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Review Article

Herbal Medicine: A Potential Therapeutic Approach for Breast Cancer in Near Future

Veerappa Hugar[1], Daneshwari S Kanashetti[2,*], Nayan Kamal Dwevedi[3]

[1] *MD Scholar, Department of Rasashastra and Bhaishajya Kalpana, Ayurveda Mahavidhyalaya, Hubli, Karnataka, India*
[2] *PhD scholar, Department of Dravyaguna,Institute of Medical Sciences, Banaras Hindu University, Varanasi*
[3] *Former Dean, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi*

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* *Corresponding author.*
Daneshwari S Kanashetti
daneshwari@bhu.ac.in

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ABSTRACT

The use of naturally occurring compounds to stop carcinogenesis is expanding. It has been shown that a variety of herbal extracts and pure active compounds produced exclusively from plants have potent anti-cancer properties. Herbs can play a supportive role in promoting complete recovery, alleviating side effects, and addressing cancer-related issues. Haridra- *Curcuma longa*, Guduchi- *Tinospora cordifolia*, Atasi- *Linum ussitatissimum*, Kalajaji- *Nigella sativa*, Lashuna- *Allium sativum*, Ashwagandha- *Withania somnifera*, Kalamegha- *Andrographis paniculata*, Trapusha- *Podophyllum hexandrum*, Shigru- *Moringa ptyrygosperma*,Bhumyalaki- *Phyllanthus niruri*, Pippali- *Piper longum* etc. are various plants having scientific evidence of anticancer property.Numerous *in vitro* and *in vivo* studies have suggested that these medications have potential for treating breast cancer. Studies focused on molecular pathways have aided in the discovery of the main therapeutic strategies for treating breast cancer. The focus of future research should be on patient-centered translational trials for breast cancer. These will strengthen the therapeutic effectiveness of our Ayurvedic medication. This review seeks to offer experimental support and a greater understanding of the molecular processes by which various herbs function as chemotherapeutic agents against distinct forms of breast cancer.

Keywords: Anti-cancer; Ayurvedic herbs; Plant based medicine; Breast cancer

INTRODUCTION

Ayurveda, a form of Indian medicine with a history spanning more than 5000 years, has gained significant popularity in recent years. Plant-based preparations, integral to Ayurvedic healing practices, have consistently shown efficacy in treating various chronic illnesses, including cancer. Breast cancer is a condition in which breast's cells develop uncontrollably, forming a mass of tissue known as a tumor. There are no symptoms if the growth is within the duct or lobule where it first appeared, but it may spread and infiltrate nearby tissue, eventually affecting nearby lymph nodes and other organs. Frequently, a painless breast lump is observed as a common occurrence. Breast thickness, changes to the breast's size, shape, or appearance, skin changes like redness, pitting, or dimpling, changes to the nipple's appearance or the skin surrounding it (areola), and/or abnormal nipple discharge are all signs of breast cancer. A further symptom may be brought on by advanced breast tumors that pierce through the skin and spread to other body areas.

According to the World Health Organization, cancer is one of the worst problems that has been rapidly growing in the twenty-first century, has now taken the title of most dangerous killer in the world. According to GLOBOCAN 2020 data, breast cancer is currently one of the most frequently diagnosed malignancies and the fifth cause of cancer-related deaths, with an anticipated 2.3 million new cases worldwide [1].

The WHO Global Breast Cancer Initiative (GBCI) aims to prevent 2.5 million breast cancer deaths worldwide between 2020 and 2040 by reducing the annual global breast cancer mortality rate by 2.5%. 25% of breast cancer deaths among women under the age of 70 would be avoided by 2030 and 40% by 2040 if the global rate of breast cancer mortality was reduced by 2.5% annually. Health promotion

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for early detection, prompt diagnosis, and comprehensive breast cancer management are the three foundations for achieving these goals[2].

The cost of systemic treatment, including chemotherapy or hormone therapy, extends beyond the treatment itself to encompass the management of potential severe side effects. Advanced diagnostic tools like immunohistochemistry and molecular pathologic analysis are imperative for personalized cancer treatment. However, the escalating prices of these targeted therapies pose a significant financial burden on even the most robust healthcare systems, highlighting the challenges in the rapidly evolving landscape of cancer care. Although scientists are doing everything, they can to combat this illness, a certain treatment is still sought. Due to India's vast collection of medicinal plants, the use of plants as a source of medicine has a long history and is a significant part of the country's healthcare system.

From ancient times, the use of natural medications in Ayurveda, the oldest indigenous medical system in India, has been known to prevent or suppress a variety of malignancies. An absolute treatment for the disease is expected from the complementary and alternative medicine system, even though mainstream cancer therapy is known to be plagued by drug-induced hazardous side effects. As a result, researchers are increasingly more interested in researching plant-based medicines for the treatment of cancer. Plant-based medicines aid in complete recovery, minimize side effects, and ease cancer-related difficulties.

Several herbs are currently being examined phytochemically and clinically for their ability to treat cancer. Almost 25% of medications used in the past 20 years have a direct plant source, with the remaining 25% being natural compounds that have undergone chemical modification[3]. Ayurveda is a thorough medical system that is simple to include into contemporary national healthcare and treatments. Even though Ayurveda has been practiced for thousands of years, many of its fundamental concepts are like those of contemporary medicine. Evidence-based research in Ayurveda is becoming more popular both in India and overseas. This article provides a summary of Ayurvedic herbs that demonstrate potential anticancer effects, along with the current data supporting their efficacy.

MATERIAL AND METHODS

Published articles on recent developments in anticancer properties of drugs explained in Ayurveda, including original articles from Pubmed, Elsevier, Science direct, Springer, Web of Science and AYUSH portal databasesetcwere taken into consideration for the report. Information is gathered from more than 60 published articles including review and original articles. The search criteria are restricted to the role of herbal plants in combating Breast cancer *in vitro* and *in vivo* studies.

Breast Cancer Cell Lines and its Significance with Breast Tumor Subtype

Breast tumor exhibits great heterogeneity and several subgroups. Based on the immunohistochemical expression of hormone receptors, these subtypes are typically divided into four categories: estrogen receptor positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor positive (HER2+), and triple-negative breast cancer(TNBC), which lacks the expression of any of the previously mentioned receptors[4]. Based on these types cancer cell lines are characterized using the same nomenclature, i.e., luminal A, luminal B, HER2 positive, and triple negative subtypes, with triple negative cells being further divided into A and B to cover its heterogeneity and widely used in the name of basal A and B[5].

- **Luminal A:** ER-positive, PR-positive, and HER2-negative tumors fall into this category. Hormone treatment and chemotherapy are probably beneficial for Luminal A breast cancers. Most used luminal A cell lines are MCF-7, T47D.
- **Luminal B:** ER positive, PR negative, and HER2 positive tumors fall within this category. Chemotherapy is probably beneficial for luminal B breast cancers, while hormone therapy and HER2 therapy may also be helpful. MDA MB 361, BT483, MDA MB 415 are the examples of luminal B subtype tumors.
- **HER2 positive:** This category includes tumors that are HER2 positive but ER and PR negative. Chemotherapy and HER2-targeted treatments are expected to be beneficial for HER2-positive breast malignancies. MDA MB 361, MDA MB 453 are examples of this category.
- **Triple negative (basal like):** This category includes tumors that are ER, PR and HER2 negative. BT 549, MDA MB 468, MDA MB 231 and 4T1 are triple negative breast cancer cell lines[4]. Luminal A, luminal B, HER 2+ and triple negative tumors show better to worst prognosis sequentially. Various ayurvedic plants exhibiting breast cancer combating activity based on current researches are put together here.

Haridra- Curcuma longa

Curcumin extracted from Haridra was tested on MCF-7 breast cancer cell line resulting in cell apoptosis acting through p53-dependent pathway[6]. It also possesses inhibitory effect on cell proliferation when tested on MDA-MB-231 and BT-483 cell lines in a time- and dose-dependent manner. Along with anti-proliferative effect, it inhibits/downregulates NF-κB expression[7]. Its antiproliferative effects are estrogen dependent in ER positive MCF-7 cells, being more prominent in estrogen-containing medium and in the presence of exogenous 17-beta estradiol[8]. As a phytoestrogen, curcumin competitively blocked endogenous estrogen, which also helped to slow the proliferation

of breast cancer cells[9]. Curcumin substantially reduced the onset of mammary adenocarcinoma on the fourth day following DMBA injection in an animal study of breast cancer[10]. In a xenograft mice model of human breast cancer, the combination of curcumin and paclitaxel (Taxol) significantly reduced lung metastasis of breast cancer in comparison to either curcumin or paclitaxel alone[11].

Haridra was assessed both therapeutically and prophylactically, by using two different routes of administration, i.e., oral, and topical. It showed a considerable anticancer activity against MNU-induced mammary cancer in rats, the anticancer activity was more pronounced and significant, especially with topical application, in preventative treatment groups. When compared to the therapeutic treatment groups, the preventive topical administration of turmeric showed a better degree of tumor development inhibition and significant reduction in mean tumor volume. When compared to the other groups, prophylactic topical administration of turmeric has demonstrated higher effectiveness in lowering tumor incidence rates[12].

Guduchi- Tinospora cordifolia

50% methanolic extract of its stem shown substantial anticancer activity against MDA-MB-231 human breast cancer cell line *in vitro*. Its chloroform fraction also inhibited growth of MDA-MB-231 and MCF-7 breast cancer cells by inducing ROS abrogated apoptosis[13,14]. Similarly, ethanolic extract of Guduchi shows cytotoxic effect in dose dependent manner on MCF-7 and MDA MB 231 breast cell lines by apoptosis and arresting the cell cycle at G2/M phase[15]. Secondary metabolites including anthraquinones, terpenoids, saponins, rutin and quercetin are pharmacologically active compounds identified which are responsible for breast cancer combating effect[14,16]. Compound formulation prepared from Guduchi significantly inhibit tumor progression of DMBA induced breast tumor in Sprague-Dawley rats[17].

Atasi- Linum usitatissimum

A research group induces tumor in mice by injecting human breast cancer cells. While cancer propagates, mice were given with basal diet for 8 weeks after cancer cells' injection. One group was fed with 10% flax seeds while another group continued basal diet. Rate of cancer growth was reduced by 45% by flax seeds. Mammary glands morphogenesis in mice is improved by flax seeds. The examination of female mice fed with 10% flax seeds diet showed improved number of terminal end buds and terminal ducts in their mammary glands. They have extra epithelial cell division. All females show increased differentiation. Relatively low incidence of breast tumor has been shown by female after injection of carcinogens in mammary glands. As a result, increased differentiation in mammary tissues of mouse, prevention of malignancies, reduction of tumor development are possible by flax seeds in female offspring, making less vulnerable to carcinogens[18–20].

Kalajaji- Nigella sativa

Thymoquinone extracted from *N. sativa* was treated to MDA-MB-468, T-47D and MCF-7 cells, and its anticancer efficacy was assessed. It upregulated the expression of p53 gene which is tumor suppressor. Procaspase-3 and Bax are translated upregulated, which promotes G(1) phase arrest. Additionally, downregulation of the gene expression of survivin, Bcl-2, and Bcl-xL together with inhibition of cyclin D1 and cyclin E, PARP cleavage. It shows anti-metastatic effect on triple-negative MDA-MB-231 breast cancer cells by downregulating the expression of CXCR4 in a dose dependent manner[21–23]. Higher concentration of *N. sativa Linn.* seed oil (50 g/mL) altered the morphology of breast cancer cells and reduced their viability and proliferation[24].

Lashuna- Allium sativum

It shows significant antiproliferative and antimotility effect against MCF-7 and MDA-MB-231cell lines by activating caspase 9 indicating cytotoxicity by apoptosis[25]. Another study reported that fresh garlic extract ceased the proliferation and changed morphology of MCF 7 breast cancer cell line due to phenotypical changes occurred[26]. Diallyl sulfide extracted from Garlic inhibited growth of MDA-MB-468 cancer cell line significantly. When it is tested *in vivo* in Ehrlich Ascites Carcinoma (EAC) tumor induced Swiss albino mice it effectively reduced tumor growth. The probable action of cell death is due to apoptosis by enhancing the expression of caspase-3 and hindering p53's oxidative destruction as it is a tumor suppressor protein[27]. Garlic acts as preventive food to fight against primary breast carcinoma proved by a case control study on 345 patients. Thus, intake of garlic was linked to a lower incidence of breast cancer[28,29].

Ashwagandha- Withania somnifera

Ashwagandha leaves aqueous extract was shown to have anticancer properties, which were examined *in vitro* and *in vivo* tests utilizing the MCF-7 cell line in a dose dependent manner[30]. Withaferin A decreases mouse tumor size and area which support its use in the treatment of pulmonary metastasis of breast tumors after injection in a mouse model[31]. Ashwagandha extract reduced the growth of xenografted tumors by 60% compared to the untreated control, preventing the proliferation of xenografted MDA-MB-231 cells in nude mice after 8 weeks of therapy. Additionally, *in vitro* MDA-MB-231 cell growth was suppressed by its root extract. Using the MDA-MB-231 cell line and 4T1 cell line, respectively, human xenograft and mouse mammary carcinoma models were employed to demonstrate dose-dependent delay of tumor development and the occurrence of metastatic lung nodules. Standard *W. somnifera* root

extract and Withaferin A produced a minimally harmful inhibition[32,33]. When cells were treated with withania, a concentration-dependent decline in cell viability was seen. Administration of withania slowed the development of tumors in MDA-MB-231 xenografts made from female nude athymic mice. Additionally, the mechanism of FOXO3a and Bim in Withania-mediated apoptosis in xenografts was examined. There is evidence that FOXO3a and Bim are involved in the control of Withania-mediated apoptosis from the tumors of mice treated with Withania, which showed decreased cell proliferation and enhanced apoptosis[34]. *W. somnifera* with chemotherapy and chemotherapy alone (control) were evaluated for effectiveness in a prospective, non-randomized clinical study of female breast cancer patients. The patients received a vegetarian capsule containing 2 g of withania root extract orally during their chemotherapy treatment. This study concluded that the addition of *W. somnifera* to chemotherapy might reduce fatigue and enhance quality of life in breast cancer patients[35].

Kalamegha- Andrographis paniculata

Breast cancer cell lines A431 and MDA-MB231 are highly responsive to andrographolide (ANDR), a pharmaceutical component derived from *A. paniculata*. It has the potential to be developed as a therapeutic target in breast malignancies since it inhibits MMP-7 production through TIMP1 up-regulation, inhibits breast cancer invasion, and operates via the NFkB signal transduction pathway without triggering pyroptosis[36] . In another study the growth of several cancer cell lines, including MDA-MB-231, BT-549, MCF-7, MDA-MB-361, and T47D, was markedly inhibited by andrographolide. When studied *in vivo* it decreased tumor angiogenesis and proliferation in human breast cancer xenograft model. It could suppress the proliferation and angiogenesis of breast cancer cells through disrupting the p300/COX-2 and VEGF signaling pathway[37].

Also, by lowering THOC1-promoted cancer stem cell features, andrographolide inhibits the malignancy of triple-negative breast cancer[38]. It inhibits each stage of cancer development through lipid dependent cancer pathways. It is believed that to maintain the growth of cancer, cancer cells can endure the undesired metabolic effects of plasma lipid levels. As a result of changes in cholesterol, lipid raft amount and structure may directly affect signal transmission, which results in oncogene activation[39].

Trapusha- Podophyllum hexandrum

Methanolic extract of the plant shows potential anticancer activity against MCF-7 cancer cell line[40]. By changing the Chk-2 signaling pathway in MCF-7 breast cancer cells, the 4'-Demethyl-Deoxypodophyllotoxin Glucoside from *P. hexandrum* shows potential anticancer properties[41]. Podophyllotoxin present in the root of *P. hexandrum* was able to inhibit MCF-7 human breast cancer cell line about 50% at a dose of 1 nM[42]. After 48 hours of treatment, podophyllotoxin-polyacrylic acid conjugate micelles exhibit significantly (p 0.01) increased *in vitro* cytotoxicity against both sensitive and resistant human breast cancer cells (MCF-7 and MDA MB-231)[43].

Shigru- Moringa ptyrygosperma

By reducing cell motility and colony formation in breast cancer cell lines, moringa extracts serve as an anti-cancer agent. Upon treatment with the extracts of Moringa leaves and bark, low cell survival, high apoptosis, and G2/M enrichment were also found[44]. There was a clear cell growth inhibition of human breast cancer cell lines MCF-7, MDA-MB-468, and MDA-MB-231 in a dose and specific duration for the inhibition of cells after different doses of plant leaf extract were taken and introduced into cancer cell lines[45]. Rutin, Vicenin-2, and Quercetin-3-O-glucoside,phytochemicals from Moringa shows highest binding energy to BRCA1 gene, the inherits of which are diagnosed with Breast cancer[46].

Bhumyalaki- Phyllanthus niruri

Breast cancer induced in mice using the carcinogen DMBA, *P. niruri* exhibits anti-angiogenic activity and suppress inflammatory pathways[47]. Four species from Phyllanthus genus were known to cause apoptosis and hinder the metastasis of breast carcinoma cells (MCF-7). By inhibiting the extracellular signal-related kinase (ERK) pathway and decreasing the production of matrix metalloproteins 2 and 9, Phyllanthus species reduced the metastasis and proliferation of breast cancer. The four Phyllanthus species' most probable targets for preventing MCF-7 metastasis are the ERK and hypoxia pathways[48]. *P. niruri* in combination with *Curcuma longa* exhibited potential anticancer property. In silico analysis of Curcumin and Phyllanthin causes marked metastatic inhibition of Breast cancer through various pathways[49].

Pippali- Piper longum

Piperine, a chief alkaloid component present in *P. longum* has showed potent anticancer effect dose dependently against 4T1 tumor growth and remarkably inhibit lung metastasis of 4T1 mammary carcinoma *in vitro* and *in vivo* model[50]. Also, it acts in breast cancer through various mechanisms such as diminished cell cycle, increased cell apoptosis, MDR inhibition, signaling pathway inhibition, and decreased metastatic promoters[51].

DISCUSSION

This review provides evidence of data suggesting that, these nine herbs possess chemo-preventative and chemo-

therapeutic effects on breast cancer. The results demonstrated both *in vitro* and *in vivo* anti-cancer effects of these herbs, accompanied by their respective outcomes. Mode of action in breast cancer includes cell apoptosis & arresting cell cycle, inhibition of cell proliferation, downregulation of NF-kB expression & CXCR4, blocking endogenous estrogen, upregulation of p53 gene expression, FOXO3a and Bim mediated cell apoptosis, inhibition of MMP-7 production, binding to BRCA1 gene, MDR inhibition and decreasing metastatic promoters. The active constituents of these herbs acting on different pathways of breast cancer is p53 dependent pathway, Procaspase-3 and Bax, Caspase 9, NF-kB signal transduction pathway, p300/COX-2 & VEGF signaling pathway, matrix signal related kinase (ERK) and hypoxia pathway. Majority of studies were conducted using MCF-7, T-47D and MDA MB 231 cell lines as these are most common luminal A and triple negative breast cancer types. The active constituents present in certain herbs may synergistically complement standard chemotherapy drugs, augmenting their anti-cancer properties. With combination of herbal drug, the toxicity of the chemotherapy medications decreased, while their efficacy increased. It is necessary to do additional investigations with substantial clinical trials to determine the risk-benefit ratio of combining the active compound's nano formulation like curcumin with chemotherapy medicines. Each herb has several active ingredients that frequently work in concert to produce therapeutic benefits, reduce the likelihood of side effects, and eliminate the need for supplementary medication to treat cancer cachexia.

CONCLUSION

To address both cancer treatment and prevention, it's essential to utilize Ayurvedic herbs that target multiple pathways simultaneously. It could prove helpful in both lessening the side effects of chemotherapy drugs and improving their effectiveness as supportive treatment. These herbal medicines may be used as a supplemental therapy to help patients to feel better and endure cancer treatment better. In most cases, an alternative therapy is used in place of conventional care. Now is the time to increase awareness, support the use of Ayurvedic cancer treatments, and advocate an integrated approach to tumor care and treatment.

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