Proceedings of ICMMGH 2026 Symposium: Cell and Molecular Biology: Understanding Immune Cell Functions
DOI: 10.54254/2753-8818/2026.PJ30390

Traditional Chinese Herbal Medicine for the Treatment of Four Major Triple-negative Breast Cancer Subtypes

Baomin Mao

Second Clinical College, Shanxi University of Traditional Chinese Medicine, Jinzhong, China
miyamao77@163.com

Abstract. Triple-negative breast cancer (TNBC), a subtype of breast cancer, is negative for estrogen receptor (ER), progesterone receptor (PR), and proto-oncogene HER2. TNBC constitutes roughly 10% to 20% of all diagnosed breast cancer cases. Due to its lack of hormone receptors and the HER2 target, TNBC is generally more aggressive, has a high recurrence and metastasis rate, and has a low five-year survival rate. TNBC shows no sensitivity to either endocrine therapy or HER2-targeted therapeutic regimens, with relatively limited options available for its treatment. The Lehmann classification divides TNBC into four major subtypes, allowing for targeted treatment plans to improve the prognosis of TNBC. Traditional Chinese medicine (TCM) individualized treatment plans are formulated based on syndrome differentiation, utilizing various bioactive compounds to mobilize the body's self-regulating abilities to restore health. Many TCM compounds exhibit antitumor, anti-inflammatory, immunomodulatory, and pro-apoptotic effects. Compared to chemotherapy, TCM is safer and has fewer side effects. It can inhibit cancer cell growth and spread, reduce disease progression, enhance immune function, improve endocrine function and metabolism, reduce the side effects of anticancer drugs, and improve patients' quality of life, providing clinical alternative and adjuvant treatment options. This review integrates TCM with mainstream oncology, highlighting its potential in unique subtypes and theoretically explaining its mechanisms of action. It also explores an innovative therapeutic approach, "holistic regulation combined with targeted therapy." This approach leverages the multi-target properties of TCM to inhibit local tumor progression while modulating the body's overall immune and metabolic balance, reducing the risk of tumor cell resistance and potentially developing safer, more effective, and less side-effect-prone treatments for TNBC.

Keywords: triple-negative breast cancer, Salvia miltiorrhiza, dandelion, bee venom, Hedyotis diffusa

1. Introduction

TNBC carries a high risk of metastasis and recurrence after treatment, resulting in reduced survival rates [1]. Nearly 40% of patients with stage I-III TNBC relapse within 2 to 3 years after standard treatment [1,2]. The overall 5-year relative survival rate for patients with TNBC is 77%, which is 8% to 16% lower than that for hormone receptor-positive breast cancer [3,4].

DOI: 10.54254/2753-8818/2026.PJ30390

Treatment plans are now customized not only based on the stage of the disease but also based on the specific molecular subtype of the tumor [5]. In 2016, Lehmann's research group based in the United States identified a distinct association between transcriptome profiles and clinical characteristics, a finding that offers significant guidance for the rational selection of targeted therapeutic strategies [6]. The team divided patients into TNBC-4 subtypes, namely M, LAR, BL1 and BL2.

As of this year, several traditional Chinese medicines have been proven effective against TNBC-4. These include herbs such as Hedyotis diffusa, dandelion, salvia miltiorrhiza, and bee venom. TCM often contains multiple chemical components, targeting multiple targets when inhibiting tumor growth, unlike some Western medicines that may only target a single target. For example, the flavonoids in Hedyotis diffusa have antioxidant and anti-inflammatory properties, inhibiting free radical production and reducing cell damage. They also inhibit tumor cell proliferation and metastasis by modulating tumor cell signaling pathways [7]. The anthraquinones in Hedyotis diffusa mainly have antibacterial effects. The quinone structure can disrupt the integrity of bacterial cell membranes and can be used for anti-tumor, anti-inflammatory, and antioxidant purposes [8]. They simultaneously target multiple pathways—tumor-cell proliferation signaling, apoptosis control, and angiogenesis—suppressing cancer from multiple angles and minimizing resistance risk. Furthermore, TCM focuses on regulating the overall state of the body. While inhibiting tumor growth, it can also improve the symptoms of cancer patients and enhance their quality of life. For example, they can alleviate symptoms such as fatigue and pain in cancer patients and regulate immune and endocrine function, thereby maintaining a relatively balanced state of the body and promoting tumor suppression.

TNBC classification is an evolving field, with the current mainstream development based on TNBC-4, and new research is gradually being integrated into clinical practice. The anti-cancer principles of traditional Chinese herbal medicine are also becoming increasingly clear and can be used as a clinical medication strategy, which in turn will help to more accurately classify TNBC subtypes. This review defines the four TNBC subtypes, maps each to its corresponding TCM strategy, and advances the development of precise, subtype-targeted therapies.

2. Luminal Androgen Receptor (LAR)

2.1. Definition and characteristics

The LAR subtype is characterized by high-frequency androgen receptor (AR) mutations, activation of hormone regulatory pathways, luminal differentiation phenotype, and activation of the PI3K-AKT pathway. Lymph node metastasis is more common in LAR, with nearly 47% of LAR subtype patients experiencing regional metastases. The use of PI3K/AKT inhibitors can significantly improve the clinical benefit rate of LAR [6].

2.2. Corresponding traditional Chinese medicine treatment

2.2.1. Hedyotis diffusa

First, quercetin, one of the core active ingredients of Hedyotis diffusa, has been shown to act on the PI3K/AKT pathway. Quercetin can reduce the phosphorylation level of key proteins in this pathway, inhibit the activation of the PI3K/AKT pathway, thereby reducing the proliferation of breast tumor cells and promoting their apoptosis [9].

DOI: 10.54254/2753-8818/2026.PJ30390

Second, after using Hedyotis diffusa extract (SHLP), changes occurred in apoptosis-related genes, and the PI3K-AKT signaling pathway was inhibited. SHLP can exert synergistic regulatory effects through pathway enrichment to achieve anti-cancer effects [10].

2.2.2. Dandelion

First, stem cell inhibition. For the MDA-MB-231 and MDA-MB-468 cell lines, dandelion extract was able to disrupt their stem cell-like characteristics. The specific mechanisms included reducing the proportion of ALDH+ cells and inhibiting the formation of mammary globules; downregulating the expression of CSC-related markers such as FOXM1, SOX2 and NANOG [11].

Secondly, metabolic interference. In vitro experiments have shown that dandelion extract interferes with the metabolism of glycerophospholipids and unsaturated fatty acids by inhibiting the CHKA/PI3K/AKT/FADS2 axis, thereby blocking the formation of tumor cell membranes [12].

Third, it induces apoptosis. The hydroalcoholic extract of dandelion (HADE) is effective against 4T1 breast tumor cells, mainly through apoptosis and autophagy. With increasing HADE concentration, the survival rate of 4T1 cells decreases, DNA fragmentation increases, and the morphological characteristics of apoptosis become more pronounced. Simultaneously, the number of acidic vesicle organelles increases in 4T1 cells, and the proportion of cells engaging in autophagy significantly rises [13].

3. Mesenchymal(M)

3.1. Definition and features characteristics

The M subtype highly expresses mesenchymal cell markers (such as Vimentin, Snail, and Slug). It is characterized by abundant fibroblasts and collagen deposition surrounding the tumor cells. The tumor cell exhibits weak adhesion, strong migration and invasion capabilities. Clinically, M subtype is more prone to early distant metastasis, with metastatic sites including the lungs, bones, and brain. Lung metastasis is particularly prevalent.

3.2. Salvia miltiorrhiza treatment for M subtype

Salvia miltiorrhiza can exert its anti-breast cancer effect through multiple targets and pathways, covering key aspects such as cancer cell proliferation, apoptosis, metastasis, and drug resistance.

Tanshinone IIA, the core active ingredient in Salvia miltiorrhiza, can serve as the key fat-soluble component of Salvia miltiorrhiza in its anti-triple-negative breast cancer effects. It exerts its effects through four types of pathway molecules, and some of its effects are concentration-dependent [14]. First, it inhibits the PI3K/Akt/mTOR signaling pathway, reduces PI3K and Akt phosphorylation and mTOR expression, and activates pro-apoptotic proteins, inducing apoptosis in tumor cells; second, it inhibits the NF-κB signaling pathway, relieves its anti-apoptotic effect, and activates the Caspase cascade reaction; third, it downregulates the anti-apoptotic protein Bcl-2, upregulates the phosphorylation of the tumor suppressor protein p53, promotes the expression of the apoptosis gene Bax protein, and drives cell apoptosis; fourth, it regulates the miR-125b/STARD13 axis, downregulates the pro-cancer miR-125b, upregulates its target gene STARD13, and hinders the growth of breast tumor cells.

Salvia miltiorrhiza also contains tanshinone I, which mainly works by inhibiting the STAT3 signaling pathway, preventing IL-6-induced JAK1/2 (STAT3 upstream kinase) and STAT3 phosphorylation activation, while inhibiting the interaction between STAT3 and its downstream

DOI: 10.54254/2753-8818/2026.PJ30390

cancer-promoting target genes (anti-apoptotic Bcl-2, pro-proliferative Cyclin B1, and pro-metastasis MMP2), doubly inhibiting cancer cell proliferation and metastasis, and enhancing apoptosis sensitivity.

M subtype has a high metastatic characteristic, among which the probability of lung metastasis is extremely high. Dihydrotansidone I (DHT), contained in Salvia miltiorrhiza, can block key pathways promoting lung metastasis of breast cancer in the tumor microenvironment, thereby inhibiting lung metastasis of breast cancer by suppressing the formation of extracellular traps of neutrophils. In the 4T1 breast cancer spontaneous metastasis model experiment, when DHT was administered at a dose of 20 mg/kg, the development and distribution ratio of metastatic lesions in lung tissue were reduced by 74.9% [15]. Other studies have shown that Salvia miltiorrhiza Bunge Aqueous Extract (SME) can reduce the viability of cancer cells and decrease the lung metastasis rate of breast cancer cells by inhibiting the STAT3-CCL2 signaling pathway [16].

4. Basal-Like 1 (BL1)

4.1. Definition and features characteristics

Basal-like 1 TNBC is a subtype of triple-negative breast cancer that highly expresses basal-like cell markers and genes related to DNA damage repair. It has high proliferative activity, usually manifested by tumor cells with basal-like morphology, which is associated with the expression of basal cell keratin. The BL1 subtype exhibits active expression of proliferation-related genes and DNA repair genes [17].

4.2. Been venom treatment for BL1 subtype

Bee venom is a complex biologically active mixture containing peptides, enzymes, physiologically active amines and other substances that can help treat cancer [18]. Recent studies have shown that its key components have potential value in breast cancer intervention, inhibiting breast cancer progression through multiple pathways while also helping to improve cancer-related symptoms.

Melittin, a cationic peptide in bee venom (approximately 40%-50% dry weight), has significant antibacterial, insecticidal, and cell-dissolving properties [19,20]. It can induce breast cancer cell death through direct action and arrest cells at key division stages such as the G2/M phase, preventing them from completing normal division and proliferation [21].

In addition, Adolapin, a component of bee venom, has clear anti-inflammatory activity and can help relieve breast cancer-related discomfort by regulating inflammatory responses [22]. In addition, bee venom also contains phospholipase A2, hyaluronidase (enzymes), histamine, epinephrine (physiologically active amines), and amino acids (non-peptides). Although their direct anti-breast cancer effects have not yet been clearly established, they may enhance the activity of core components through synergistic effects.

5. Basal-Like 2 (BL2)

5.1. Definition and features characteristics

Basal-like 2, while retaining some of the characteristics of the "basal-like phenotype", has become a subtype of TNBC that requires special attention due to its enrichment of growth factor signaling pathways, overexpression of immune-related genes, pathways, cytokines, and cells, reduced tumor size, and better patient survival. Furthermore, it is positive for CD8, CTLA-4, and PD-L1, and

DOI: 10.54254/2753-8818/2026.PJ30390

targeted drugs such as PD1, PDL1, CTLA4, and ID01 can be used for treatment [23]. The activity of the glycolysis and gluconeogenesis metabolic pathways in the BL2 subtype is enhanced, making the cells more capable of migration and invasion than the BL1 subtype [15].

5.2. Spatholobus suberectus treatment for BL2 subtype

Spatholobus suberectus repens is a non-toxic plant. It has significant effects on promoting blood circulation, regulating menstruation and relieving pain. Pharmacological studies have shown that Spatholobus suberectus repens has antioxidant, antitumor and anti-diabetic effects [24]. 243 chemical components have been identified in chicken blood vine, including flavonoids, lignin, organic acids, terpenoids and other compounds [25]. Among them, the treatment of TNBC is derived from the natural isoflavone compound (-)-Sativan (SA) it contains, which acts through multi-target regulation [26].

On the one hand, SA can upregulate the expression of miR-200c in TNBC cells. This microRNA can directly target and inhibit the translation of PD-L1 mRNA, relieve the inhibition of immune cells by the PD-1/PD-L1 pathway, restore the killing ability of CTL cells against TNBC cells, and block tumor immune escape.

On the other hand, SA can regulate proteins. It regulates proteins related to epithelial-mesenchymal transition (EMT), reducing the migration and invasion abilities of cancer cells. It also regulates apoptosis-related proteins, inhibiting the proliferation of TNBC cells.

6. Conclusion

TNBC is a highly aggressive subtype of breast cancer, characterized by poor prognosis and limited treatment options. This review, based on the therapeutic effects and mechanisms of action of different TCM in the Lehmann classification, confirms the unique value of TCM in the treatment of TNBC. Hedyotis diffusa, through quercetin and its extracts, inhibits the PI3K/AKT pathway via multiple pathways, while dandelion targets the stem cell characteristics of TNBC and interferes with lipid metabolism; both provide effective strategies for inhibiting metastasis and blocking proliferation in the LAR subtype. Tanshinone IIA, tanshinone I, dihydrotanshinone I, and water extracts of Salvia miltiorrhiza intervene in cancer cell proliferation, apoptosis, and metastasis through mechanisms such as regulating multiple signaling pathways and inhibiting the formation of extracellular traps in neutrophils, showing great effectiveness against the M subtype. Bee venom can induce cell death, block the cell cycle, and alleviate inflammatory symptoms, exhibiting a dual effect of "cancer suppression + symptomatic improvement." It shows great potential in the BL1 subtype; Spatholobus suberectus can block tumor immune escape and metastasis in the highly invasive BL2 subtype. In summary, TCM's "holistic regulation + combined targeted therapy" approach, with its advantages of multiple targets, low risk of drug resistance, and ability to regulate the body's overall state, provides more ideas for the precise adjuvant treatment of various subtypes of TNBC. Despite its promising prospects, current research is mostly focused on in vitro experiments and animal models; further in-depth exploration is needed regarding dosage control and safety verification in human clinical applications. Future efforts should strengthen translational medicine research to promote the standardized application of traditional Chinese medicine in the clinical treatment of TNBC.

DOI: 10.54254/2753-8818/2026.PJ30390

References

[1] Krishnamurthy S., Poornima R., Challa V.R., Goud Y.G. (2012) Triple negative breast cancer—our experience and review. Indian J Surg Oncol, 3: 12–16.

[2] Voduc K.D., Cheang M.C., Tyldesley S., Gelmon K., Nielsen T.O., Kennecke H. (2010) Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol, 28: 1684–1691.

[3] Howard F.M., Olopade O.I. (2021) Epidemiology of triple-negative breast cancer: a review. Cancer J Sudbury Mass, 27: 8–16.

[4] Jemal A., Bray F., Center M.M., Ferlay J., Ward E., Forman D. (2011) Global cancer statistics. CA Cancer J Clin, 61: 69–90.

[5] Jeffrey S.S., Rees C.A., Pollack J.R., et al. (2000) Molecular portraits of human breast tumors. Nature. Aug 17; 406(6797): 747-52.

[6] Lehmann B.D., Jovanović B., Chen X., Estrada M.V., Johnson K.N., Shyr Y., et al. (2016) Refinement of triple-negative breast cancer molecular subtypes: implications for neoadjuvant chemotherapy selection. PLoS ONE. 11: e0157368.

[7] Yao Y., Rao C., Zheng G., Wang S. (2019) Luteolin suppresses colorectal cancer cell metastasis via regulation of the miR384/pleiotrophin axis. Oncol Rep. Jul; 42(1): 131-141. doi: 10.3892/or.2019.7136.

[8] Han X., Zhang X., Wang Q., Wang L., Yu S. (2020) Antitumor potential of Hedyotis diffusa Willd: A systematic review of bioactive constituents and underlying molecular mechanisms. Biomed Pharmacother. Oct; 130: 110735. doi: 10.1016/j.biopha.2020.110735.

[9] Queting Chen, Yuanzhuang Xu, Jianhua Ma, Gaotao Zhang, Zhengyu Yin, Donghao Zhang, et al. (2025) Network Pharmacology Integrated Experimental Validation Uncover Quercetin as the Key Ingredient of Hedyotis diffusaAnti-BRCA. Chemical blology and drug design, Volume 105, Issue 4, April, e70112.

[10] Tingting Ma, Ganlin Zhang, Cunfang Dai, Boran Zhang, Kexin Cao, et al. (2020) Scutellaria barbata and Hedyotis diffusa herb pair for breast cancer treatment: Potential mechanism based on network pharmacology. Journal of Ethnopharmacology, Volume 259, 15 September, 112929.

[11] Xinxin Deng, Yanna Jiao, Huifeng Hao, Zhengwang Guo, Guo An, Wenlong Zhang, et al. (2025) Dandelion extract suppresses the stem-like properties of triple-negative breast cancer cells by regulating CUEDC2/β-catenin/OCT4 signaling axis. Journal of Ethnopharmacology, Volume 342, 27 February, 119408.

[12] Shan Wang, Huifeng Hao, Yanna Jiao, Jialei Fu, Zhengwang Guo, et al. (2022) Dandelion extract inhibits triple-negative breast cancer cell proliferation by interfering with glycerophospholipids and unsaturated fatty acids metabolism. Front Pharmacol. Sep 6; 13: 942996.

[13] Ahmadi S., Saberivand A., Jalili C., Asadpour R., Khordadmehr M., Saberivand M., et al. (2023) Hydroalcoholic extract of Taraxacum officinale induces apoptosis and autophag in 4T1breast cancer cells. Vet Res Forum. Sep 15; 14(9): 507-513.

[14] Pengyu Zhang, Wendi Liu, Yuan Wang. (2023) The mechanisms of tanshinone in the treatment of tumors. Sec. Experimental Pharmacology and Drug Discovery, Front. Pharmacol., 26 October.

[15] Huan Zhao, Bing Han, Xuan Li, Chengtao Sun, Yufei Zhai, et al. (2022) Salvia miltiorrhiza in Breast Cancer Treatment: A Review of Its Phytochemistry, Derivatives, Nanoparticles, and Potential Mechanisms. Sec. Pharmacology of Anti-Cancer Drugs. Front, Pharmacol., 05 May.

[16] Liangliang Gu, Ruoqing Li, Ruirui Wang, Mengqing Hu, Peiyun Wu, et al. (2025) Salvia miltiorrhiza Bunge aqueous extract inhibits lung metastasis of breast cancer by inhibiting recruitment of M2-like macrophages via CCL2-STAT3 axis. Medical Oncology (Northwood, London, England), 27 June.

[17] Lehmann B.D., Bauer J.A., Chen X., Sanders M.E., Chakravarthy A.B., Shyr Y., Pietenpol J.A. (2011) Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. Jul; 121(7): 2750-67. doi: 10.1172/JCI45014.

[18] Khor S.X.Y., Khongphinitbunjong K., Owatworakit A., Mah S.H., Tang Y.Q. (2024) Honeybee Venom: A Potential Source of Anticancer Components. Protein Pept Lett. 31(10): 796-805.

[19] Bindlish A., Sawal A. (2024) Bee Sting Venom as a Viable Therapy for Breast Cancer: A Review Article. Cureus. Feb 25; 16(2): e54855.

[20] Liu C.C., Hao D.J., Zhang Q., et al. (2016) Application of bee venom and its main constituent melittin for cancer treatment. Cancer Chemother Pharmacol. 78: 1113-30.

[21] Prince G, Assi A, Aoude M, Kourie HR, Haddad F. (2025) Melittin, A Potential Game-changer in the Fight Against Breast Cancer: A Systematic Review. Anticancer Agents Med Chem. 25(15): 1077-1084.

[22] Cherniack E.P., Govorushko S. Toxicon. (2018) To bee or not to bee: The potential efficacy and safety of bee venom acupuncture in humans. 154: 74–78. doi: 10.1016/j.toxicon.2018.09.013.

DOI: 10.54254/2753-8818/2026.PJ30390

[23] Ziqi Chen, Yumeng Liu, Minchuan Lyu, Chi Ho Chan, et al. (2025) Classifications of triple-negative breast cancer: insights and current therapeutic approaches. Cell Biosci. Feb 1; 15: 13.
[24] Huang X., Fei Q., Yu S., Liu S., Zhang L., Chen X., Cao L., Wang Z., Shan M. (2023) A comprehensive review: Botany, phytochemistry, traditional uses, pharmacology, and toxicology of Spatholobus suberectus vine stems. J Ethnopharmacol. Aug 10; 312: 116500.
[25] Pan Y., Luo X, Gong P. (2016) Spatholobi caulis: A systematic review of its traditional uses, chemical constituents, biological activities and clinical applications. J Ethnopharmacol. Dec 5; 317: 116854.
[26] Peng F., Xiong L., Peng C. (2020) Sativan Inhibits Tumor Development and Regulates miR-200c/PD-L1 in Triple Negative Breast Cancer Cells. Front Pharmacol. Mar 13; 11: 251.