Revolutionizing Breast Cancer Treatment: Herbal Strategies Against Stem Cells

Asefa Ibrahimbhai Chauhan, **Devanshi Jatinbhai Warde**

Sal Institute of Pharmacy, Gujarat, India

Corresponding author: Asefa Ibrahimbhai Chauhan

Email: asefa.chauhan@yahoo.com

Doi: 10.5281/zenodo.15719328

Received: 25 April 2025

Accepted: 25 May 2025

Abstract:

Severe forms of cancer are life-threatening due to the uncontrolled growth and spread of abnormal cells that invade and destroy healthy tissues and organs. The largest number of female deaths globally is attributed to breast cancer. Early diagnosis and treatment, such as radiology, surgery, chemotherapy, and medications, can be used to control or cure the disease. However, adverse effects like excessive hair loss, nausea, multidrug resistance, infections, and often relapsing of the metastasis can lead to complications. Given this trend, the demand for natural products sourced from medicinal plants and foods is rising. Plant-derived bioactive compounds are revolutionary treatment options. Targeted therapy against Breast cancer stem cells (BCSCs) is increasingly recognized as a critical strategy to overcome therapeutic resistance and achieve lasting remission. In this context, herbal products have emerged as promising agents due to their multi-targeted mechanisms of action, mitigated toxicity, and potential to modulate key signalling pathways involved in BCSC maintenance. Compounds such as curcumin, resveratrol, sulforaphane, berberine, and honokiol have shown potential in inhibiting BCSC-related pathways like Wnt/β-catenin, Notch, and PI3K/Akt in preclinical studies. This review evaluates the current landscape of herbal interventions in BCSC-targeted therapy and underscores the need for further research to bridge the gap between preclinical promise and clinical practice.

Keywords: Breast Cancer, herbal therapy, phytochemicals, Breast cancer stem cells (BCSCs), self-renewal, targeted therapy

1. Introduction

Affecting women worldwide, breast cancer becomes more common with increasing age. In 2022, the global incidence reached approximately 2.3 million new cases, with an age-standardized rate of about 47.8 per 100,000 women and a lifetime risk of 1 in 20. In India, it stands as the most frequent cancer in women, with an estimated incidence rate of around 25.8 per 100,000 (higher in urban areas) and a lifetime risk of about 1 in 28 [1]. According to the data from the Global Cancer Observatory 2022 report, breast cancer is a major contributor to global cancer mortality, ranking fourth among the top 15 cancer sites. The available treatment options are characterized by a multimodal approach, integrating surgical intervention, radiation therapy, chemotherapy, hormonal therapy, targeted agents, and immunotherapy, frequently

administered in combination. However, there are hurdles. The intrinsic heterogeneity of breast cancer necessitates personalized treatment strategies; however, the accurate prediction of therapeutic response and the circumvention of drug resistance remain significant obstacles. Metastasis, the principal determinant of mortality, presents a substantial clinical challenge once dissemination has occurred. Inequities in access to prompt and high-calibre medical care exacerbate the heterogeneity observed in treatment outcomes for breast cancer. Research is increasingly focused on innovative strategies, including the selective targeting of breast cancer stem cells and the effective management of intricate and aggressive subtypes directed towards the improvement of overall patient survival [2].

The defining features of cancer stem cells are their capacity to initiate tumour growth in immunodeficient mice and to generate the bulk of the tumour through differentiation of their offspring, a process fuelled by their self-renewal ability. They are of greater influence to understand tumour development. Characterized by a high degree of invasiveness, the capacity for clonal evolution, and the ability to enter dormancy, these cells also facilitate angiogenesis and stimulate cell motility. In addition to their established role in tumorigenesis, a growing body of evidence implicates their contribution to tumour progression and the metastatic cascade [3]. Natural products hold a central position in the development of anticancer therapies. Their diverse chemical structures and biological activities have historically served as a crucial foundation for drug discovery, particularly in oncology. These naturally occurring compounds offer inherent advantages, including structural complexity and a natural optimization for biological interactions, rendering them invaluable resources for the creation of novel and effective treatments for cancer [4]. The objective is to develop improved therapeutic strategies for this proliferative and life-threatening disease, to give enhanced efficacy and a reduction in adverse effects.

2. Breast Cancer Stem Cells (BCSCs): A Detailed Overview

There are two types of Breast Cancer- ductal and lobular; further divided to multiple subtypes- luminal A and B, basal-like triple negative breast cancer (TNBC), HER2+, claudin-low which are classified by molecular and histological phenotypes. Each type and subtype of Breast Cancer are categorized as non-invasive and invasive. BCSCs express variety of specific markers such as $CD44^{+}/CD24^{-}$, CD326 (EpCAM), epithelial specific antigen (ESA), and aldehyde dehydrogenase (ALDH) activity in different types of Breast Cancer. Unlike CD24, which identifies differentiated breast cancer cells, CD44 marks stemness on the surface of BCSCs. CD44's interaction with hyaluronic acid (HA) and extracellular matrix proteins, including osteopontin (OPN) and matrix metalloprotease (MMP), facilitates its potential control over cell adhesion, migration, and proliferation signalling in BCSCs, possibly in concert with receptor tyrosine kinases (RTKs). Furthermore, CD44 mediates key signalling pathways like Rho GTPases, Ras-MAPK, and PI3K/Akt, which are crucial for regulating cell adhesion, migration, invasion, and the epithelial-mesenchymal transition (EMT) [5]. Moreover, cells exhibiting the CD44+/CD24−/ALDH+ markers have notably lower PR and ER mRNA levels when contrasted with CD44−/CD24+ cells. ALDH activity appears to be a more reliable indicator of tumour-forming ability in living organisms than CD44/CD24 markers. The ALDH enzyme plays a crucial role in oxidizing aldehydes within cells and is essential for stem cell differentiation [6]. The maintenance of stemness, regulation of self-renewal, promotion of metastasis, and development of therapeutic resistance in Cancer Stem cells are influenced by a range of signalling pathways, including MAP kinase, PI3K/Akt/NFκB, TGF-β, hedgehog (Hh), Notch, Wnt/β-catenin, and Hippo. Dysfunction in these pathways within normal stem cells can drive their conversion to CSCs [5]. A relationship exists between CD24 and the Sonic hedgehog (SHH) pathway, as evidenced by the observation that reducing CD24 expression in breast cancer cells enhances proliferation, invasion, and tumorigenicity through increased levels of SHH, GLI1, and MMP2. CD24 exerts a suppressive effect on the malignant phenotype of BCSCs by downregulating SHH expression via STAT1 inhibition [7]. Examinations on a new HA- CD44- intermediated PKCϵ signalling medium that regulates the stem cell marker

(Nanog)- associated miR- 21 product and results indicate that HA- CD44- actuated PKCϵ stimulates Nanog phosphorylation, which in turn, activates Nanog signalling- regulated miR- 21 product [8].

3. Herbal Compounds and Extracts Targeting BCSCs

Plants produce a variety of natural compounds as a protective response to environmental stressors, functioning as inherent defences with antioxidant, antifungal, and antibiotic properties. Humans encounter these substances, termed phytoestrogens—nonsteroidal polyphenols exhibiting structural resemblances to 17-β-estradiol, through their dietary intake. This structural mimicry enables phytoestrogens to interact with estrogen receptors with differing binding strengths, resulting in both estrogenic and anti-estrogenic actions. Phytoestrogens like **curcumin**, **resveratrol**, **sulforaphane**, **berberine**, and **honokiol** are inspected. The investigation of these compounds is particularly relevant in the context of breast cancer, as considerable research explores their potential role in modulating the risk and progression of this disease, as well as their possible utility in mitigating hormone-related symptoms [9].

Curcumin

Curcumin ((1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), the principal polyphenolic component of turmeric (Curcuma longa Linn), has been extensively investigated for its broad spectrum of biological properties, including anti-inflammatory, antioxidant, anti-infection, and anticancer activities. This potent antitumor agent is safe for human consumption and exerts its anticancer effects by inhibiting cancer cell proliferation and migration, inducing apoptosis, and increasing the sensitivity of cancer cells to chemotherapy drugs through the modulation of Bcl-2 family proteins. Furthermore, curcumin has demonstrated the ability to overcome multidrug resistance in a variety of cancers [10]. Curcumin inhibits the self-renewal ability as well as induce apoptosis, that can provide in treatment of chemotherapy combination therapy like with Mitomycin C(MMC) [11].

Resveratrol

Resveratrol((E)-5-(2-(4-hydroxyphenyl) ethenyl) benzene-1,3-diol), a polyphenolic stilbene featuring an aromatic benzene moiety substituted with three hydroxyl groups, exhibits significant antioxidant activity through the neutralization of reactive oxygen species (ROS), thereby potentially mitigating neoplastic cell transformation. The anticancer properties attributed to resveratrol include the induction of cell cycle arrest, apoptosis, and differentiation, as well as the inhibition of neoplastic cell proliferation. Given its structural homology with diethylstilbestrol, a synthetic estrogen, resveratrol is categorized as a phytoestrogen [12]. Recent research indicates resveratrol can prevent mammosphere formation and breast cancer development (even with estrogen present in rats) by activating the NRF2 pathway. The effectiveness of the cell death in these BCSCs was linked to the presence and function of the DAXX protein. Also, resveratrol reduced the self-renewal of BCSCs promoted by cancer-associated fibroblasts by lowering Bmi-1 and Sox2. Another way resveratrol works is by boosting Argonaute2 activity (a key part of RNA interference) and increasing tumour-suppressing miRNAs to inhibit BCSCs [9][13].

Sulforaphane

Sulforaphane(1-isothiocyanato-4-(methylsulfinyl) butane), is an Isothiocyanate found in its inactive storage form as glucoraphanin, and its major source is broccoli, an important plant from the family *Brassicaceae* [14]. Sulforaphane is increasingly utilized in the treatment of triple-negative breast cancer. Sulforaphane inhibits CSCs by reducing the production of IL-6 and IL-8, as well as NF-κB activity. Combining sulforaphane with taxane chemotherapeutic agents

such as paclitaxel or docetaxel can enhance their efficacy against most triple-negative breast cancer cells, and importantly, sulforaphane counteracts the cytokine production and breast CSC expansion induced by these taxanes in laboratory experiments [15].

Berberine

Berberine (5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a] quinolizinium), is present in the roots and stems of various plants such as berberis species and is called botanical alkaloid. It has anti-inflammatory, antidiarrheal and antifungal effects in clinical use and is reported to have anticancer and antimetastatic properties in MCF-7 cells [16]. Berberine enhances radiation sensitivity in breast cancer cells (MCF-7, MDA-MB-468) by arresting their growth and reducing RAD51 protein, suggesting it could improve radiotherapy. Combining berberine with doxorubicin reduced the survival of MCF-7 cells (both regular and mammospheres) more effectively, showing a synergistic anticancer effect. This combination, as well as each drug alone, lowered Nanog and miRNA-21 gene levels in mammospheres. Berberine might fight breast cancer by reducing these genes, making cells more sensitive to doxorubicin and creating a stronger combined effect. [17].

Honokiol

A bioactive natural product obtained from *Magnolia* species, honokiol (3',5-Di(prop-2-en-1-yl) [1,1'-biphenyl]-2,4'-diol), has garnered significant attention in cancer research. Recent studies have demonstrated its anti-inflammatory, anti-angiogenic, anti-oxidative, and antineoplastic effects in laboratory experiments and animal models. Notably, honokiol exerts its effects by modulating several signalling pathways of considerable relevance to both the initiation and progression of cancer, including nuclear factor kappa B (NF-κB), signal transducers and activator of transcription 3 (STAT3), epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (m-TOR) [18]. Honokiol further demonstrated the ability to reduce the activity of AKT (protein kinase B) and the mammalian target of rapamycin, specifically by decreasing their phosphorylation. Moreover, it inhibited the enzymatic activity of γ-secretase by reducing the expression of its constituent proteins, with a notable effect on anterior pharynx-defective 1 [19].

4. Preclinical and Clinical Evidence

Clinical trials have shown that certain plant chemicals can effectively treat various cancers, both on their own and with existing therapies. Since current cancer treatments often leave behind cancer stem cells, leading to recurrence and progression, targeting these CSCs with plant chemicals, alone or in combination, presents a promising new approach to cancer treatment [20]. Identifying BCSC biomarkers is a growing focus in breast cancer research, though their clinical use is currently limited despite links to diagnosis and prognosis; these markers hold significant potential to advance diagnosis, tumour understanding. The development of new BCSC-targeted treatments is essential for eliminating treatment-resistant cells and preventing recurrence to achieve successful breast cancer eradication. Multitarget inhibitors show promise against BCSC drug resistance [21]. Metformin, an FDA-approved drug currently used to treat type 2 diabetes, has recently been investigated for its ability to reduce the frequency of BCSCs in Triple Negative Breast Cancer. Studies indicate that it achieves this by targeting KLF5 for degradation and preventing the activation of its downstream target genes, Nanog and FGF-BP1, suggesting a substantial therapeutic potential within the TNBC patient population [22].

5. Limitations and Challenges

The limitations of current cancer treatments, including intrinsic/acquired therapy resistance and the rise of chemo-resistant cancer stem cells that fuel metastasis, necessitate the development of reliable cancer stem cell models to identify better

therapies [23]. Natural compounds from readily available fruits and vegetables could disrupt the biological and metabolic processes of CSCs, suppressing these pathways and potentially inhibiting or eliminating CSCs. It's important to note that these findings are primarily from lab and animal studies, with only a few compounds reaching preclinical evaluation. Furthermore, the anticancer effects of some herbal compounds, like Eupatilin on breast cancer, remain largely unexamined, and novel targeting pathways require more in-depth research [24].With demonstration of such promising actions, this is theorized and there is a lack of consumption of herbal compounds as anti-cancer strategy [25].The heterogeneity and plasticity of cancer stem-like cells contributes to treatment resistance. There is a current lack of understanding of tumour cellular heterogeneity and plasticity, which limits the development of more effective therapeutic strategies [26].

6. Future Direction

Preclinical evidence increasingly indicates that cancer stem cells contribute to chemo- and radio resistance in breast cancer, yet this hasn't significantly impacted clinical outcomes. More effective therapies targeting CSCs are needed to overcome resistance. While preclinical data are promising, their full clinical translation awaits demonstrated efficacy of CSC-targeting drugs in trials [3]. The current knowledge we have for cancer, related to metastasis, proliferation, and treatment is limited. To further investigated and develop targeted mechanisms a combination of agents that affect multiple signalling pathways is a powerful strategy [27] [28].

7. Conclusion

With a surge in fatalities and abnormalities, cancer isa life-threatening disease. Therapeutic strategies aimed at BCSCs can focus on disrupting their diverse functional and molecular features, encompassing BCSC markers, the signalling pathways controlling self-renewal, their interactions within the tumour microenvironment, and the pathways responsible for drug resistance mediated by these cells. There is a need to further investigate the cancer stem cell targeting efficacy of natural products, their efficacy via multiple signalling pathways, and their combinatorial efficacy with other drug candidates. This review outlines how phytoestrogens can be used to target BCSCs, with a particular focus on combination therapies. Overall, it highlights promising approaches for stem cell-targeted breast cancer treatment. The review emphasizes the need for improved strategy and robust pathways to overcome the current limitations like heterogeneity, lack of evidence, drug-herb interactions, and to develop novel approaches for anti-cancer phytoestrogens that successfully transition from promising lab studies to effective use in patients.

References:

1. World Health Organization: WHO & World Health Organization: WHO. (2024, March 13). *Breast cancer*. https://www.who.int/news-room/fact-sheets/detail/breast-cancer
2. Barrios, C. H. (2022). Global challenges in breast cancer detection and treatment. *TheBreast*, *62*, S3–S6. https://doi.org/10.1016/j.breast.2022.02.003
3. Economopoulou, P., Kaklamani, V. G., &Siziopikou, K. (2012). The role of cancerstem cells in breast cancer initiation and progression: Potential Cancer Stem Cell-Directed therapies. *The Oncologist*, *17*(11), 1394–1401.https://doi.org/10.1634/theoncologist.20=12-0163
4. Jenča, A., Mills, D., Ghasemi, H., Saberian, E., Jenča, A., Forood, A. M. K., Petrášová, A., Jenčová, J., Velisdeh, Z. J., Zare-Zardini, H., &Ebrahimifar, M. (2024). Herbal Therapies for Cancer Treatment: A Review of Phytotherapeutic Efficacy. *Biologics*, *Volume 18*, 229–255. https://doi.org/10.2147/btt.s484068

5. Yousefnia, S., Forootan, F. S., Forootan, S. S., Esfahani, M. H. N., Gure, A. O., &Ghaedi, K. (2020). Mechanistic pathways of malignancy in breast cancer stem cells. *Frontiers in Oncology*, *10*. https://doi.org/10.3389/fonc.2020.00452
6. Tanei, T., Morimoto, K., Shimazu, K., Kim, S. J., Tanji, Y., Taguchi, T., Tamaki, Y., & Noguchi, S. (2009). Association of Breast Cancer Stem Cells Identified by Aldehyde Dehydrogenase 1 Expression with Resistance to Sequential Paclitaxel and Epirubicin-Based Chemotherapy for Breast Cancers. *Clinical Cancer Research*, *15*(12), 4234–4241. https://doi.org/10.1158/1078-0432.ccr-08-1479
7. Suyama, K., Onishi, H., Imaizumi, A., Shinkai, K., Umebayashi, M., Kubo, M., Mizuuchi, Y., Oda, Y., Tanaka, M., Nakamura, M., & Katano, M. (2016). CD24 suppresses malignant phenotype by downregulation of SHH transcription through STAT1 inhibition in breast cancer cells. *Cancer Letters*, *374*(1), 44–53. https://doi.org/10.1016/j.canlet.2015.12.013
8. Bourguignon, L. Y., Spevak, C. C., Wong, G., Xia, W., & Gilad, E. (2009). Hyaluronan-CD44 Interaction with Protein Kinase Cϵ Promotes Oncogenic Signaling by the Stem Cell Marker Nanog and the Production of MicroRNA-21, Leading to Down-regulation of the Tumor Suppressor Protein PDCD4, Anti-apoptosis, and Chemotherapy Resistance in Breast Tumor Cells. *Journal of Biological Chemistry*, *284*(39), 26533–26546. https://doi.org/10.1074/jbc.m109.027466
9. Nguyen, M., &Osipo, C. (2022). Targeting breast cancer stem cells using naturally occurring phytoestrogens. *International Journal of Molecular Sciences*, *23*(12), 6813. https://doi.org/10.3390/ijms23126813
10. Zhou, Q., Sun, Y., Lu, Y., Zhang, H., Chen, Q., & Su, S. (2017). Curcumin reduces mitomycin C resistance in breast cancer stem cells by regulating Bcl-2 family-mediated apoptosis. *Cancer Cell International*, *17*(1). https://doi.org/10.1186/s12935-017-0453-3
11. Fan, H., Liang, Y., Jiang, B., Li, X., Xun, H., Sun, J., He, W., Lau, H. T., & Ma, X. (2016). Curcumin inhibits intracellular fatty acid synthase and induces apoptosis in human breast cancer MDA-MB-231 cells. *Oncology Reports*, *35*(5), 2651–2656. https://doi.org/10.3892/or.2016.4682
12. Bhaskara, V. K., Mittal, B., Mysorekar, V. V., Amaresh, N., & Simal-Gandara, J. (2020). Resveratrol, cancer and cancer stem cells: A review on past to future. *Current Research in Food Science*, *3*, 284–295. https://doi.org/10.1016/j.crfs.2020.10.004
13. Hagiwara, K., Kosaka, N., Yoshioka, Y., Takahashi, R., Takeshita, F., &Ochiya, T. (2012). Stilbene derivatives promote Ago2-dependent tumour-suppressive microRNA activity. *Scientific Reports*, *2*(1). https://doi.org/10.1038/srep00314
14. De Lima Coutinho, L., Tortelli, T. C., Junior, & Rangel, M. C. (2023). Sulforaphane: An emergent anti-cancer stem cell agent. *Frontiers in Oncology*, *13*. https://doi.org/10.3389/fonc.2023.1089115
15. Burnett, J. P., Lim, G., Li, Y., Shah, R. B., Lim, R., Paholak, H. J., McDermott, S. P., Sun, L., Tsume, Y., Bai, S., Wicha, M. S., Sun, D., & Zhang, T. (2017). Sulforaphane enhances the anticancer activity of taxanes against triple negative breast cancer by killing cancer stem cells. *Cancer Letters*, *394*, 52–64. https://doi.org/10.1016/j.canlet.2017.02.023
16. El-Benhawy, S. A., El-Sheredy, H. G., Ghanem, H. B., & El-Soud, A. a. A. (2020). Berberine can amplify cytotoxic effect of radiotherapy by targeting cancer stem cells. *Breast Cancer Management*, *9*(2). https://doi.org/10.2217/bmt-2020-0007
17. Ebeid, S. A., Moneim, N. a. a. E., Ghoneim, H. E. M., El-Benhawy, S. A., & Ismail, S. E. (2020). Combination of doxorubicin and berberine generated synergistic anticancer effect on breast cancer cells through down-regulation of NANOG and MIRNA-21 gene expression. *DOAJ (DOAJ: Directory of Open Access Journals)*. https://doi.org/10.30476/mejc.2019.81277.0
18. Arora, S., Singh, S., Piazza, G., Contreras, C., Panyam, J., & Singh, A. (2012). Honokiol: a novel natural agent for cancer prevention and therapy. *Current Molecular Medicine*, *12*(10), 1244–1252. https://doi.org/10.2174/156652412803833508
19. Kaushik, G., Ramalingam, S., Subramaniam, D., Rangarajan, P., Protti, P., Rammamoorthy, P., Anant, S., & Mammen, J. M. (2012). Honokiol induces cytotoxic and cytostatic effects in malignant melanoma cancer cells. *The American Journal of Surgery*, *204*(6), 868–873. https://doi.org/10.1016/j.amjsurg.2012.09.001

20. Naujokat, C., & McKee, D. L. (2020). The “Big Five” Phytochemicals Targeting Cancer Stem Cells: Curcumin, EGCG, Sulforaphane, Resveratrol and Genistein. *Current Medicinal Chemistry*, *28*(22), 4321–4342. https://doi.org/10.2174/0929867327666200228110738
21. Landeros, N., Castillo, I., & Pérez-Castro, R. (2023). Preclinical and clinical trials of new treatment strategies targeting cancer stem cells in subtypes of breast cancer. *Cells*, *12*(5), 720. https://doi.org/10.3390/cells12050720
22. Shi, P., Liu, W., Tala, N., Wang, H., Li, F., Zhang, H., Wu, Y., Kong, Y., Zhou, Z., Wang, C., Chen, W., Liu, R., & Chen, C. (2017). Metformin suppresses triple-negative breast cancer stem cells by targeting KLF5 for degradation. *Cell Discovery*, *3*(1). https://doi.org/10.1038/celldisc.2017.10
23. Telang, N. (2023a). Drug-resistant stem cell models for the hormone-responsive luminal a breast cancer. *Medical Research Archives*, *11*(2). https://doi.org/10.18103/mra.v11i2.3556
24. Bozorgi, A., Khazaei, S., Khademi, A., & Khazaei, M. (2020). Natural and herbal compounds targeting breast cancer, a review based on cancer stem cells. *PubMed*, *23*(8), 970–983. https://doi.org/10.22038/ijbms.2020.43745.10270
25. Vekaria, M., &Tirgar, P. (2020). Promising Anticancer Potential of Herbal Compounds against Breast Cancer: A Systemic Review. *Asian Journal of Pharmaceutical Research and Health Care*, *13*(2), 202–218. https://doi.org/10.18311/ajprhc/2021/26698
26. Brooks, M. D., Burness, M. L., &Wicha, M. S. (2015). Therapeutic implications of cellular heterogeneity and plasticity in breast cancer. *Cell Stem Cell*, *17*(3), 260–271. https://doi.org/10.1016/j.stem.2015.08.014
27. Makena, M. R., Ranjan, A., Thirumala, V., & Reddy, A. P. (2018). Cancer stem cells: Road to therapeutic resistance and strategies to overcome resistance. *Biochimica Et BiophysicaActa (BBA) - Molecular Basis of Disease*, *1866*(4), 165339. https://doi.org/10.1016/j.bbadis.2018.11.015
28. Telang, N. (2023). Natural products as drug candidates for breast cancer (Review). *Oncology Letters*, *26*(2). https://doi.org/10.3892/ol.2023.13935