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The Mechanism and Clinical Research Progress of Tcm Treatment of Breast Cancer

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Abstract:

Breast cancer, a prevalent malignant tumor, exhibits intricate pathogenesis and rapid disease advancement. Recent analyses of both national and global scientific literature reveal the efficacy of traditional Chinese medicine (TCM) monomers or formulations in modulating biological processes. These interventions target genes and signaling pathways, leading to the inhibition of breast cancer cell proliferation, induction of apoptosis, and modulation of cancer cell resistance to chemotherapy and endocrine therapy. Moreover, emerging clinical investigations indicate the effectiveness of TCM formulations, acupuncture in conjunction with TCM, or integrative TCM and Western medicine regimens in treating breast cancer patients. These findings not only offer preliminary evidence of TCM's potential efficacy and benefits in improving treatment outcomes and reducing toxicity in tumor diseases but also address existing limitations in Western medicine approaches to breast cancer treatment. Consequently, it is advisable to collaboratively establish a distinctive diagnostic and therapeutic framework that integrates TCM and Western medicine. Such an approach aims to diminish recurrence and mortality rates among breast cancer patients, enhance patient survival outcomes, and facilitate pertinent clinical endeavors.

Keywords: Traditional Chinese medicine; Breast cancer; Mechanism; Research progress.

1. Background

1.1 Tumor Pathogenesis

In China, the incidence and mortality rates of malignant tumors have been steadily rising, making them the primary cause of population mortality. In 2020 alone, China reported 4,568,754 new cases of malignant tumors, representing 23.7% of the global total. Breast cancer emerged as the most prevalent type, followed by lung, colorectal, gastric, liver, and esophageal cancers in terms of incidence[1]. Similarly, malignant tumors accounted for approximately 3,002,899 deaths in China during 2020, contributing to 30.2% of global tumor-related mortalities. Notably, lung cancer exhibited the highest age-standardized mortality rate (ASMR), followed by liver, gastric, esophageal, colorectal, and breast cancers[2]. Consequently, this study will delve into the pathogenesis of tumors, considering genetic and epigenetic alterations alongside the tumor microenvironment[3].

1.1.1 Genetic changes and Epigenetic mechanisms

During recent decades, the pathogenesis of cancer has been a focal point of clinical research teams[4]. For cancer intervention, some research teams have found that hereditary and alterations in the epigenome may contribute to initiation of cancer[5].

The activation of proto-oncogenes and the deactivation of tumor-suppressing genes are critical occurrences in the pathogenesis of cancer. Remote cis-regulatory elements, also known as enhancers, undergo modification by distinct epigenetic marks, playing an essential role in controlling the expression of tissue-specific genes[6]. Consequently, inheritable epigenetic modifications are fundamental to the development of cancer[6]. Interruptions in epigenetic mechanisms, such as chromatin remodeling via histone modifications, DNA methylation, and pathways regulated by miRNAs, lead to alterations in the epigenome, thus affecting the biochemical processes implicated in the initiation and progression of tumors

1.1.2 Tumor Microenvironment

The tumor milieu, or microenvironment, constitutes a dynamic framework encompassing neoplastic cells, the extracellular matrix (ECM), and stromal tissues. Alongside genetic and epigenetic changes within cancerous cells, the tumor microenvironment exerts comparable significance in the initiation, advancement, and dissemination of malignancies[7].

Tumor genesis isn't solely influenced by genetic modifications within the malignant cell populace but also shaped by interactions among the extracellular matrix (ECM) and various cell types within the tumor milieu. The tumor microenvironment encompasses elements like the ECM, soluble cytokines, stromal cells, or infiltrating lymphocytes, such as CD4 T cells, myeloid-derived suppressor cells, macrophages, and neutrophils. Among these immune cell subsets, tumor-infiltrating macrophages (TIMs) are the predominant cellular component in the tumor milieu and are recognized as pivotal players in cancer progression. TIMs secrete transforming growth factor-β (TGF-β) to modulate cellular metabolism, consequently activating the HIF1α/Tribbles pseudokinase 3 (TRIB3) signaling cascade, which holds a crucial role in reshaping tumor advancement[8].

1.2 Mechanisms of Tumor Metastasis

Tumor metastasis involves various factors, including changes in the characteristics of tumor cells themselves and alterations in the host environment. Alterations in the tumor microenvironment are critical factors influencing tumor metastasis[9]. Currently, tumor metastasis is generally believed to occur in two main steps. Firstly, proliferation of cells at the primary tumor site, angiogenesis, and invasion of tumor cells breaking through the extracellular matrix barrier. Subsequently, tumor cells proliferate at secondary sites to form solid tumors.

1.2.1 The microenvironment of the primary tumor site

The microenvironment encompassing the primary tumor site predominantly comprises tumor-infiltrating macrophages, tumor-related fibroblasts, myeloid-derived suppressor cells, mast cells, etc[10]. These cellular components have the capability to secrete diverse cytokines and chemokines to facilitate tumor metastasis. Distinct tumor microenvironments can promote metastasis by modulating tumor cell proliferation, controlling the expression levels of genes associated with metastasis, stimulating angiogenesis, and enhancing extracellular matrix breakdown., it was observed that tumor-associated macrophages (TAMs) can stimulate invasion and metastasis of gastric cancer cells via the Kindlin-2 pathway. TAMs release TGF-β, which governs the expression of Kindlin-2 through the nuclear factor-kappa B (NF-κB) pathway, thereby contributing to the advancement of gastric cancer via the TGFβ2/NF-κB/Kindlin-2 axis[11].

1.2.2 Metastatic Site Microenvironment

The propagation of malignant cells at the secondary tumor site is a prerequisite for the establishment of metastatic lesions, and the microenvironment of the metastatic destination organ dictates the potential formation of metastatic foci. The lungs, liver, skeletal system, and brain represent the most frequent target organs for tumor metastasis. Distinct target organs have the capacity to release varied cytokines for attracting tumor cells and fostering cellular proliferation, angiogenesis initiation, and eventual metastatic focus formation[12]. Throughout this process, neoplastic cells can also release diverse cytokines conducive to their own survival through paracrine signaling, shaping a conducive microenvironment for colonization. Current investigations have unveiled that tumor metastasis exhibits certain organotropism, with the liver emerging as a prevalent metastatic locus. Malignancies demonstrating a preference for liver metastasis encompass uveal melanoma, colorectal carcinoma, pancreatic adenocarcinoma, revealed that aberrant hepatic lipid metabolism can foster hepatic metastasis of breast carcinoma and melanoma. The underlying mechanism involves tumor cells triggering adjacent hepatocytes to engage in triglyceride lipolysis. The resultant lipolysis byproducts enter neoplastic cells via fatty acid transport protein 1 and fuel tumor cell proliferation through mitochondrial oxidative metabolism[13].

1.3 Theoretical Approaches to Tumor Treatment

Traditional Chinese medicine (TCM) treatment can improve clinical symptoms, enhance patient quality of life, prolong survival, and synergize with radiotherapy and chemotherapy to enhance efficacy while reducing adverse reactions to radiotherapy and chemotherapy. With the increasingly rich experience in modern TCM in the prevention and treatment of tumors, many physicians have put forward their own academic views on the etiology, pathogenesis, and differential diagnosis and treatment of tumors. These views have been effectively validated in clinical practice, gradually forming a representative set of academic ideologies. Four widely recognized and continuously evolving theoretical approaches to TCM tumor treatment are outlined below, aiming to provide new insights for guiding further clinical practice in TCM oncology.

1.3.1 Theory of Carcinogenic Toxins

The theory of carcinogenic toxins is one of the important innovations in recent years in the theoretical understanding of TCM oncology. It proposes that "carcinogenic toxins" are specific pathogenic factors of tumors. Tumors often begin with qi stagnation, which leads to stagnation of bodily fluids, stasis of blood, and the generation of carcinogenic toxins. The interaction between carcinogenic toxins and phlegm stasis forms the core pathogenesis and syndrome of tumors . Professor Cheng Haibo's team summarized the basic pathogenesis of colorectal cancer metastasis as "deficiency of righteous qi, invasion of car-

cinogenic toxins, mutual conglomeration of dampness and heat stasis," and the main treatment principle as "anti-cancer detoxification, supporting the righteous qi, expelling pathogenic factors[14].

1.3.2 Theory of Treating Tumors from the Perspective of Ulcer Management

Master of Chinese Medicine Liu Shangyi proposed the concept of "treating ulcers internally as one would treat wounds externally," applying the treatment philosophy of ulcer management to tumor prevention and treatment. By combining the theories of ulcer management and tumor treatment, the academic concept of "treating ulcers to control tumors from the perspective of ulcer management" was formed, establishing a theoretical system of treating tumors from the perspective of ulcer management, including ulcer diagnosis and treatment, ulcer therapy, and ulcer medications. This theory is applicable to tumors in cavity organs rich in mucosa, such as esophageal cancer, gastric cancer, colorectal cancer, uterine cancer, and bladder cancer[15].

Professor Liu Shangyi advocates the use of medicines for treating internal membrane ulcers to treat diseases involving internal mucosal ulcers. Commonly used ulcer medicines include Dong Ling Cao, Mao Zha Cao, and Lu Lu Cao for clearing heat and detoxification; E Zhu, Wu Gong, and Shui Zhi for promoting blood circulation and removing blood stasis; Gui Jia, Bie Jia, Yu Zhu, and Shi Hu for tonifying and nourishing; and Fang Feng, Qiang Huo, Jing Jie, Di Fu Zi, and Bai Xian Pi for dispelling wind. In addition to decoctions, Professor Liu Shangyi emphasizes the combination of acupuncture, moxibustion, and poultice therapy. He often combines self-made warm and yang-removing ointments (comprising Chuan Wu, Cao Wu, Mu Xiang, Gan Jiang, and Zhi Zi) to apply to protruding unbroken tumors on the body surface, controlling cancer-related pain and preventing tumor metastasi.

1.3.3 Theory of Surviving with Tumors [16]

Professor Zhou Daihan proposed the academic concept of "living with tumors," emphasizing the harmonious coexistence of tumor cells with normal cells in the human body. The key point is to maintain the tumor cells in an inactive state, stabilize tumor size, alleviate clinical symptoms, and focus on gradually controlling the growth and spread of tumor cells, thus improving the quality of life and prolonging survival. The ultimate goal is to achieve living with tumors .

In clinical treatment, Professor Zhou Daihan insists on the principle of combining syndrome differentiation and disease identification with strengthening the righteous qi and expelling pathogenic factors[17]. In early-stage tumors, the emphasis is on eliminating pathogenic factors. In the middle stage, both reinforcing the righteous qi and attacking pathogenic factors are used, with more emphasis on attacking in the early stage and supplementing in the middle stage or using a combination of attacking and supplementing. In the late stage, the emphasis is on supplementing while attacking, with equal attention to supporting the righteous qi and expelling pathogenic factors. For example, in the treatment of liver cancer, according to the stage and characteristics of the disease, it can be divided into three types: early-stage liver heat-blood stasis, mid-stage liver excess with spleen deficiency, and late-stage liver-kidney yin deficiency. Treatment options include Yin Chen Hao Tang, Si Jun Zi Tang, and Er Zhi Wan as basic prescriptions, combined with appropriate modifications using herbs such as Ba Yue Zha, Ban Zhi Lian, Wu Gong, and Xi Huang Cao based on the pathological characteristics of liver cancer and treatment of jaundice.

1.3.4 Theory of Strengthening the Righteous Qi to Treat Cancer

Professor Liu Jiaxiang advocates for the principle of "strengthening the righteous qi to treat cancer" throughout the entire process of tumor treatment. He believes that the root cause of tumor pathogenesis is the deficiency of righteous qi in the body, and the invasion of pathogenic factors is only one of the external conditions that promote tumor formation. The tumor lesion is only a local manifestation caused by the deficiency of righteous qi in the body and subsequent infection with external pathogenic factors. The evolution process is actually related to the changes in the strength of righteous qi in the body[18].

2. Mechanism of TCM in Cancer Treatment 2.1 Anti-Mutagenic Effect

2.1.1 Regulation of Tumor Suppressor Genes by Chinese Herbal Medicine

The most prevalent aberrant manifestation of tumor suppressor genes involves alterations in p53. In physiological contexts, p53 is activated in response to DNA damage or carcinogenic cues, triggering the upregulation of target genes implicated in cell cycle arrest and apoptosis induction, thereby exerting anti-neoplastic effects.

Contemporary investigations suggest that numerous bioactive compounds in traditional Chinese herbal medicine positively impact p53 expression. Gan et al. demonstrated that total flavonoids extracted from Ampelopsis grossedentata can enhance p53 and caspase-3 expression, pivotal in apoptosis, by activating the PI3K/Akt/P53 signaling pathway, consequently suppressing the Bcl-2 gene and bolstering Bax expression, culminating in apoptosis induction in hepatocellular carcinoma cell. Piperine derived from Fructus Tsaoko robustly induces cellular apoptosis

and halts the cell cycle progression. Its mechanism involves the upregulation of p53 and Bax expression, concurrent with the inhibition of cell cycle proteins CDK2 and CyclinA, alongside the anti-apoptotic protein Bcl-xl[19].

2.1.2 Regulation of Oncogenes by TCM

Under normal circumstances, oncogenes are in a state of low expression or dormancy within cells. In tumor cells, oncogenes are abnormally activated, leading to the upregulation of various signaling pathways and downstream protein expressions, promoting cell proliferation. Simultaneously, they inhibit the tumor-suppressing effects of tumor suppressor genes, ultimately resulting in impaired apoptosis and immune evasion, among other alterations, which contribute to tumorigenesis[20].

Van Lohuizen initially discovered the Bmi-1 gene during investigations into insertion mutation sites in Emu-myc transgenic mice. Bmi-1, an integral member of the polycomb group genes (PcG) family, exhibits elevated expression in diverse malignancies, functioning as an oncogene. Glinsky et al. identified heightened Bmi-1 levels across various tumors, spanning epithelial (prostate cancer, lung cancer, breast cancer, ovarian cancer, bladder cancer) and non-epithelial (acute leukemia, glioblastoma, medulloblastoma, lymphoma, melanoma) malignancies, closely correlating with tumor initiation, invasion, and metastasis. Chaihu Rupi Granules, primarily comprising Chaihu, Baishao, Danggui, Qingpi, Yujin, Gualoupi, Zhebeimu, Ezhu, Juhua, Muli, Xiakucao, Wangbuliuxing, Baizhu, and Fuling, exhibit the potential to diminish Bmi-1 expression. Furthermore, they enhance p63 expression, a homolog of the p53 gene, thereby impeding cellular proliferation and instigating apoptosis.

2.1.3 Regulation of Other Tumor-Related Genes by TCM

Apart from modulating oncogenes and tumor suppressor genes, traditional Chinese medicine (TCM) also exhibits regulatory effects on various other genes associated with tumorigenesis. In recent times, several research groups have uncovered that the ethanol extract derived from Hedyotis diffusa can hinder the expression of vascular endothelial growth factor-A (VEGF-A) and its specific receptor VEGFR2, thereby impeding the Hedgehog pathway, which fosters tumor proliferation and metastasis. This inhibition results in the curtailment of colorectal cancer progression[21].

2.2.1 Inducing Cell Apoptosis

Kerr discovered and defined apoptosis as a non-inflammatory process of programmed cell death. In tumor cells, abnormalities in apoptosis-related genes, proteins, and signaling pathways inhibit cell apoptosis, making induction of apoptosis an important approach in cancer therapy TCM can regulate tumor cell apoptosis through multiple pathways. Matrine can upregulate the p53 gene and inhibit the expression of apoptosis-inhibiting factors such as survivin, c-Myc, and cyclin D1, thereby inhibiting proliferation and promoting apoptosis in human breast cancer Bcap-37 cells ; Alizarin can inhibit proliferation and promote apoptosis of human endometrial carcinoma (EEC) cells by modulating the miR-106b/P1EN/Akt/mTOR signaling pathway[22]; Berberine can promote apoptosis of colorectal cancer cells by affecting various genes, signaling pathways, and apoptosis-related factor[23].

2.2.2 Modulating Autophagy

Autophagy, also known as programmed cell death, is a major pathway that, along with apoptosis, promotes the death of tumor cells. Autophagy plays a dual role in the development of tumors: protective autophagy promotes tumor proliferation, metastasis, and drug resistance, while cytotoxic autophagy inhibits tumor proliferation and promotes tumor cell apoptosis [24].

Traditional Chinese medicine (TCM) exerts regulatory effects on both types of autophagy in tumor cells. Studies have shown that matrine exhibits bidirectional regulation of cell autophagy. Matrine can significantly induce autophagy in leukemia K562 cells and K562/IM cells. However, when autophagy is inhibited by 3-methyladenine (3-MA), the inhibitory effect of matrine on the proliferation of K562/IM cells significantly increases, suggesting that the autophagy induced by matrine in leukemia K562 cells and K562/IM cells is protective autophagy. Additionally, matrine can activate autophagy-related genes Beclin1 and Lc3A/B, induce cytotoxic autophagy in lung cancer A549 cells, and impair the intracellular autophagic degradation pathway, leading to metabolic disturbances and inhibition of tumor cell proliferation, thereby achieving anti-tumor effects. The regulatory effects of other Chinese herbal medicines on cell autophagy are also diverse. For example, astragaloside IV can inhibit the expression of P62 protein, increase the ratio of Lc3I/LC3II, and suppress protective autophagy in lung cancer A549 cells. Furthermore, astragaloside IV can inhibit the phosphorylation levels of P13K, Akt, and mTOR, suppress the P13K/Akt/mTOR signaling pathway, upregulate the expression of Beclin1, and enhance the autophagic activity of tissue cells[25].

2.2.3 Other Modulatory Effects of Traditional Chinese Medicine on Tumor Cells

In addition to apoptosis and autophagy, some traditional Chinese medicines (TCMs) achieve anti-tumor effects by modulating cellular energy metabolism. The growth

and proliferation of cells require energy supply. In tumor tissues, due to the aggregation of a large number of tumor cells and their rapid proliferation, cells located far from blood vessels experience relative oxygen deficiency. As a result, most cells in tumor tissues are in a state of hypoxia. Furthermore, due to the influence of acidic environments on tumor cells, aerobic glycolysis becomes the primary means for tumor cells to obtain energy. Studies have shown that turmeric, salvia miltiorrhiza, sophora flavescens, and others can effectively inhibit aerobic glycolysis in tumor cells, thereby suppressing tumor cell growth[26].

2.3 Immune Enhancement Mechanism

Research has found that small molecule TCM drugs with anti-tumor immune effects mostly belong to polysaccharides, flavonoids, diterpenoids, and flavonoid compounds. They can directly or indirectly enhance the activity of immune cells, increase the cytotoxicity of immune cells against tumor cells, and improve the tumor immune microenvironment, thereby better exerting anti-tumor effects.

2.3.1 Impact of Small Molecule TCM Drugs

The inherent immune system acts as the initial barrier against pathogen intrusion, primarily depending on diverse immune cells to execute defensive roles. For instance, macrophages have the capability to engulf and digest certain pathogens and trigger other immune cells to counteract pathogens (Chen et al., 2019). In a research study focusing on non-small cell lung cancer, it was observed that Astragalus polysaccharide (APS) could augment the polarization rate of M1/M2 macrophages, regulate the M1/M2 macrophage population, stimulate M1 macrophages to produce more pro-inflammatory mediators, and enhance the expression of MHC-II molecules, thereby ameliorating immune responsiveness and augmenting macrophage-mediated killing and engulfment of tumor cells to suppress tumor growth (Wang et al., 2019). In another investigation, APS was identified to activate the TLR4 signaling pathway and NF-kB/REL signaling pathway to stimulate macrophage function, resulting in increased release of NO and TNF-α, thus impeding tumor cell proliferation[27].

2.3.2 The effect of small molecule TCM drugs on the adaptive immune system

Shanker et al. [28]found that the adaptive immune system can elicit highly specific immune responses to particular antigens and participate in the clearance of pathogens and late-stage pathogen cells. Modern research indicates that small molecule TCM drugs can exert anti-tumor effects by modulating T cells, B cells, and related tumor cell factors[29]. Zhao et al. [30]demonstrated that Saikosaponin A could increase the levels of IL-12 and IFN-γ in serum, reduce the levels of IL-4 and IL-10, promote Th1 differentiation by upregulating IL-12 receptor and phosphorylated STAT4 expression, and significantly inhibit the growth and proliferation of breast cancer cells. Kim et al. [31]found that Astragalus polysaccharide (ASP) could enhance the immune function of B cells and directly inhibit the adhesion of tumor cells, thereby inhibiting tumor growth and metastasis[32].

3. Research Progress in TCM Treatment of Breast Cancer

In TCM perspective, breast cancer belongs to the category of “mammary carcinoma.” Its etiology and pathogenesis mainly involve dampness, heat, toxins, phlegm, stasis, and accumulation, which consume the body’s qi, blood, yin, yang, jin, and ye. Treatment should adhere to the principle of tonifying the body’s vitality and dispelling pathogenic factors. Modern research has demonstrated that TCM therapies play an irreplaceable role in comprehensive cancer treatment. Among them, significant progress has been made in the field of breast cancer prevention and treatment with Chinese herbal medicine. Integration of various TCM and Western medical approaches optimizes clinical treatment strategies for breast cancer.

3.1 The mechanism of TCM in treating breast cancer

Treatment of breast cancer should emphasize supporting the body’s vital energy while also addressing heat-clearing, detoxification, blood-activating, stasis-resolving, and swelling-reducing aspects to achieve the goal of eliminating pathogenic factors and promoting health. Therefore, the following discussion will focus on the mechanisms of TCM and TCM formulae in regulating signaling pathways and targeting genes. It will elaborate on the mechanisms of blood-activating and stasis-resolving herbs, heat-clearing and detoxifying herbs, and qi-tonifying herbs in the treatment of breast cancer[33].

3.1.1 Research Progress on the Mechanisms of Blood-Activating and Stasis-Resolving Chinese Herbal Medicine

Modern research has shown that the progression of breast cancer is closely related to targeted genes. Both individual Chinese herbal medicines and herbal formulas can not only regulate the expression of targeted genes to inhibit the proliferation of breast cancer cells but also promote the apoptosis of cancer cells. Zhu et al. found that Rhodiola rosea can indirectly regulate key nodal genes in negative breast cancer. The main mechanism is that the effective component of Rhodiola rosea, salidroside, can bind to ATP-binding cassette transporter 11, thymidylate synthase,

and checkpoint kinase 1 protein. Yu et al. suggested that the effective component of Salvia miltiorrhiza, salvianolic acid IIA, can effectively upregulate the gene expression of STAT4 in breast cancer cells, thereby effectively intervening in the clinical treatment of breast cancer.

It can be seen that blood-activating and stasis-resolving Chinese herbal medicines can effectively treat breast cancer by regulating different targeted genes in cancer cells. We further speculate that Angelica sinensis, Spatholobus suberectus, and other herbs with similar effects to Rhodiola rosea and Salvia miltiorrhiza may have similar or identical pharmacological effects in preventing and treating breast cancer[34].

3.1.2 Research Progress on the Mechanism of Heat-Clearing and Detoxifying Chinese Herbal Medicines

Research has shown that tumor cell proliferation, migration, and invasion into normal tissues are closely related to the JAK2/STAT3, EGF/EGFR/HER2, and Wnt/β-catenin signaling pathways. Therefore, by modulating the activation of these pathways, it is possible to effectively reduce the resistance of tumor tissues to Western chemotherapy and endocrine therapy. Studies suggest that the anticancer mechanism of heat-clearing and detoxifying Chinese herbal medicines may involve modulation of the JAK2/STAT3, EGF/EGFR/HER2, and Wnt/β-catenin signaling pathways.

Liu et al. found that the active ingredient, Leonurine, in Motherwort could effectively inhibit the activation of the JAK2/STAT3 signaling pathway, thereby enhancing the cytotoxicity of chemotherapy drugs against cancer cells. This may be an important mechanism by which Motherwort increases the sensitivity of breast cancer tissue cells to chemotherapy drug, Docetaxel. Sun et al. discovered through experiments that Aloe-emodin, found in Aloe vera, can effectively reduce the resistance of breast cancer cell lines to endocrine therapy by regulating the EGF/EGFR/HER2 signaling pathway. In addition, Sun et al. found that Artemisinin could effectively intervene in the occurrence and development of breast cancer. The main intervention mechanism is closely related to the regulation of the expression of S-phase kinase-associated protein 2 gene and cyclin-dependent kinase inhibitor 1A gene by the active ingredient Artemisinin. However, when Artemisinin intervenes in these two targeted genes, there are certain toxicological phenomena that need further study.

The above research findings demonstrate that the mechanism of heat-clearing and detoxifying Chinese herbal medicines in the treatment of breast cancer is related to the modulation of the JAK2/STAT3, EGF/EGFR/HER2, and Wnt/β-catenin signaling pathways. However, the intervention mechanisms of other signaling pathways related to heat-clearing and detoxifying Chinese herbal medicines still require further investigation.

3.1.3 Research progress on the mechanism of tonic Chinese herbal medicines

Research indicates that among clinical treatments for breast cancer, the frequency of use of tonifying Chinese herbal medicines is the highest. Traditional Chinese medicine regards the strength of the body's vital energy as crucial in resisting diseases. Zhang et al. found that the Chinese herb Astragalus membranaceus can effectively prolong the survival period of patients by regulating the expression of the POLR2D gene, thereby exerting anticancer effects. Modern research has also demonstrated that breast cancer patients with higher expression of the POLR2D gene usually have a shorter survival period[35].

The pharmacological mechanism of tonifying Chinese herbal medicines in treating breast cancer not only involves the regulation of target genes but also involves necessary interventions in the Wnt/β-catenin signaling pathway. The effective intervention of Chinese herbal medicine in the Wnt/β-catenin signaling pathway is a recent research hotspot in the mechanism of tonifying Chinese herbal medicines for treating breast cancer. Xing & Li found through animal experiments that glycyrrhetinic acid can improve osteoporosis induced by low estrogen levels after endocrine therapy for breast cancer by regulating estrogen levels and the Wnt/β-catenin pathway. Li et al. demonstrated through experiments that the active ingredient of Astragalus membranaceus, astragalus polysaccharide, can effectively inhibit the proliferation and invasion of triple-negative breast cancer cells by regulating the Wnt/β-catenin pathway.

The above studies all support that the monomeric components in tonifying Chinese herbal medicines can effectively treat breast cancer by intervening in the Wnt/β-catenin pathway. In addition, formula compositions of different Chinese herbal medicines may also produce anticancer effects by regulating the Wnt/β-catenin pathway. This has positive implications and clinical guidance significance for controlling tumor lesions, inhibiting cancer cell metastasis, and preventing complications or recurrence of breast cancer lesions after surgery.

3.2 The clinical research status of TCM in the treatment of breast cancer.

With the deepening understanding of the biological and pathological characteristics of breast cancer, a comprehensive treatment approach incorporating adjuvant TCM such as herbal medicine, acupuncture, and moxibustion can be considered alongside conventional therapies based on tumor staging and patient's physical condition. This

approach aims to improve breast cancer patients' relevant symptoms and alleviate adverse reactions caused by radiotherapy and chemotherapy. Currently, we will mainly introduce the clinical research status of traditional Chinese medicine adjuvant therapy for breast cancer from the following perspectives.

3.2.1 The clinical research progress of modern TCM in the treatment of breast cancer

Breast cancer patients typically exhibit various TCM patterns, including deficiency patterns such as qi deficiency, yin deficiency, combined qi and yin deficiency, and spleen-kidney deficiency, as well as excess patterns like blood stasis, damp obstruction, qi stagnation, and toxic heat. Some patients may even present with a mixture of deficiency and excess patterns With the deepening of clinical research, many new theories have emerged regarding the common TCM patterns observed in breast cancer patients, which are closely related to their personality traits, blood viscosity, and treatment methods.

According to investigations, liver-qi stagnation pattern and disharmony between the Chong and Ren channels are prevalent TCM patterns among breast cancer patients.

Other studies indicate a correlation between TCM patterns of breast cancer patients and the number of chemotherapy sessions. For instance, after 6 to 8 chemotherapy sessions, patients may develop patterns such as qi deficiency with dampness obstruction, heart-yin deficiency, and liver-qi stagnation. Predictive models have also been established, showing practical value in predicting the occurrence rates of various TCM patterns in breast cancer patients after postoperative endocrine therapy for menopausal syndrome.

These research findings provide essential reference points for clinicians to apply TCM differential diagnosis and treatment to breast cancer patients of different types. They can better guide clinical practitioners in using Chinese herbal medicine to regulate patients' immune function or in combining with Western medicine treatments to address the diverse conditions of breast cancer patients.

3.2.2 TCM treatment to ameliorate postoperative complications and mitigate adverse effects of endocrine therapy

Although radical surgery for breast cancer or endocrine therapy can effectively improve patients' clinical symptoms, various complications are also prone to occur. Currently, research on TCM for improving postoperative complications of breast cancer mainly focuses on interventions for upper limb swelling after breast cancer surgery and postmenopausal syndrome after endocrine therapy.

In clinical trials, it has been found that modified Tao Hong Si Wu Tang can effectively assist in treating upper limb swelling after breast cancer surgery and provide satisfactory analgesic effects. Another clinical study suggests that modified Ban Xia Xie Xin Tang has significant efficacy in treating postmenopausal syndrome in patients with breast cancer after menopause. This treatment not only effectively relieves patients' symptoms of cold and heat imbalance, irritability, and depression but also significantly improves their physical strength and quality of life without affecting estrogen levels in the body. Therefore, for patients with breast cancer recurrence due to abnormal hormone levels, treatment with modified Ban Xia Xie Xin Tang may be considered.

3.2.3 TCM alleviates the toxic side effects of chemotherapy drugs.

In recent years, there have been numerous clinical studies on the combined use of TCM and chemotherapy to alleviate the toxic side effects of chemotherapy drugs in breast cancer patients. Several studies have demonstrated that TCM, either alone or in combination with acupuncture, moxibustion, and other therapies, can effectively alleviate the toxic side effects experienced by breast cancer patients undergoing chemotherapy[36].

Zhan Qian et al. suggested that Modified Ba Zhen Tang has a high clinical value in preventing declines in white blood cells, neutrophils, and hemoglobin levels after chemotherapy for breast cancer. Their clinical trial showed that prophylactic administration of Modified Ba Zhen Tang can help reduce the incidence of bone marrow suppression. Qiang Rui et al. found through clinical research that Modified Ban Xia Xie Xin Tang has a significant therapeutic effect on postmenopausal breast cancer patients experiencing menopausal syndrome after endocrine therapy; it not only effectively alleviates symptoms such as mixed cold and heat, irritability, and depression but also significantly improves patients' physical strength and quality of life without affecting estrogen levels[37]. Chen Bingxun et al.'s clinical summary indicated that Modified Ba Zhen Tang combined with neoadjuvant chemotherapy achieved significant efficacy in treating breast cancer, improving clinical treatment effectiveness by approximately 25.5% compared to chemotherapy alone. Wang Maoyun et al. suggested that Modified Ba Zhen Tang combined with polysaccharide iron complex significantly improved symptoms of post-chemotherapy anemia, as well as hemoglobin and red blood cell count indices, effectively enhancing patients' quality of life. Studies have also shown that Modified Ba Zhen Tang combined with vitamins C and E can effectively improve post-chemotherapy skin pigmentation[38].

These cases demonstrate the effective combination of

TCM with various clinical therapies to meet the diagnostic and therapeutic needs of different breast cancer patients. However, there is currently no literature indicating a clear dose-response relationship in the use of TCM as an adjunct to chemotherapy to alleviate the toxic side effects of chemotherapy drugs in breast cancer patients[39].

3. Conclusion4. Conclusion

Currently, the main manifestations of TCM in intervening in the diagnosis and treatment of breast cancer include improving postoperative complications, alleviating side effects of endocrine therapy, and reducing the toxicity of chemotherapy drugs. Additionally, some modern medical experts have actively explored methods of TCM-assisted therapy for breast cancer, such as the clinical principle of "inducing ulcer to treat tumor" proposed by experts like Liu Shangyi. According to this principle, the treatment of breast cancer can be approached from three aspects: "treating ulcer to diagnose tumor," "treating tumor with ulcer therapy," and "treating tumor with ulcer medicine," providing new diagnostic and therapeutic strategies for TCM treatment of breast cancer, while also enriching the academic thoughts and treatment concepts of TCM oncology.

Future research should conduct precise and systematic evidence-based medicine analyses of TCM therapies and prescriptions widely used in clinical practice to provide more reliable evidence support for clinical practice. Such work will further promote the development of TCM in the field of breast cancer treatment, providing patients with more effective treatment options and better quality of life.

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