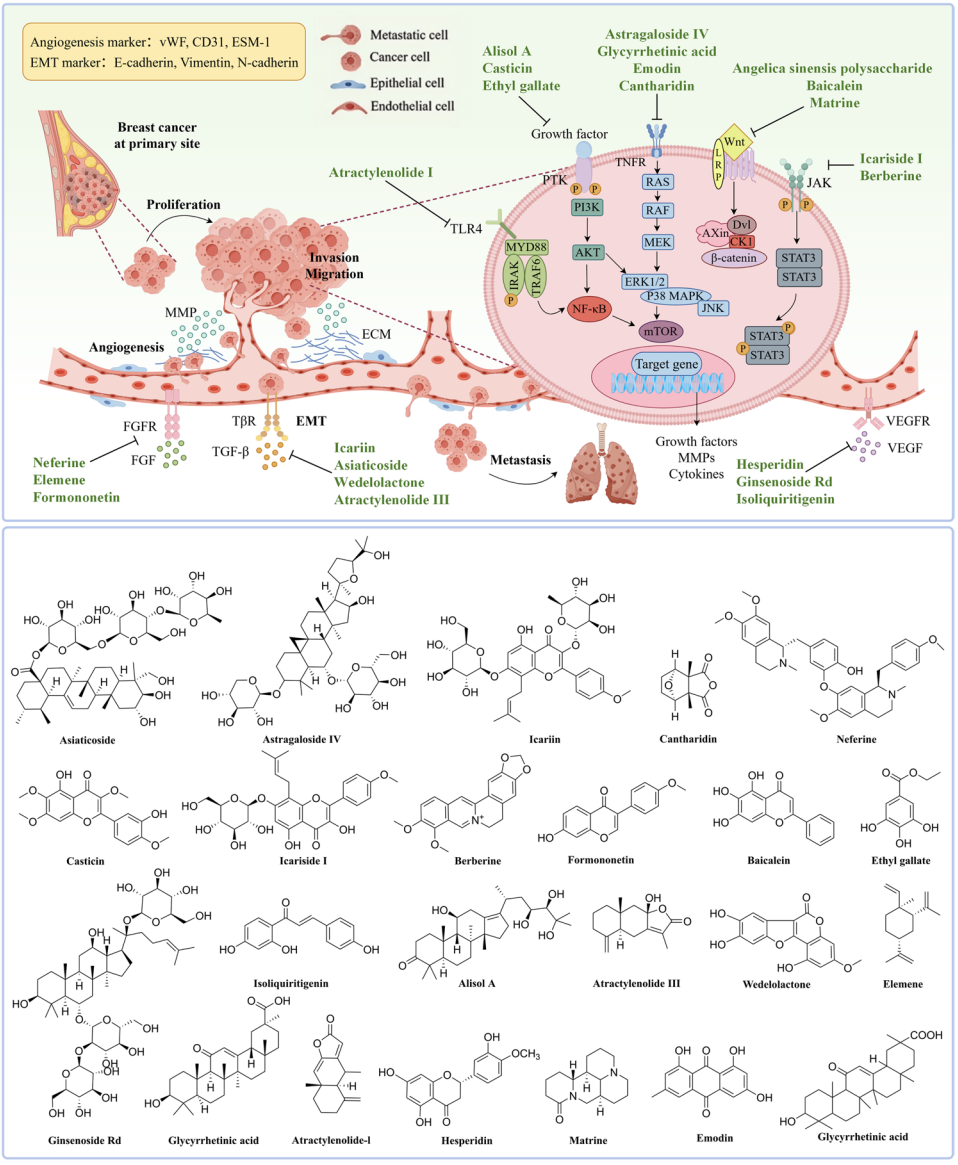

Fig. 6 Bioactive ingredients of TCM inhibit the metastasis of BC. ↑: activation; ⊥: inhibition

microvasculature of distant organs (e.g., bone, lung, liver, and brain), they become lodged, adhere to the endothelium, and extravasate into the target tissue, where successfully colonized cells induce angiogenesis to secure nutritional support, evade immune surveillance, and proliferate to establish clinically detectable metastatic lesions [207]. Thus, metastasis constitutes a highly complex process and involves multiple mechanisms including detachment from the primary tumor, local invasion, immune evasion, and reprogramming of the tissue microenvironment (Fig. 6).

EMT, which confers metastatic properties to tumor cells by enhancing their invasiveness, facilitating tissue invasion, and enabling distant organ colonization, has emerged as a key regulator of BC metastasis. This dynamic progress is characterized by downregulation of epithelial markers (E-cadherin) and upregulation of mesenchymal markers (N-cadherin and Vimentin). It is well-established that among the signaling pathways regulating EMT, TGF-β is one of the earliest identified inducers, especially in advanced cancers, where it has been implicated in cancer cell metastasis and drug resistance [209]. TGF-β binds to its receptor (TβR), activating the downstream mediators SMAD2 and SMAD3. These activated SMADs then form a complex with SMAD4 and translocate to the nucleus. The TGF-β/SMAD pathway thus serves as a key regulator of cancer progression and metastasis [210]. Asiaticoside inhibits P2X purinoceptor 7 (P2RX7)-mediated TGF-β/SMAD signaling by upregulating the expression of peroxisome proliferator-activated

receptor gamma (PPARG), thereby inhibiting TNBC cell migration, invasion, and EMT [211]. Furthermore, atractylenolide III, osthole, and wedelolactone also suppress EMT through TGF-β/SMAD pathway regulation, demonstrating therapeutic potential against BC [212–214]. Long non-coding RNAs (lncRNAs) modulate TGF-β/SMAD activation, notably, icariin downregulates lncRNA NEAT1 to attenuate TGF-β/SMAD signaling, potentiating its EMT-inhibitory effects [215].

In tumor cells, various signals from TME, such as Wnt, growth factor receptor signaling, RAS/MAPK, and changes in ECM play important roles in the EMT process and angiogenesis. The crosstalks of various pathways are indispensable for constant expression of EMT-associated transcription factors. The toll-like receptor 4 (TLR4) is the first identified member of the TLR family that has been described as a promoter of cell invasiveness and angiogenesis in BC [216]. Long et al.. demonstrated that atractylenolide-I, a novel TLR4-antagonizing agent, inhibits TLR4-NF-κB pathway and thus inhibiting cell migration and invasion [217]. In addition, there is evidence indicating that canonical Wnt/β-catenin pathway is frequently activated in BC and induces cancer stem cells to undergo EMT [218]. Angelica sinensis polysaccharide inhibits miR-3187-3p expression and then promotes PCDH10 expression, which is a member of the procadherin family and regulates the Wnt/β-catenin pathway to inhibit the progression of BC. Thereby, angelica sinensis polysaccharide inhibits the activation of the Wnt/β-catenin signaling pathway to suppress cancer cell migration and proliferation [219]. Nischarin, which exhibits low expression in BC, shows negative correlations with ER status and Wnt/β-catenin signaling. He et al.. have proved that baicalein upregulates nischarin expression, subsequently downregulates β-catenin and Axin 1, which inhibits the activation of Wnt signaling pathway, thereby reduces BC cell migration and invasion [220]. The activated STAT network in both cancer cells and tumor-associated endothelial cells is indispensable for breast tumor progression to overt metastasis. Consequently, targeted inhibition of the JAK/STAT pathway offers a promising theoretical foundation and potential therapeutic strategy for BC management. Supporting this approach, the epimedium flavonoid icariside I effectively downregulates the expression of the metastasis-related genes matrix metalloproteinase (MMP)-9 and vimentin by inhibiting STAT3 phosphorylation [221]. JAK/STAT pathway also interacts and activates PI3K and RAS signaling pathways [222].

It is well known that growth factor-mediated induction of RTKs and MAPK are overactivated in a variety of cancers, which play crucial roles in multiple pro-tumor processes, including cell growth, apoptosis regulation and ECM gene expression. The MAPK and PI3K/AKT pathways constitute a central oncogenic signaling nexus that drives tumorigenesis through complementary mechanisms. Numerous related pathway inhibitors are considered potential therapeutic agents in BC. Formononetin and casticin are found in many plants, which can inhibit the expression of MMP and suppress the initiation of EMT through PI3K/AKT pathways. As depicted before, alisol A inhibits the proliferation of cancer cells through autophagy induction and cell cycle arrest at G0/G1 phase. Moreover, alisol A downregulates the expression of MMP-2/9 to suppress cell metastasis by inhibiting the activities of PI3K/AKT/mTOR and NF-κB [223]. Ethyl gallate, isolated from the natural plant, is a phenolic acid derivative. Cui et al. that treatment of ethyl gallate significantly downregulates cell adhesion, migration, and invasion by the PI3K/AKT/NF-κB pathway [224]. Dried *Mylabris* specimens have been used for many years in China to treat BC. Its active constituent, cantharidin, has been proved to inhibit BC by arresting the cell cycle, promoting apoptosis, and regulating autophagy. Cantharidin also is a potent and selective inhibitor of protein phosphatase 2 A (PP2A). This inhibition decreases phosphorylation levels within the MAPK signaling pathway, thereby exerting potent inhibitory effects on BC growth and metastasis [225]. Licorice, derived from the dried roots and rhizomes of *Glycyrrhiza uralensis* Fisch., is recorded in the pharmacopoeias of China, Japan, US, and Europe. It contains more than 400 ingredients, among which glycyrrhetinic acid specifically inhibits p38 MAPK activity and its downstream activator protein-1 (AP-1), thereby suppressing MMP-2 and MMP-9 expression in BC cells and inhibiting their invasion. Importantly, glycyrrhetinic acid achieves these effects without causing weight loss or inducing liver/kidney toxicity in BC animal models [226].

Tumor angiogenesis is a pathophysiological process in which new blood vessels sprout from pre-existing vasculature to supply nutrients, oxygen, and cellular networks that support tumor growth, contribute to cancer progression, metastasis, and drug resistance [227]. The mechanisms underlying tumor angiogenic pathways are diverse and are typically activated by various angiogenic stimuli. The receptors for these stimuli interconnect to form specialized signaling pathways, among which vascular endothelial growth factor receptor (VEGFR) serves as a key mediator of tumor angiogenesis and is established as a major therapeutic target for anti-angiogenic therapy [228]. Hesperidin, a natural ingredient available in the diet, has been reported to suppress tumor angiogenesis and reduce microvessel density through downregulating VEGF, VEGFR, and CD105 [229]. HIF-1α bound to hypoxia-responsive elements has been reported to increase the expression of VEGF/VEGFR pathway, which in turn activates AKT/mTOR/p70S6K pathway,

and jointly triggers multiple functions such as tumor cell proliferation, angiogenesis, and metastasis during tumorigenesis. Ginsenoside Rd inhibits angiogenesis is a novel inhibitor of HIF-1α/VEGF and AKT/mTOR/p70S6K pathways [230]. However, isoliquiritigenin not only inhibits VEGFR activity by directly interacting with the ATP-binding site of VEGFR, but also blocks VEGF expression via promoting HIF-1α the proteasomal degradation of HIF-1α [231]. Ephrin-B2 is essential for the full signaling activity of VEGFR. Targeting ephrin-B2, berberine down-regulates AKT and ERK1/2 downstream of VEGFR, thereby inhibiting the expression of MMP2 and MMP9 [232]. The *fibroblast growth factor receptor (FGFR)* abnormalities were detected in about 18% BC patients, which can promote proliferation, differentiation, survival, migration, and angiogenesis of cancer cells. Approximately 18% of BC patients exhibit abnormalities in the FGFR, which promotes cancer proliferation, differentiation, survival, migration, and angiogenesis. Key downstream signaling pathways of the FGF/FGFR axis include the Ras/Raf-MEK-MAPK pathway, the PI3K/AKT pathway, and the STAT pathway [233]. Formononetin inhibits both the interaction of FGF with FGFR and the downstream signaling of STAT3 and the PI3K/AKT pathway. Moreover, formononetin inhibited the expression of TGF-β, CD31, COX-2, and angiopoietin-2 (Ang-2) to inhibit vascular maturation [234]. Neferine, a major bisbenzylisoquinoline alkaloid, suppresses miR-374a expression and downregulates FGFR expression, thereby exerting anti-angiogenic effects through the inhibition of the PI3K/AKT and MEK/ERK signaling pathways [235].

Bioactive ingredients of TCM improving immunity of host

Tumor immune escape presents a significant challenge in cancer treatment, characterized by the upregulation of immune inhibitory molecules and dysfunction of immune cells [236]. Tumor immunotherapy seeks to restore normal anti-tumor immune responses to control

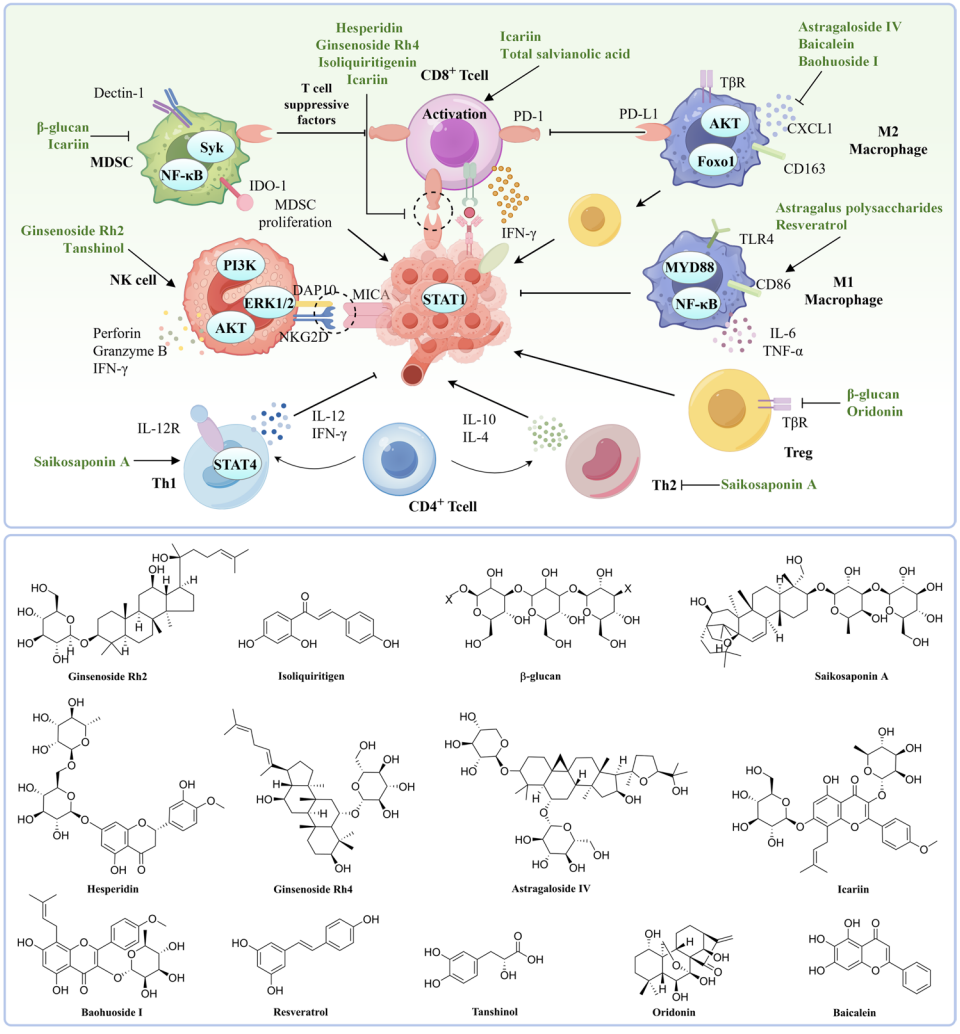

Fig. 7 Bioactive ingredients of TCM improve the immunity of host. ↑: activation; ⊥: inhibition

and eliminate tumors effectively. Immune cells, such as tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), natural killer cells (NKs), and Tregs, play an essential role in the immune system. TCM, with its inherent multi-component, multi-target, and multi-pathway properties, not only directly induces tumor cell death but also potently modulates diverse immune cell populations, thereby enhancing anti-tumor immunity and therapeutic efficacy [237] (Fig. 7).

β-glucan extracted from Poria, can reverse the tumor immunosuppressive microenvironment induced by Gemcitabine [238]. β-glucan inhibits the differentiation of bone marrow-derived MDSCs in Gemcitabine-treated E0771 cells through the Dectin-1 pathway, directly suppressing the expansion of MDSCs. In addition, β-glucan downregulates the expression of IDO1 on MDSCs while promoting the expression of MHC-II, CD86, TNF-α, and IL-6 [239]. MDSCs can inhibit the secretion of perforin and interferon-γ in $CD8^+$ T cells, thereby preventing the killing of tumor cells [240]. β-glucan revised Gemcitabine-induced $CD8^+$ T cells depletion in the tumor and spleen [239]. Icariin upregulates the expression of SIRT6 and impairs the NF-κB pathway, producing the similar effect as β-glucan. In addition, it can also inhibit the proliferation of Tregs and transcription of programmed death ligand 1 (PD-L1) [241]. PD-L1 is the primary ligand for programmed death receptor 1 (PD-1) and activated T cells express the PD-1 receptor [242]. Flaxseed lignans, a plant estrogen structurally analogous to human estrogen, enhances the efficacy of PD-1/PD-L1 inhibitor against BC by modulating the gut microbiota and regulating immunity to remodel the TME [243]. Oridonin can also regulate Tregs differentiation to inhibit the growth of TNBC. Oridonin promotes the degradation of TβRI and TβRII proteins, thereby inhibiting TGF-β1 signaling and ultimately inhibiting Tregs differentiation, effectively increasing $CD8^+$ T cell response [244]. Hesperidin inhibits the expression of PD-L1 via downregulation of AKT and NF-κB signaling in TNBC [245]. Ginsenoside Rh4 reduces PD-L1 expression by inhibiting HDAC2/JAK2/STAT1 [246]. Isoliquiritigenin is a flavonoid present in Glycyrrhizae Radix et Rhizoma. Isoliquiritigenin-intercepted ERK and Src signaling pathways led to the disappearance of PD-L1 by diminishing ZEB1/2 and enhancing miR-200c in BC cells [247].

TAMs are heterogeneous and plastic cell populations in the TME, constantly transitioning between M1 and M2 phenotypes [248, 249]. Recent studies have shown that pro-angiogenic factors produced in the TME may promote the recruitment of TAMs and even induce monocyte polarization to M2 phenotype macrophages [250]. Research has shown that the combination of total salvianolic acid and anti-PD-L1 can reduce the release of inflammatory factors IL-6 and MCP-1, inhibit the expression of macrophage chemokines CXCL1, CXCL2, CXCL3, CCL2, and GM-CSF, thereby inhibiting the infiltration of M2 macrophages into tumor tissue, increasing the number of $CD4^+$T cells and $CD8^+$T cells in the spleen and lymph, and ultimately suppressing immune escape [251]. Astragaloside IV, a lanolin-alcohol type of tetracyclic triterpenoid saponin, results in the deactivation of the AKT/Foxo1 signaling pathway via suppressing TGF-β and the deactivated AKT/Foxo1 inhibited the TAMs polarized toward M2 phenotype [252, 253]. In addition, baohuoside I inhibits the M2 polarization of TAMs, thereby reducing the expression and secretion of CXCL1, and ultimately inhibiting the metastasis of BC cells [254]. β-Glucan can promote TAMs M1 polarization while inhibiting M2 polarization by promoting Nur77 expression [255]. Astragalus polysaccharides can also promote M1 polarization in TAMs, activate the TLR4-MyD88-dependent pathway through TLR4 and subsequently promote the expression of TRAF-6, NF-κB, and AP-1. Finally, the production of IL-6 and TNF-α is enhanced to regulate the immune system and exert anti-tumor effects [256].

NK cells are a subset of lymphocytes derived from the development and differentiation of hematopoietic stem cells in the immune system. Tanshinol, a water-soluble active component of Salviae Miltiorrhizae Radix et Rhizoma, can interfere with the activation of SMAD2/3 triggered by TGF-β1 to propel the formation of NKG2D-DAP10 complex [257]. In addition, tanshinol could activate PI3K-ERK1/2-PLCγ2 signaling cascade that is involved in NK cell degranulation, restore the synthesis and secretion of perforin and IFN-γ interfered by TGF-β1, thereby restoring the tumor-killing activity of NK cells and plays an anti-tumor role in BC [257]. Ginsenoside Rh2, extracted from Ginseng Radix et Rhizoma, promotes the activity of the NKG2D-MICA signaling axis by directly binding to ERp5, thereby enhancing the cytotoxic effect of NK cells [258]. The balance between T helper cell type 1 (Th1) and Th2 is associated with antitumor immunity in BC. Saikosaponin A, isolated from Bupleuri Radix, increases $CD8^+$ T cells and $CD4^+$ T cells infiltrated in tumors to enhance antitumor immunity. Besides, saikosaponin A activates IL-12/STAT4 pathway to increase serum IFN-γ and IL-12 levels and decreases in serum IL-4 and IL-10 levels, which shift Th1/Th2 balance toward Th1 [259].

Structural modification of TCM-derived compounds in the treatment of BC

Natural products from TCM possess new chemical structures and unique biocompatibility, making them an important source of innovation in drug discovery [363]. Many modern pharmaceuticals are developed through the structural modification of natural products. For

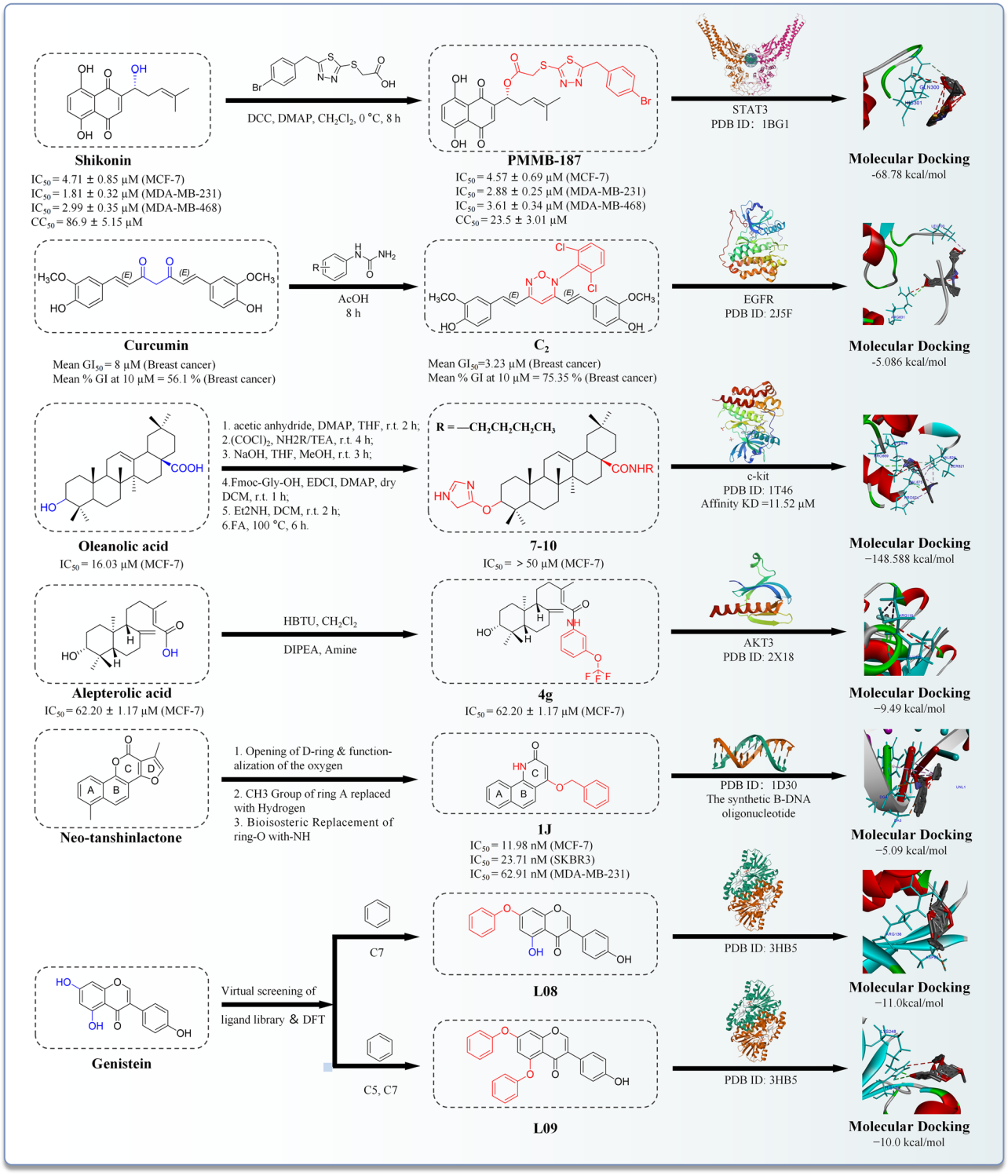

Fig. 8 Structural modification of TCM-derived compounds in the treatment of BC

example, docetaxel, an anti-cancer drug, is derived from the semi-synthetic of 10-deacetylbaccatin III, which is abundantly extracted from the branches and leaves of *Taxus chinensis (Pilger) Rehd*. Dihydroartemisinin is the main antimalarial drug that improves pharmacokinetic properties based on artemisinin. From 1981 to 2019, natural products and plant mixtures accounted for 4.6% of FDA approved drugs, while natural product derivatives accounted for an additional 18.9%. This indicates that synthetic derivatives of natural products are usually

more likely to be approved as drugs than themselves, and structural modifications will become a key bridge for successfully converting natural products into new pharmaceuticals [364]. At present, we have found many natural products that play a significant role in the progress of breast cancer treatment. However, the challenges such as non-selective cytotoxicity, low water solubility, poor bioavailability, low bioactivity, weak affinity and scarcity of sources in natural products limit their development to new pharmaceuticals. Based on the above shortcomings, we have summarized the compounds that have been studied for structural modification, including shikonin, curcumin, oleanolic acid, alepterolic acid, neo-tanshinlactone and genistein, aiming to provide ideas for structural modification of natural products (Fig. 8).

Shikonin, which features a naphthoquinone scaffold, exhibits antitumor and anti-metastatic activity by suppressing the STAT3 activation both in vitro and in vivo. However, its clinical utility is limited due to the promiscuous targeting and consequent non-selective cytotoxicity. The hydroxyl group on the side chain of shikonin provides an ideal modification site for optimization, and the most effective compound (R)-1-(5,8-dihydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-4-methylpent-3-en-1-yl 2-((5-(4-bromobenzyl)-1,3,4-thiadiazol-2-yl) thio)acetate (PMMB-187) was obtained by using scaffold growth strategy. STAT3 inhibitors typically occupy two or more adjacent subpockets within the SH2 domain, i.e. pY-X (Δ592–605), pY + 0 (591, Δ609–620), and pY + 1 (Δ626–639) pockets. The interaction between the pTyr705 residue and the pY + 0 pocket plays an important role in the binding process. PMMB-187 mainly embeds into the pY-X and pY + 0 subpockets of the SH2 domain. In addition, the modified component also forms hydrogen bonds with GLN635 and SER636, as well as other non-covalent interactions to increase binding affinity. Finally, through cellular and animal experiments, it was found that the derivative PMMB-187 of shikonin inhibits constitutive/inducible STAT3 activation, STAT3 nuclear localization, STAT3 transcriptional activity, and the expression of STAT3 target gene to inhibit cell proliferation and induce apoptosis [365]. In addition, the toxicity is significantly reduced both in vivo and in vitro. PMMB-187 demonstrates better anti-tumor effects than shikonin, which suggests that this type of natural product derivatives may facilitate the discovery of potent drugs.

Curcumin, one of the most extensively studied natural products, faces limitations in clinical applications due to factors such as low bioavailability and rapid metabolism. Chemical modification of curcumin diketone function can synthesize three semi- synthetic analogues containing pyrimidine ketone moiety. Among them, 1-(2,6-Dichlorophenyl)-4, 6-bis ((E)-4-hydroxy-3-methoxystyryl) pyrimidin-2(1 H)-one (C2) demonstrated better antitumor activity against MCF-7 cells compared to both curcumin and the other two curcumin derivatives. C2 exhibited a GI50 value of 2.00 μM in MCF-7 cells. EGFR represents a highly attractive target for antiproliferative agents. Molecular docking studies revealed that C2 binds within the active site of EGFR, exhibiting a calculated binding affinity of −5.086 kcal/mol. Furthermore, C2 displays significant interactions with the residues ALA 743, VAL 726, THR 790, LYS 745, LEU 799, ASP 800, GLY 721, LEU 781, CYS 775, LEU 844, CYS 797, SER 720, and PHE 723 [366]. In summary, the chemical modification of the diketone function to generate pyrimidinone analogues proved to be more promising for antitumor efficacy than analogous modifications yielding Biginelli-type curcumin derivatives.

C-Kit is a type III receptor tyrosine kinase that is highly expressed in breast cancer. Research has revealed that the amide group and imidazole ring of nilotinib formde hydrogen bonds with the amino acid residues ASP 810, GLU 640, and ILE 808 of the c-Kit protein to exert antitumor effect [367]. The amino acid residue ASP 810 was the key amino acid for the binding of the c-Kit protein with inhibitors. Oleolic acid, a chemical name of (3β)-3-hydroxyolean-12-en-28-oic acid, exerts anti-tumor pharmacological properties. However, the solubility of oleolic acid in water is low and the lipid-water distribution coefficient is not favorable. Therefore, structural modification of oleolic acid to transform the C-3 position into the imidazole ring and the C-28 position into the amide group. The derivative 3-O-(4'-imidazole)-12-en-olean-28-acyl-butylamine (7–10) indicate same inhibitory effect on MCF-7 cells to nilotinib. After the biomolecular interaction analysis, the binding response value of derivative 7–10 to c-Kit protein is positively correlated with compound concentration, and the affinity KD value is 11.52 μmol/L. Molecular docking studies revealed that derivative 7–10 interact with multiple amino acid residues of the c-Kit protein, such as ASP 810, ARG 791, IEU 644, CYS 809, VAL 654, etc. The binding affinity between derivative 7–10 and c-Kit is − 148.588 kcal/mol, which is similar to nilotinib (−147.460 kcal/mol) [368].

Alepterolic acid, a diterpene found in the fern Aleuritopteris argentea, deserves further structural modification due to its potential biological activity. It has been reported that derivatives of alepterolic acid exhibit pronounced anti-breast cancer activity. The amino moiety-tethered alepterolic acid derivatives displayed better potency against breast cancer cells. A series of derivatives were obtained by structural modification of alepterolic acid, and it was found that N-[m-(trifluoromethoxy) phenyl] alepterolamide (4 g) exert the strongest inhibitory ability on MCF-7 cells. Research found that the mechanism of the derivative 4 g inhibits MCF-7 may be through interference with the AKT/p70S6K signaling

pathway. Molecular docking confirmed that derivative 4 g showed similar docking scores with AKT1, AKT2 and AKT3, with AKT3 being identified as the most favorably docked kinase. The docking score of derivative 4 g in the active site of AKT3 was determinde to be −9.49 kcal/mol. Derivative 4 g formed hydrogen bond interactions with LEU 292, GLN 78, LYS 266 and ARG 270 as well as interacted with the π-alkyl of CYS 307, CYS 293, TYR 269, VAL 268 and TYR 18. Additionally, it formed van der Waals interactions with LYS 20, LYS 294, ILE 83, THR 81, LEU 262, VAL 190, TRP 79, ASP 271 and GLU 17 [369]. Therefore, derivative 4 g may be novel potential AKT inhibitor.

Neo-tanshinlactone, isolated from the root of *Salvia miltiorrhiza* Bge., serves as a promising lead compound for the development of novel anti-breast cancer drugs due to its synthetic feasibility and amenability to strategic modifications within its complex ring system [370, 371]. Through the modification of the neo-tanshinlactone D-ring, 13 derivatives were synthesized. Among these, 4-(Benzyloxy)benzo[h]quinolin-2(1 H)-one (1 J) demonstrated the most potent anticancer activity against the MCF-7, SKBR-3, and MDA-MB-231 breast cancer cell lines. In derivative 1 J, the D-ring was opened and a new lactam scaffold was achieved. After the analyses of UV-visible absorption, fluorescence emission spectral titrations and circular dichroism, it was revealed that the conformation and structure of DNA is changed after 1 J-DNA complexation. Subsequently DAPI displacement assay and molecular docking studies confirmed that 1 J binds tightly into the minor groove of DNA. 1 J showed minor grove binding interaction with DNA at AT-rich region and induced DNA double strand breaks (DDSBs), which activated the ATM, Chk2 and p53 in response to DNA damage signals induced via ERK and p38. This led to the caspase-3 and PARP cleavage mediated apoptosis in MCF-7 cells [372]. Thus, structurally edited NTL derivative showed strong anti-breast cancer activity via DNA damage pathway.

Genistein, the active compound found in *Glycyrrhiza uralensis* Fisch., exhibits notable anti-breast cancer efficacy. However, its binding affinity is relatively weak, necessitating the modification of the hydroxyl group of genistein. This modification involves substituting it with functional groups, such as COOH, NH2, OCH3, benzene, and NH-CH2-CH2-OH to enhance its binding affinity. Analysis using PASS prediction demonstrates that the genistein derivatives show improved anti-breast cancer activity. Following an investigation of in silico ADME, AMES toxicity and hepatotoxicity estimations, it was found that these genistein derivatives could serve as effective oral medications against breast cancer. According to the findings from docking analysis, the maximum scores were reported as −11.0 kcal/mol and −10.0 kcal/mol in derivatives 08 and 09 against breast cancer (PDB ID: 3HB5). The protein structure corresponding to PDB ID: 3HB5 is 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1), which catalyzes the final step in the synthesis of estradiol and androstenediol in breast tumor tissue, stimulating breast cancer progression. Additionally, derivatives 08 and 09 met the ADMET profile parameters, exhibiting good water solubility and high gastrointestinal absorption. Further validation through 100-ns molecular dynamics simulations confirmed their stability in inhibiting PDB ID: 3HB5, with minor fluctuations observed in RMSD and RMSF measurements. Moreover, they demonstrated promising outcomes in SASA, Rg, MolSA, and PSA evaluations [373]. These findings prompt us to utilize PASS prediction, molecular docking, ADMET and molecular dynamics simulations to explore the structural modifications of natural products for drug design.

Potential limitations and perspectives of available TCM in the treatment of BC

Based on systematic analysis of prior clinical studies (the results presented in Tables 2 and 3), we recognize that the core constraint of TCM, currently is an adjunct to the standard therapies for BC, lies in the severe lack of high-quality clinical evidence adhering to evidence-based medicine principles. Existing studies often have significant methodological flaws. Most RCTs fail to adequately implement allocation concealment or blinding, compromising the evaluation of efficacy through a high risk of performance and detection bias. Notably, insufficient sample sizes reduce statistical power, hindering the detection of TCM's potential efficacy as an adjuvant therapy and increasing the risk of false-positive or false-negative results. Furthermore, the absence of long-term follow-up precludes assessment of critical endpoints (e.g., overall survival and recurrence rates). Additionally, non-standardized data documentation and non-transparent reporting, such as failures to specify TCM constituents, dosages, or AEs, further compromise the credibility and reproducibility of researches. Collectively, these design flaws spanning randomization rigor, blinding implementation, sample size adequacy, follow-up completeness, and data integrity have undermined the reliability and generalizability of existing studies [374, 375], thereby restricting TCM's progression beyond an adjunctive therapeutic role.

A large number of clinical studies have clearly demonstrated that the combination of TCM and WM in the treatment of BC significantly outperforms WM alone. However, there are obvious limitations in the evaluation of the results of combination therapy in current clinical practice, which focuses excessively on the improvement of disease status, such as tumor size and prolonged

survival, while neglecting other crucial evaluation indices. First, there is a serious lack of systematic and standardized safety assessments for TCM (especially complex formulas) and its combination therapy with WM. This includes a shortage of rigorously designed long-term safety studies, with particularly insufficient attention paid to unique AE patterns that may arise from combination therapies. Notably, studies for the systematic recording and proactive reporting of AEs are alarmingly scarce. This paucity results in potential safety risks being routinely underestimated or ignored. The lessons learned from past experiences are profound. For example, Aristolochia containing aristolochic acid can induce nephropathy [376], while *Polygonum multiflorum* Thunb. and its main active ingredients such as anthraquinones are associated with hepatotoxicity [377]. Secondly, research on the complex interactions between TCM and WM is severely lacking. This includes both pharmacodynamic interactions and pharmacokinetic changes related to absorption, distribution, metabolism, and excretion. This gap in basic research makes it difficult to accurately predict and optimize combination drug regimens, potentially compromising efficacy or elevating risks. In addition, the quality of TCM is a key factor affecting the safety and efficacy. Problems such as adulteration during procurement, excessive pesticide residues, significant variations in active ingredient content across batches or sources, and heavy metal contamination significantly undermine the quality controllability of TCM and compromise the stability of their clinical efficacy. These issues further exacerbate the safety hazards associated with combination therapies.

Another factor limiting the widespread global adoption of TCM is its unique diagnostic and therapeutic philosophy. As a paradigm of individualized medicine, TCM requires highly dynamic clinical practice through its core principles of syndrome differentiation and formula modification based on symptom evolution. Even for patients with the same disease, treatments need to be adjusted according to individual syndrome patterns, disease stage, and physical constitution. This personalized medicine approach stands in sharp contrast to WM's paradigm of standardized molecular subtyping and targeted therapies [378]. Furthermore, diagnostic challenges pose significant barriers. TCM's diagnostic process and efficacy evaluation, relying on the four methods of observation, auscultation-olfaction, inquiry, and palpation, is heavily dependent on practitioner experience and lacks quantitative standards grounded in objective biomarkers or imaging evidence. This inherent subjectivity inevitably invites scientific skepticism within contemporary evidence-based medical frameworks [18]. Consequently, when clinical researchers impose artificial constraints on TCM dosage adjustments and formula modifications to comply with study standardization protocols, dynamic clinical practice is forced into static prescription templates. This pseudo-standardization fundamentally distorts authentic therapeutic evaluation. Furthermore, the lack of high-quality and standard guidelines further exacerbates the heterogeneity of treatment outcomes. In acupuncture, for example, treatment efficacy is highly dependent on the operator. The acupoint selection, manipulation techniques, and stimulation parameters significantly influence the results. These methodological inconsistencies impede the reproducibility of findings and ultimately undermine international scientific recognition of the reliability of TCM treatment.

As proposed by modern medical theory, identifying the specific target proteins and mechanisms of action of drugs is essential for understanding their effectiveness. Current research on TCM focuses on individual targets or pathways, aligning with the framework of modern medicine. However, this approach, which typically examines single-target mechanisms, diverges from the holistic and complex nature of TCM. TCM views the human body as an interconnected whole rather than focusing on isolated components [379]. As a result, concentrating exclusively on single targets or pathways may not fully capture the true mechanisms underlying TCM and could lead to a limited or even inaccurate understanding of its efficacy. However, the complex composition of TCM and the variety of active ingredients make it difficult to clarify its multiple mechanisms of action [380]. In addition, numerous derivatives with enhanced bioactivity have been obtained by structural modification of these active ingredients. However, a large number of studies have been remaining at the cellular level to validate the target sites of these derivatives, while the studies of verifying their drug efficacy and conducting safety evaluations at the animal level are relatively scarce, which affects the potential for drug development.

The aforementioned issues critically constrain the modernization and internationalization of TCM and its value realization within modern healthcare systems. Future research on TCM mechanisms must break through the limitations of single-target approaches and establish research strategies consistent with TCM's holistic philosophy, adhering to the closed-loop pathway: derived from clinical practice, verified through experimentation-returned to clinical practice. In research design, there should be a transition from randomized controlled trials to personalized pragmatic randomized controlled trials, establishing appropriate clinical efficacy evaluation technologies and methods aligned with TCM characteristics through three dimensions: advantageous populations, optimized treatment protocols, and efficacy indicator systems. Simultaneously, it is essential to establish a syndrome-centered evidence-based research

paradigm, standardize real-world clinical studies, and achieve multidimensional data mining. Concurrently, actively establish and improve TCM safety evaluation systems. To develop standardized guidelines covered the origin of medicinal materials, prescription compatibility, manufacturing processes, quality control, and pharmacovigilance, while also establishing TCM evaluation centers compliant with Good Agricultural Practice (GAP), Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and Good Clinical Practice (GCP) [381–383]. Furthermore, develop an innovative novel clinical diagnosis and treatment system for TCM "disease-syndrome integration". Primarily based on TCM's traditional "syndrome differentiation" through the four diagnostic methods, while also supplemented by modern biological indicators including laboratory tests, imaging examinations, and genetic tests, develop TCM syndrome diagnostic information collection and analysis equipment to unify Western standardized treatment with TCM's personalized strategies. Finally, using advanced technologies, including genomics, proteomics, metabolomics, network pharmacology, and artificial intelligence, to investigate TCM's in vivo metabolic processes, active components, and complex interactions. Construct "component-target-pathway" networks elucidating TCM's multi-component, multi-target, and multi-pathway characteristics. Through modern scientific approaches, clarify the scientific essence of TCM formulas to systematically interpret the "Principle-Method-Formula-Component" scientific framework, facilitating integration between traditional medicine and modern scientific systems while establishing a solid foundation for TCM's modernization and global integration [384, 385].

Conclusion

BC is influenced by a range of complex and multifactorial risk factors. Previous research has identified several key risk factors, including obesity, smoking, and alcohol consumption, all of which can disrupt endocrine function. The pathophysiology of BC is shaped by the interaction of these multiple etiological factors and various pathophysiological mechanisms, which together contribute to the disease's complexity. It is widely understood that BC does not arise from a single genetic abnormality but rather involves a perturbation in a broad array of cell types, including cancerous cells, immune cells, epithelial cells, vascular cells, stromal cells, and hormones. This complexity necessitates a holistic perspective and a multi-target therapeutic approach. WM alone often falls short in addressing these multifaceted pathologies. Numerous herbal components have demonstrated immune-protective and tumor-suppressive effects, offering potential therapeutic avenues. With a rich history spanning thousands of years, TCM provides an extensive theoretical framework and clinical knowledge base, making it a valuable resource in the prevention and complementary treatment of various cancers, including BC. In this review, we summarize the latest experimental and clinical research on the use of TCM in the treatment of BC, including the application of TCM formulas, herbal extracts, and non-drug therapies. Our aim is to provide a comprehensive theoretical foundation for the integration of TCM in BC management and to highlight its potential role in enhancing therapeutic outcomes.

Abbreviations

6MWD	6-Minute Walk Distance
17β-HSD1	17β-hydroxysteroid dehydrogenase type 1
A.D.	Anno Domini
AC-T	Doxorubicin and Cyclophosphamide followed by Taxane
AEs	Adverse events
AIF	Apoptosis-inducing factor
AIs	Aromatase inhibitors
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Ang	Angiopoietin
ANT	Anthracycline-based chemotherapy
AP-1	Activator protein-1
AVLT	Auditory-verbal learning test
ASCT2	Cysteine transporter 2
AST	Aspartate aminotransferase
ATG	Autophagy-related proteins
B.C.	Before Christ
BC	Breast cancer
BCRL	Breast cancer-related Chronic Lymphedema
BD-II	Beck depression inventory-II
BDNF	Brain-derived neurotrophic factor
BFI	Brief fatigue inventory
BGP	Bone gla protein
BMD	Bone mineral density
BPI	Brief pain inventory
BPI-SF	Brief pain inventory-short form
BPI-WP	Brief pain inventory worst pain
CA	Cancer associated antigens
CAF	Cyclophosphamide + Doxorubicin + Fluorouracil
CBR	Clinical benefit rate
CBT-I	Cognitive behavioral therapy for insomnia
CDKs	Cyclin-dependent kinases
CDT	Comprehensive decongestive therapy
CEA	Carcinoembryonic antigen
CEF	Cyclophosphamide epirubicin fluorouracil
CI	Confidence interval
CINV	Chemotherapy-induced nausea and vomiting
CIPN	Chemotherapy-induced peripheral neuropathy
CKI	Compound kushen injection
CK-MB	Creatine kinase-mb
CTC	Circulating tumor cells
cTnI	Cardiac troponin I
DCR	Disease control rate
DDSBs	DNA double strand breaks
DFS	Disease-free survival
DCIS	Non-invasive ductal carcinoma in situ
ECM	Extracellular matrix
ECOG-PS	Eastern cooperative oncology group performance status
EMT	Epithelial–mesenchymal transition
EOT	End of treatment
ER	Estrogen receptor
FA	Fatty acid
FACT	Functional assessment of cancer therapy
FACT-B	Functional assessment of cancer therapy-breast
FACT-COG	Functional assessment of cancer therapy - cognitive function

FACT-GOG-Ntx	Functional assessment of cancer therapy - gynecologic oncology group-neurotoxicity
FAO	Fatty acid oxidation
FasL	Fas ligand
FASN	Fatty acid synthase
FEER	Erythrocyte immune adherence enhancing rate
FEMT	Five-element music therapy
FGFR	Fibroblast growth factor receptor
FOXM1	Forkhead box protein M1
GB	Gallbladder meridian
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLUT	glucose transporter
GLP	Good Laboratory Practice
GPNA	L-γ-glutamyl-p-nitroanilide
GPX4	Glutathione peroxidase 4
GSH	Glutathione
HADS	Hospital anxiety and depression scale
HAMA	Hamilton anxiety scale
HER2	Human epidermal growth factor receptor 2
HFNS	Hot flushes and night sweats
HIF-1α	Hypoxia-inducible factor-1α
HO-1	Heme oxygenase-1
HR	Hormone receptor
HT	Heart meridian
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
IQR	Interquartile range
ISI	Insomnia severity index
K/KD/KI	Kidney meridian
KPS	Karnofsky performance status
LC3	Microtubule-associated protein 1 A/1B-light chain 3
LI	Large intestine meridian
LN	Laminin
LncRNAs	Long non-coding RNAs
LR	Liver meridian
LU	Lung meridian
LVEF	Left ventricular ejection fraction
MD	Mean differences
MDA	Malondialdehyde
MDM2	Mouse doubleminute 2 homolog
MDSCs	Myeloid-derived suppressor cells
MMP	Matrix metalloproteinase
MRS	Menopause rating scale
NK	Natural killer cell
NRS	Numeric rating scale
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OXPHOS	Oxidative phosphorylation
P2RX7	P2X purinoceptor 7
PICP	Procollagen type I carboxy-terminal propeptide
PC	Pericardium meridian
PCIII	Procollagen type III
PD-1	Programmed death receptor 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PFS-R	Piper Fatigue Scale-Revised
PNQ	Patient neurotoxicity questionnaire
PP2A	Protein phosphatase 2 A
PPARG	Peroxisome proliferator-activated receptor gamma
PR	Progesterone receptor
PSQI	Pittsburgh sleep quality index
Rb	Retinoblastoma-associated proteins
RBC-ICR	Red blood cell immune complex rosette
RCT	Randomized controlled clinical trials
REM	Rapid eye movement
ROS	Reactive oxygen species
RR	Relative risk
s-CTX	Serum C-terminal telopeptide of type I collagen
SE-electin	Soluble E-selectin
SIO	Society for integrative oncology
SJ/TE	Triple energizer/sanjiao meridian
Skp2	S-phase kinase-associated protein 2
SMD	Standard mean difference
SOD	Superoxide dismutase
SP	Spleen meridian
s-PINP	Serum N-terminal propeptide of type I procollagen
SREBP1	Sterol regulatory element binding protein 1
ST	Stomach meridian
TAMs	Tumor-associated macrophages
TBIL	Total bilirubin
TCM	Traditional Chinese Medicine
TEAS	Transcutaneous electrical acupoint stimulation
TFR	Transferrin receptor
Th	T helper cell
TLR4	Toll-like receptor 4
TME	Tumor microenvironment
TPS	Tissue polypeptide specific antigen
TrxR	Thioredoxin reductase
TSGF	Tumor specific growth factor
TβR	TGF-β receptor
ULK1/2	Unc-51-like kinase
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WASO	Wake after sleep onset
WHOQOL-BREF	World Health Organization Quality of Life-BREF
WM	Western Medicines

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Author contributions
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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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