International Journal of Drug Development and Research

Mangla and Kohli, Int J Drug Dev & Res 2018, 10:1

Research Article

Combination of Natural Agent with Synthetic Drug for the Breast Cancer Therapy

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Received January 31, 2018; **Accepted** February 08, 2018; **Published** February 15, 2018

Abstract

Introduction: Breast cancer is the major cause of death worldwide. Urgently treatment is needed. A number of undesired side effects sometimes occur during the conventional therapy of cancer. Bioactive compounds derived from plant are the most popular alternative medicine which may reduce adverse effects. Various herbal compounds have been identified and showed very promising anti-cancer properties. **Methodology:** The review was systematically conducted by searching the databases of MEDLINE, PubMed, Web of Knowledge, Google Scholar and Science Direct for original research articles and books using relevant search terms. **Results:** The potential of combining phytomedicine or natural products with synthetic drugs or introducing these into conventional treatment regimens are not yet systematically explored. Combinatorial strategy may hold promise in development of therapies and chemoprevention strategies against ER-positive breast tumors. **Discussion:** The screening for synergetic effects of such combinations is technically demanding and complex, also in the context of drug/herb interactions, but likely to substantially advance pharmacotherapy and future medicine. **Conclusion:** It has been concluded that combined effect may improve the treatment effectiveness in combating proliferation of cancer cells, enhancing therapeutic efficacy, as well as abrogating drug resistance.

Keywords: Breast cancer; Synergic effect; Herbal agent; Synthetic drugs; Bioactive compounds

Introduction

Cancer is dangerous and deadly disease. Early stage of detection may help to cure or improve the life span of the patient. Worldwide, the 2nd foremost reason of the death is breast cancer. All over the world, the total of women diagnosed with breast tumor is higher than one million [1]. There are several factors associated with the breast tumor, for example old age, gender, diet, a first child being born at an old age, consumption of alcoholic beverages, body movement, family history, intake of progesterone or estrogen, lifestyle and endocrine aspects as well including both exogenous and endogenous. There are some other important factors that lead to breast cancer, like radiation therapy of the breast, previous benign and mammographic density [2]. Male are also have some breast cells and tissue that have the possibility to form breast cancer. Figure 1 demonstrated that how the cancer developed from heathy cells [3].

Stages in Breast Cancer

Stage 0

Describe as non-invasive breast cancers. It consists of three types of breast carcinoma [4].

a) Ductal carcinoma in situ (DCIS): this condition is non-invasive and the abnormal cells are found in lining of the breast duct, but the spreading of the abnormal cells is not outside the tissues of breast.

b) Lobular carcinoma in situ (LCIS): in this condition, the abnormal cells are present in the lobules of the breast. This rarely occurs as invasive cancer. Presence of abnormal cells in lobules increases the risk of breast cancer.

c) Paget disease of the nipple: in this condition, abnormal cells are found in nipple only.

Stage I

It is divided into subcategories known as IA and IB.

a) Stage IA: the cancer measures upto 2 cm or small and not found or spread outside the breast; no lymph nodes are involved

b) Stage IB: small clusters are found in the lymph nodes. There is no tumor in the breast; instead, small groups of cancer cells-larger than 0.2 mm but not larger than 2 mm.

There is a tumor in the breast that is no larger than 2 cm, and there are small groups of cancer cells-larger than 0.2 mm but not larger than 2 mm.

Stage II (invasive)

breast cancer**:** It is divided into Stage IIa and Stage IIb.

a) Stage IIa: tumor present, 2 cm< tumor<5 cm^2. Cancer has not spread to the lymph nodes.

b) Stage IIb: 2 cm<tumor<5 cm^2. Cancer spreads to 1 to 3 axillary lymph nodes or to the lymph node near the breastbone.

Stage III (locally advanced)

breast cancer: It is divided into IIIA, IIIB and IIIC.

a) Stage IIIa: tumor >5 cm and cancer spreads to 1 to 3 axillary lymph nodes.

b) Stage IIIb: the tumor spreads to 9 axillary lymph nodes.

c) Stage IIIc: tumor may be of any size causing swelling or ulcer and has spread to chest wall. Cancer has spread to 10 or more axillary lymph nodes.

Stage IV (metastatic) breast cancer

In this stage, the cancer spread to the body, beyond the breast, underarm and internal mammary lymph nodes to other parts of the body near to or distant from the breast (Figure 2).

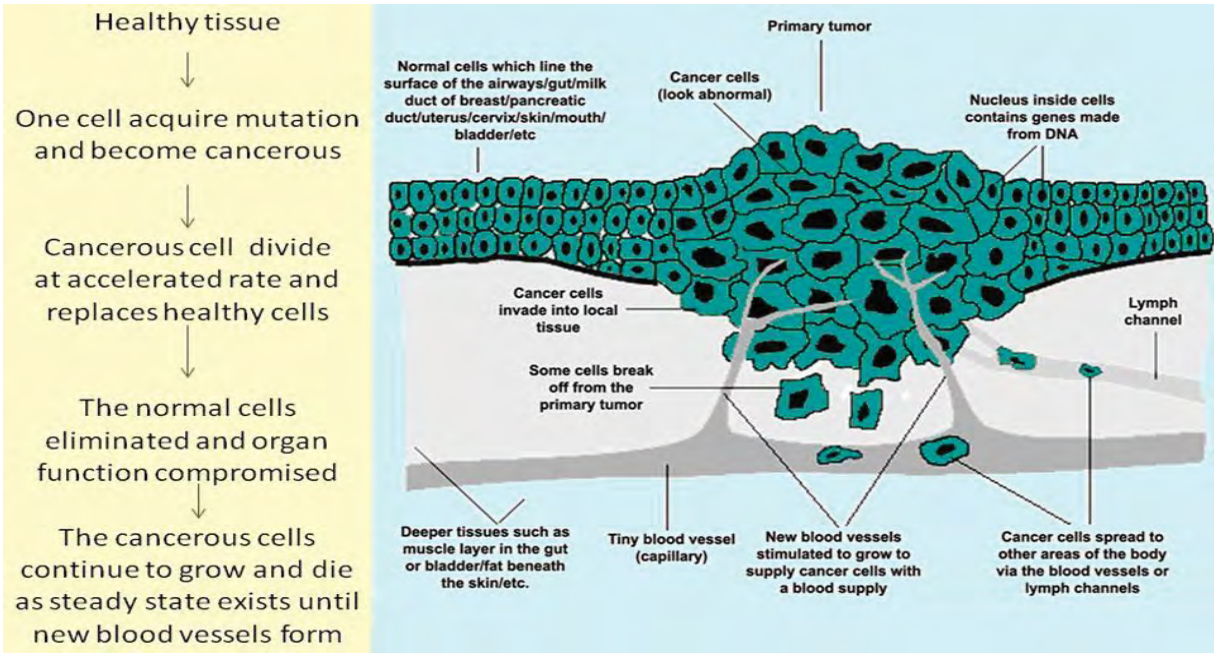

Figure 1: Development of cancer [5].

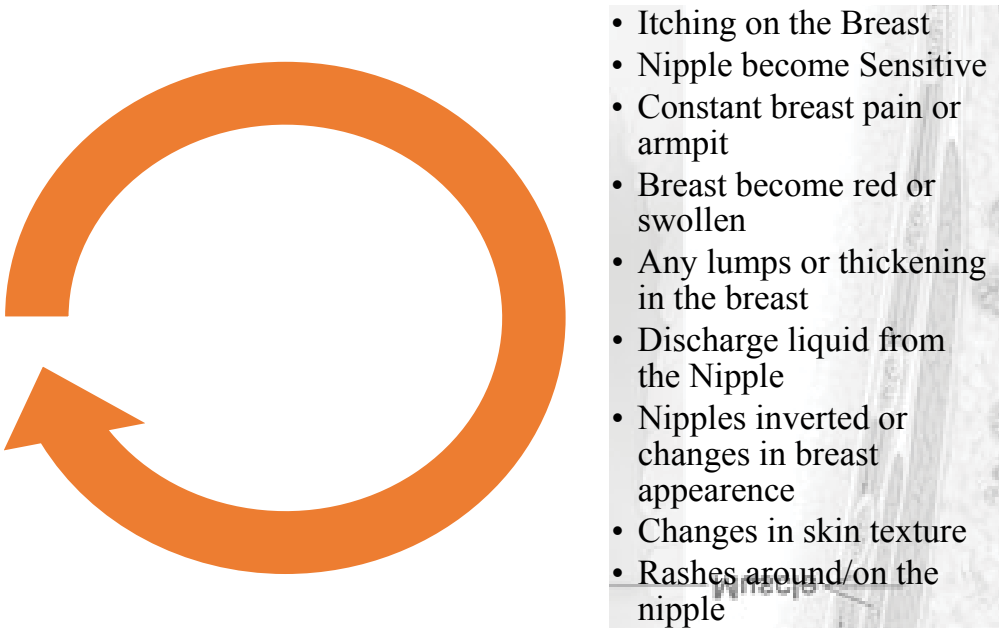

Figure 2: Breast cancer signs.

Methodology

The review was systematically conducted by searching the databases of MEDLINE, PubMed, the Web of Knowledge, Google Scholar, and Science Direct for original research articles and books using relevant search terms or their combinations: "Breast cancer, Anticancer drug, Synergic effect, Herbal agent, Synthetic drugs, Bioactive compounds." Our search was not limited by date but to all relevant publications available in the English language [5].

Treatment of breast cancer

There are many treatment options for breast cancer like surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy, many chemotherapeutic but they have resistance as well as many adverse effects that prevent their usage [6,7]. Combination of these treatments also be a best approach for some cancers like surgery combined with radiation therapy, or chemotherapy, or with all these three treatments. Combination therapy is given according to

the type, size, risk and the stage of the breast cancer. Before surgery, either chemotherapy or radiation therapy is used to shrink a canner cell or tumor, thereby improving the opportunity for complete surgical removal [8].

Combination of synthetic drug and natural drug

Due to the increase risk of breast cancer, combination therapy is urgently needed. Combination therapy is useful for the patients having the last stage of breast cancer which cannot be treated by surgery or radiation therapy. The rational for the combination of plant constituents with each other or with synthetic drugs are multiple. Combination of herbal and synthetic drug improves the bioavailability of one of the drugs through facilitating the transport of the drug, reduces the dose, a change of the biological activity status of a cell the over- coming of bacterial resistance mechanisms by influencing the transport, the permeability or the efflux pump of the bacteria or the overcoming of (multi-)drug resistance mechanisms in cancer or autoimmune diseases [9,10]. Some researchers worked on the combination therapy for the treatment breast cancer as shown in Table 1.

Synthetic drugs for breast cancer

Accoding to FDA, there are several approved drugs which prevent and treat the breast cancer [11]. Evista (Raloxifene Hydrochloride), Abitrexate (Methotrexate), Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation), Ado-Trastuzumab Emtansine, Afinitor (Everolimus), Anastrozole, Aredia (Pamidronate Disodium), Keoxifene, Arimidex (Anastrozole), Aromasin (Exemestane), Capecitabine, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan, Doxorubicin Hydrochloride, Ellence (Epirubicin Hydrochloride), Epirubicin Hydrochloride, Eribulin Mesylate, Everolimus, Exemestane, 5-FU (Fluorouracil Injection), Fareston (Toremifene), Faslodex (Fulvestrant), Femara (Letrozole), Folex (Methotrexate), Fulvestrant, Gemcitabine Hydrochloride, Gemzar, Goserelin Acetate, Halaven (Eribulin Mesylate), Herceptin (Trastuzumab), Ibrance (Palbociclib), Ixabepilone, Ixempra (Ixabepilone), Kadcyla, Kisqali (Ribociclib), Lapatinib Ditosylate, Letrozole, Megestrol Acetate, Methotrexate LPF, Mexate-A, Neosar, Neratinib Maleate, Nerlynx, Nolvadex (Tamoxifen Citrate), Palbociclib, Pamidronate Disodium, Perjeta (Pertuzumab), Pertuzumab, Ribociclib, Taxol, Taxotere (Docetaxel), Thiotepa, Toremifene, Tykerb (Lapatinib Ditosylate), Verzenio (abemaciclib), Velban (Vinblastine Sulfate), Velsar (Vinblastine Sulfate), Vinblastine Sulfate, Xeloda (Capecitabine), Zoladex (Goserelin Acetate).

Dietary supplements and nutraceuticals for breast cancer therapy

A wide variety of naturally occurring compounds or bioactives from plant food have been fight against the breast cancer [12]. Most of the bioactive have been identified in vegetables, fruits, barks, leaves, spices, and grains and exhibit chemo-preventive activity [13-21]. Plant extracts contain bioactive compounds for the breast cancer therapy as shown in Table 2.

Discussion

In the national and international context of research into development of drug delivery systems, the combination therapy is the highest significance. Combination of drug targeting to breast cancer through suitable carrier system have become widely advantageous with less side effects [22-29]. The treatment of cancer is expensive, because the prescribed drugs are costly and have taken over a long period of time. Alone some synthetic drugs have various side effects due to its high dose, low solubility, low bioavailability [30-34]. So, it is important to deliver the synthetic drugs along with the natural supplement to overcome their problems. In this scenario, combination therapy is expected to reduce the dosage regimen such that the cost of the treatment and associated adverse events are reduced considerably. Such a therapy will not only be commercially successful but also helpful to the society. Side effects of conventional drug have been minimized by conjugation with natural drug and they increase the quality of life of patients [35-41].

Natural agent	Synthetic drug	Mechanism	Ref.
Curcumin	Cyclophosphamide, Paclitaxel	MCF-7, MDA-MB-231, MCF-12F in mice mammary tumors	[14]
Curcumin, Baicalein, Resveratrol	Paclitaxel	MCF-7 cells Apoptosis, inhibition of EGFR signalling	[15]
20S-protopanaxadiol	Tamoxifen	MCF-7 Xenograft Model in SCID Mice, Human breast adenocarcinoma cells	[16]
Flavonoids and isoflavonoids	Epirubicin	Human multidrug resistance 1 (mdr1) gene-transfected mouse lymphoma cell line multidrug resistance protein (MRP)-expressing human breast cancer cell line MDA-MB-231	[17]

Table 1: Some reported combination of synthetic and herbal drugs for the breast cancer therapy.

Herbal plant	Mode of action	Main constituent	Ref.
Bitter Leaf (*Vernonia amygdalina)*	Inhibition of proliferation, cell growth, DNA synthesis of breast cancer MCF7	Flavonoids, Terpenoids, saponins.	[18,19]
Brazilian ginseng (*Pfaffia paniculate)*	Antiproliferative activity in MCF-7	Pfaffic acid, pfaffosides A–G and saponins	[21]
Ashwagandha (Indian ginseng)	Antiproliferative activity in MCF-7	C28-steroidal lactone triterpenoids, withanolides	[23-25]
Amoora rohituka	Antiproliferative activity in MCF-7	Flavopiridol	[26,27]
apple peels	Antiproliferative activity in MCF-7	Quercetin and quercetin-3-β-D-glucoside (Q3G)	[28-29]
Water mint (*Mentha aquatic)*	Antiproliferative activity in MCF-7	Flavonoid, phenolic compounds	[30]
Virgin olive oil	Antiproliferative activity in MCF-7	Oleuropein aglycone	[31]
American cranberry (*Vaccinium macrocarpon*)		Flavonoids, proanthocyanidins and anthocyanins,	[32-33]

Pomegranate (*Punica granatum*)	Antiproliferative activity in MDA-ERα7 and MDA-MB-231 cells	Punicic acid	[34]
Barberry	Induction of apoptosis in MCF7	Berberine	[35]
Shikon	Inhibition of estrogen-dependent gene transcription	Shikonin	[36]
Red grapes, pea-nuts and berries	Decrease in viability, glucose consumption and ATP content in MCF7	Resveratrol	[37]
Conifer resins	Chemopreventive efficacy in breast cancer mice model	Triterpenoids	[38]
Soybean	Inhibition of DNA methylation and antiproliferative activity in MCF7 and MDAMB231	Genistein	[39]
Allium	Inhibition of apoptosis in MCF7	S-alkenyl mercaptocysteine	[40]
Tomato	Inhibition of cell proliferation in MCF7	Lycopene	[41]
Red chilli	Notch pathway inhibition of breast cancer stem cell	Capsaicin	[42]
Fenugreek	Inhibition of migration of MDAMB231 by suppressing Vav2 activity	Diosgenin	[43]
Ginger	Apoptotic Effects of in MCF7	6-Gingerol	[44]
Fruits and vegetables	Inhibition of growth of MDAMB231 and P-VEGFR2 expression, inhibited neo-vessel formation in chicken	Ellagic acid	[45]
Anise, camphor, fennel	Suppression of cell survival and antiproliferative activity in MCF7 and MDAMB-31cells.	Anethole	[46]
Green tea	Suppression of proliferation of estrogen-sensitive MCF7	Catechin	[47]
Cloves	Induction of apoptosis in MDAMB231 through E2F1/survivin down-regulation *in vitro* and *in vivo*	Eugenol	[48]
Citrus fruits	Breast tissue disposition in women with early-stage breast	Limonene	[49]
Fruits and vegetables	Apoptosis and induced cell-cycle arrest	Beta-carotene	[50]
Garlic	Detoxification of carcinogens, suppression of DNA adduct formation, inhibition of the production of reactive oxygen species, regulation of cell-cycle arrest and induction of apoptosis	Diallyl disulfide	[22]
Cruciferous vegetables	Oxidative stress induced upregulation of ATF-3 and antiproliferative activity in MCF7 cell lines.	Indole-3-carbinol	[20]

Table 2: Bioactive present in herbal plant for the breast cancer therapy.

Conclusion

Herbal remedies play an important role in the management of breast cancer. Use of herbs as an adjunct to chemotherapy not only exhibits therapeutic efficacy but is also cost effective. Plant extracts contain bioactive compounds that have been used as medicines. Combination of natural and synthetic drugs proved to be an alternate strategy to generate synergistic anticancer specially for breast cancer effects, reduced toxicity associated with individual drug, suppress resistance associated with multiple drugs and enhance the treatment effect. Combination therapy also helps to reduce the dose of the individual drug as well as improves the therapeutic efficacy [42-50].

Acknowledgements and Funding

This work was supported by the DST Inspire Fellowship, New Delhi, India.

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