HUMAN BREAST CANCER CELL LINE STUDIES IN HOMEOPATHIC SYSTEM: A CRITICAL REVIEW

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ABSTRACT

Breast carcinoma is found to be one of the most prevalent carcinoma accounting for around 11.6% of all carcinomas globally. The first human cell line was established in a Baltimore laboratory over 50 years ago by George Gey which developed into an important experimental tool in cancer research. The first breast cancer cell line to be established was BT-20 in 1958. There are now a reasonable number of breast cancer cell lines available to reflect the molecular sub-groups. Selecting the right cell line will be a powerful experimental tool information derived from these has translated into clinical benefit. Similarly, studies are being conducted with homoeopathic medicines to evaluate the cytotoxic and apoptosis-inducing activity by cell culture methods. In Indian population, it is the leading carcinoma in women. Due to alarming raise in its incidence the need for opting a proper treatment methodology is mandatory in-order to diminish the morbidity and mortality rate. As there are different types of breast carcinoma the pathophysiology of each type should be studied in order to plan a correct treatment strategy. Homeopathy offers a holistic approach in treating the patients it can have a positive impact on the sufferers. But the existing crisis is lack of an evidence-based explanation regarding the action of our drugs in certain spheres (genetic, cellular and hormonal). The objective of this study was to review the response of homeopathic preparations in specific cancer cell lines. The momentous outcomes impose further in vitro and in vivo studies to evaluate the applicability of Homoeopathic medicines in the treatment of Breast cancer.

KEYWORDS: Breast Cancer, Carcinoma, Cell line, Cell culture, Homoeopathy.

INTRODUCTION

Breast carcinoma is a type of cancer that occurs in the breast tissue where the cells undergo increased cell proliferation/uncontrollable cell growth. Mostly the breast cancers arise from the lining epithelial cells of ducts (85%) or from the lobules (15%) in the glandular tissue of breast.
In most of the cases the malady will be “in situ” which remains asymptomatic with minimal metastasis.\textsuperscript{[2,3]}

Recently researches are being done to access the efficacy of Homoeopathic preparations to evaluate its anti-cancerous activities \textit{in vitro} and \textit{in vivo}. Cell line studies are also being undertaken to access the anti-cancerous activity. Cell line studies are used as an alternative to study the biological activities. Cell lines are developed from cell culture on the basis of proliferation under appropriate conditions further developed to cell strain. Cell culture provides models for studying drug effect on cells, carcinogenesis for drug screening and development. The consistency and reproducibility are key factors for using cell culture techniques in drug studies. Selecting appropriate cell lines, environment, studying cell morphology and culturing methods have significant role in cell culture experiments.

**Epidemiology**

According to GILOBOCAN (Global Cancer Observatory) 2020 conducted by International Agency for Research and WHO on Cancer, the incidence and mortality caused by breast cancer accounts for 2.3 million new cases (11.6%) where the mortality rate of female breast cancer estimates to be 68500 (6.9%) of all cancers.\textsuperscript{[3,4]} At the end of 2020, about 7.8 million females alive diagnosed with breast cancer in past 5 years, which labels it as the world’s most prevalent cancer.\textsuperscript{[3]} A study conducted by National Breast Cancer Foundation, United States 2020, reveals 1 in 8 women may develop breast cancer in their lifetime among them the incidence of invasive breast cancer is found to be 276,480 new cases as well as non-invasive (\textit{in situ}) accounts for about 48,530 new cases. In which about 64% are diagnosed with localized ‘in-situ’ stage which guaranteed a survival rate of 5 years, 27% in regional stage, and 6% have distant (metastatic) disease. And they also traced the incidence of cancer in men and concluded that Men are more likely to be diagnosed with advanced regional or distant state breast cancer than women (51% versus 36%), because of delayed detection and lack of proper awareness.\textsuperscript{[5]} Another study conducted in Poland reveals 80% of these cancers are diagnosed in women aged fifty and above.\textsuperscript{[6]} In India breast cancer is found to be the number one cancer among females with age adjusted rate as 25.8 per 100,000 women and mortality 12.7 per 100,000 women.\textsuperscript{[7]}

**Cell line studies with dynamized medicines**

Studies concentrating on the genes targeted by homoeopathic medicines, studies exploring the mechanism of homoeopathic medicines at the cellular level for developing accurate, appropriate medicine selection. Evidences from such experimental as well as clinical trials strongly suggest the effectiveness of Homoeopathic medicine in cancer treatment.

In this cell line studies are effective method of pre-clinical methods for preliminary assessment of potentiality of Homoeopathic medicines in cancer treatment. Observations from cell line studies in with Homoeopathic medicines shows cytotoxic and apoptosis inducing properties.\textsuperscript{[74]}

**Need for the study**

As the incidence of breast cancer is ever increasing it is necessary that best evidence based treatment should be provided in the early phase of the disease. Homeopathy have an array of
indicated medicines but unfortunately it lacks studies revealing the specified action of these medicines. There is an enlarging need to get focused on such studies for tracing out the best, indicated, scientific based action potential of Homoeopathic drugs in different breast cancers which enable us in providing the best indicated care. Cell line studies will a best alternative option to study the therapeutic properties of Homoeopathic medicines.

Scope of Homeopathy

As Homeopathy adopts a holistic approach in patients, the root cause for any derangements can be traced out right from the genetic tendencies to the current predisposing factors. This is found to be having utmost importance in planning the treatment of patients. As Homeopathy can ensure such modus operandi in a safe, gentle and complete way without further deterioration of health and relapse of the disease this system can be can be trusted in dealing with such cases.

Types of Breast cancer and Risk factors\cite{8-12}

Mainly there are 4 types of breast cancers. The detailed four types of breast cancer and their risk factors were tabulated in Table 1 and Table 2.

Table 1: Types of breast carcinoma

<table>
<thead>
<tr>
<th>Types</th>
<th>Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive (Most common type)</td>
<td>i) Invasive ductal carcinoma</td>
</tr>
<tr>
<td></td>
<td>ii) Invasive lobular carcinoma</td>
</tr>
<tr>
<td>Non-Invasive</td>
<td>i) Ductal Carcinoma in Situ (DCIS)</td>
</tr>
<tr>
<td></td>
<td>ii) Lobular Carcinoma in Situ (LCIS)</td>
</tr>
<tr>
<td>Less common types</td>
<td>i) Paget Disease of the Nipple</td>
</tr>
<tr>
<td></td>
<td>ii) Cystosarcomaphyllodes (in connective tissues)</td>
</tr>
<tr>
<td></td>
<td>iii) Angiosarcoma.</td>
</tr>
<tr>
<td>Rare types</td>
<td>i) Triple-Negative type of Breast Cancer (10-20%): This cancer lacks estrogen receptors and progesterone receptors and cancer-fueling HER2 proteins on its surface which is difficult to treat and have an alarming growth rate.</td>
</tr>
<tr>
<td></td>
<td>ii) Inflammatory Breast Cancer (1-5%): Blocks the lymph nodes near breast cells.</td>
</tr>
</tbody>
</table>

Table 2: Risk factors for breast carcinoma

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hereditary (10%) BRCA1 and BRCA2 and mutation in TP53 gene</td>
</tr>
</tbody>
</table>
2 Lifestyle factors (90%) ▪ Obesity ▪ Alcohol consumption ▪ Smoking ▪ Unhealthy diet ▪ Exposure to chemicals and radiation ▪ Exposure to feminine hormones: (Oral contraceptives, estrogen progesterone therapy)

3 Menstrual and gestational history ▪ Early menarche ▪ Late menopause ▪ Late pregnancy (Giving birth for the first time after 30 years of age.)

Breast cancer cell lines and its importance

Breast cancer cell line is a cell culture developed from a single cancer cell which consists of cells having uniform genetic make-up, mostly used as a model to understand pathophysiological development of the cancer and to estimate the new treatment methodologies. [13,14] About 84 breast cancer cell lines were identified so far. Their molecular features, genetic and epigenetic properties (Genes and mutations) were studied and categorized on the basis of presence or absence of hormone receptors (Estrogen/progesterone) or other factors (Cathepsin D and HER2). [15,16] Hormones play a major role in development and growth of hormone dependent tumour cells. Estrogen receptor positive breast cancers can be effectively treated with endocrine therapies and have a better prognosis whereas Estrogen receptor negative ones are aggressive with poor prognosis due to over expression on Cathepsin – D. [17] Common breast cell cancer lines preferred for conducting in vivo and in vitro studies were tabulated in Table 3. [15,18]

Table 3: Properties of common breast cell cancer lines preferred for conducting in vivo and in vitro studies

<table>
<thead>
<tr>
<th>Cell lines</th>
<th>Estrogen receptor</th>
<th>Progesterone receptor</th>
<th>HER2</th>
<th>BRCA1 Mutation</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCF7</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>WT</td>
<td>LA</td>
</tr>
<tr>
<td>T47D</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>WT</td>
<td>LA</td>
</tr>
</tbody>
</table>
Subtypes: LA-Luminal A; TNA-Triple Negative A, TNB - Triple Negative B; H-HER2 presenting; BRCA1 Mutation: WT-Wild type., Tumor: IDC-Intraductal carcinoma, AC-Adenocarcinoma

Related studies

Studies conducted in vivo using extracts [19] and lower concentrations [20] of Viscum album in breast cancer cell lines (MCF-7[21],[20], PMC-42[20],MB-MDA435[22] and mesenchymal stem cells in mammary adipose tissue[20]) reveals positive immunomodulation along with tumor growth inhibition and reduction of metastases[23], there is a significant increase in concentration of IL-6 and IFN-γ [24] and co-administration with conventional treatments had improving effects on fatigue, insomnia and other physical functions[19]. In a clinical based study, out of 280 cases 67% were found to have good effect by Viscum album and 14% were cured.[25] In another study 94% were influenced by the Viscum album[25,26].

In studies with Q and 1C potency of Hydrasis canadensis on MCF-7[27,28,29,30], MDA-MB 468 (marginal effect[9], MDA-MB-231[28,31,32] and T47D[30,33] cell line suggests the following actions as(-) arrest in the G0/G1 phase of cell division[27,28], high inhibition on metastasis[28],TNF-α-induced MMP-9 expression, decreased cell invasion through the suppression of AP-1 DNA binding activity in MDA-MB-231 cells[32], inhibition of cell proliferation, induction of apoptosis and alteration of cell cycle distribution of breast cancer cells[30] and by suppression of both COX-2 (Inflammatory enzyme) and surviving (anti-apoptotic protein levels)[33,33].

Studies on Phytolacca with Q[35],12C [36], 30 C[37],200 C[35,36] potencies on MCF-7[35,38], MDA-MB-231[35,38] cell line suggest its capability in producing cytotoxicity which decreases cell proliferation[35,39] and promotes apoptosis and cell cycle delay/arrest[38,40]. Clinical trials shows a post-treatment response in 23 cases (35.93%) revealing disappearance of lump. Partial improvement was noticed in 22 cases (34.37%) with significant reduction in mean size (p < 0.001). Another study reveals Phytolacca decandra (200C) caused regression in 19% tumour cases while 21% of the tumours were stable or improved with treatment when patients were followed up to 10 years[42].

Conium maculatum with its 30X,200 C,1M, 50M[27] potencies on MCF 7[26], MDA-MB-231[25] cell lines confess its Antioxidant potential[28,29], its ability in inhibition of substage G of cell cycle and AKT and NF-KB leading towards apoptosis pathway.[29] Some studies shows its extract
can be used as a good external application. Conium has been used extensively for malignant affections of glands, from initiation to stony hardness such as scirrhus.

In vitro studies on Termination chebula shows its anticancerous effects on MDA-MB-231, MCF-7 cancer cell lines by its Q,3X, 6C & 30C potencies. ZOTC (Zingiber officinale and Terminalia chebula) combination shows potential action on controlling breast cancer proliferation by decreasing oxidative stress in mammary tissues induced by DMBA, protective against damages of the mammary tissue, altered serum lipids and cytokines.

Asteria rubens in its 6C and 30C potency are found to have a remarkable action on the ER/PR/Her2 receptor positive (MCF-7) cell line, they have no effect on the ER/PR/Her2 receptor negative (MDA-MB-231) breast cells as they are devoid of any estrogen, progesterone receptors and HER2 factor. Cimicifuga racemosa extracts are found to have no proliferative activity, but terminates the estrogen receptor positive MCF-7 as well as estrogen receptor negative MDA-MB231 cells by activation of caspases and induction of apoptosis.

Various studies on Echnacea angustifolia shows its massive effect on MDA-MB-231 which induced cell cycle arrest in the G1 phase and caspase-mediated apoptosis. The combination of extract and paclitaxel showed a synergistic effect on cancer cell lines in vitro. It Promotes the lymphocyte’s activity that increases the phagocytosis by macrophages and the action of natural killer cells and prompting interferon assembly, and it has also lessened the harmful consequence of radiotherapy and chemotherapy, prolongs the survival time with progressive stage of cancer and promotes increased cytokine production and builds immunity.

Thuja in its Q and high dilutions shows effective action on DMBA-induced mammary carcinoma. It exhibits reduction of tumor weight, tumor volume and possess significant potential for phyto preventive bio-efficacy against DMBA-induced mammary carcinogenesis.

Carcinocin is a nosode which mainly acts on MCF-7, HBL-100 and p53-mutated-MDA-MB-231 which primes T cells to induced apoptosis by triggering mitochondrial death cascade in cancer cells. Tamarindus indica have Cytotoxicity against MCF-7 cell lines. and have tumor inhibitory activities.

The complete summary of the existing breast cancer cell studies was corelated and tabulated based on source of medicine, extracts used, type of cell lines, types of cancer and the findings on the cells were tabulated in Table 4.
Table 4: Summary table on review of the existing studies

<table>
<thead>
<tr>
<th>Source of Medicine</th>
<th>Extracts/Q/Dilutions</th>
<th>Cell/Cancer Cell Line</th>
<th>Type of carcinoma</th>
<th>Findings/Action on the cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscum album</td>
<td>3X&lt;sup&gt;21&lt;/sup&gt;</td>
<td>MCF-7&lt;sup&gt;20,21&lt;/sup&gt;,</td>
<td>Adenocarcinoma&lt;sup&gt;20,21&lt;/sup&gt;</td>
<td>Co-administered with conventional treatments had improving effects on the CA accompanying symptoms such as fatigue, insomnia, and physical functioning&lt;sup&gt;19&lt;/sup&gt;</td>
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<td></td>
<td>Lower concentration&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Mesenchymal stem cells in mammary adipose tissue&lt;sup&gt;20&lt;/sup&gt;</td>
<td>I or II primary breast cancers&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Immunomodulation combined with tumor growth inhibition and reduction of metastases&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Viscum album extracts&lt;sup&gt;19&lt;/sup&gt;</td>
<td>MB-MDA435&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Intra Ductal Carcinoma</td>
<td>Significant increases in the concentration of IL-6 and IFN-γ&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hydrasis canadensis</td>
<td>Q, 1C&lt;sup&gt;27&lt;/sup&gt;</td>
<td>MCF-7&lt;sup&gt;27,28,29,30&lt;/sup&gt;, MDA-MB 468&lt;sup&gt;27&lt;/sup&gt; MDA-MB-231&lt;sup&gt;28,31,32&lt;/sup&gt; T47D&lt;sup&gt;30,33&lt;/sup&gt;</td>
<td>Adenocarcinoma&lt;sup&gt;15&lt;/sup&gt; Luminal breast cancer&lt;sup&gt;28&lt;/sup&gt; Paget’s disease&lt;sup&gt;34&lt;/sup&gt; Ductal breast epithelial tumor cell line&lt;sup&gt;15, 33&lt;/sup&gt;</td>
<td>Arrest G0/G1 phase of cell division&lt;sup&gt;27,28&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High inhibition on metastasis&lt;sup&gt;28&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>TNF-α-induced MMP-9 expression and cell invasion are decreased through the suppression of AP-1 DNA binding activity in MDA-MB-231 cells&lt;sup&gt;32&lt;/sup&gt; Regression of cancer&lt;sup&gt;25&lt;/sup&gt;.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inhibits cell proliferation, induced apoptosis and altered cell cycle distribution of breast cancer cells&lt;sup&gt;30&lt;/sup&gt; Induces apoptosis by suppressing both COX-2 (Inflammatory enzyme) and anti-apoptotic protein levels&lt;sup&gt;33&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phytolacca</td>
<td>Q&lt;sup&gt;35&lt;/sup&gt;, 12C&lt;sup&gt;36&lt;/sup&gt;, 30 C&lt;sup&gt;37&lt;/sup&gt;, 200</td>
<td>MCF-7&lt;sup&gt;35,38&lt;/sup&gt;,</td>
<td>Fibroadenoma&lt;sup&gt;36,41&lt;/sup&gt; Adenocarcinoma&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Produce cytotoxicity and decrease cell</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Concentration</th>
<th>Cell Lines</th>
<th>Tumor Type</th>
<th>Activity Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conium maculatum</td>
<td>30X, 200 C, 1M 50M</td>
<td>MCF 7&lt;sup&gt;44&lt;/sup&gt;, MDA-MB-231&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Fibroadenoma&lt;sup&gt;41,49&lt;/sup&gt; Malignant metastatic adenocarcinoma&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Promotes apoptosis and cell cycle delay/arrest&lt;sup&gt;38&lt;/sup&gt;. Inhibit substage G of cell cycle and AKT and NF-KB leading towards antitumorous activity against breast cancer&lt;sup&gt;47&lt;/sup&gt;. Extract can be used as external application&lt;sup&gt;48&lt;/sup&gt;. Malignant affections of glands, from initiation to stony hardness such as scirrhous&lt;sup&gt;49&lt;/sup&gt;.</td>
</tr>
<tr>
<td>Terminalia chebula</td>
<td>Q, 3X, 6C &amp; 30C</td>
<td>MDA-MB-231&lt;sup&gt;50&lt;/sup&gt;, MCF-7&lt;sup&gt;50,51,52&lt;/sup&gt;</td>
<td>Adenocarcinoma&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Anticancer activity&lt;sup&gt;50&lt;/sup&gt; ZOTC (Zingiber officinale and Terminalia chebula) combination act as a potent medication for controlling breast cancer proliferation by decreasing oxidative stress induced by DMBA(7,12-Dimethylbenzanthracene), protective against damages of the mammary tissue, altered serum lipids and cytokines&lt;sup&gt;53&lt;/sup&gt;.</td>
</tr>
<tr>
<td>Asteria rubens</td>
<td>3C&lt;sup&gt;65,66&lt;/sup&gt;, 6C &amp; 30C</td>
<td>MCF-7, MDA-MB-231&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Adenocarcinoma&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Anti-cancer activity against ER/PR/Her2 receptor positive breast cancer cells&lt;sup&gt;54&lt;/sup&gt;.</td>
</tr>
<tr>
<td>Actearecemosa</td>
<td>Extracts&lt;sup&gt;55&lt;/sup&gt;</td>
<td>MCF-7, MDA-MB231</td>
<td>Adenocarcinoma&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Terminates the estrogen receptor positive MCF-7 as well as estrogen receptor negative MDA-MB231 cells by activation of caspases and induction of apoptosis&lt;sup&gt;55&lt;/sup&gt;.</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Plant extract</td>
<td>MDA-MB-</td>
<td>Adenocarcinoma&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Cytotoxic activity on</td>
</tr>
</tbody>
</table>
| **angustifolia** | $^{56}$ | $^{231}$ | MDA-MB-231 cells, induced cell cycle arrest in the G1 phase and caspase-mediated apoptosis, the combination of extract and paclitaxel showed a synergistic effect on cancer cell lines *in vitro.*

Promote the lymphocyte’s activity that increases the phagocytosis by macrophages and the action of natural killer cells and prompting interferon assembly, and it has also lessened the harmful consequence of radiotherapy and chemotherapy.

Prolongs the survival time with progressive stage of cancer.

Promotes increased cytokine production and builds immunity.

Thuja occidentalis Q High dilution without harmful action on healthy cells. $^{61}$ $^{30C}$

MDA-MB-435 $^{59}$, MCF-7 $^{60}$ DMBA-induced mammary carcinogenesis $^{58}$ Adenocarcinoma $^{15}$ Exhibits reduction of tumor weight, tumor volume.

It is inferred that the plant Thuja occidentalis (leaves) possess significant potential for phytopreventive bioefficacy against DMBA-induced mammary carcinogenesis. $^{58}$

MCF-7 cells confirmed the transactivational role of p53 in thuja-induced apoptosis $^{60}$

Carcinocin $^{30C}$ $^{63}$ $^{200C}$

MCF-7 $^{62,63,64}$ Adenocarcinoma $^{15,62}$ Cell cycle delay/arrest and
| **Taraxacum officinale** | Extract\(^{65,66}\) | MCF-7/AZ\(^{65,66}\) MDA-MB-231\(^{67}\) MDA-MB-468\(^{67}\) | Adenocarcinoma \(^{15}\) | Decreases growth of cell lines\(^{65}\) A proliferative activity\(^{66,67}\) Prevent migration and invasion of TNBC cells through suppressing IL-10/STAT3/PD-L1 immunosuppressive signaling pathway. Promotes the polarization of macrophages from M2 to M1 phenotype. |
|-----------------------------|---------------------|----------------------------------|-----------------|-----------------|---------------------------------|
| **Calcarea carbonica**      | 1C, 6C, 12C, 30C and 200C\(^{69}\) | MCF-7 HBL-100 p53-mutated-MDA-MB-231\(^{68}\) | Ductal cancers Infiltrating cancers, including metastatic cancers\(^{69}\) | Primed T cells to induced apoptosis by triggering mitochondrial death cascade in cancer cells.\(^{68}\) |
Tamarindus indica | MCF-7<sup>70,71,72</sup> | Adenocarcinoma<sup>15</sup> | Cytotoxicity against MCF-7 cell lines,<sup>70,71</sup> Tumor inhibitory activities.<sup>72</sup>

**CONCLUSION**

This review provides evidences on the cytotoxic and anti-proliferative activity of potentized Homoeopathic medicines in cell lines. These significant results necessitate further *in vitro* and *in vivo* studies to evaluate the applicability of Homoeopathic medicines in the treatment of Breast cancer.

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