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Early Stage of Breast Cancer can be Treated by Evidenced Based Herbal Drugs: A Scientific Analysis

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Abstract

Breast cancer is a pandemic non-communicable disease in the world. In early stage, most of the women are neglecting the disease but in advanced stage it is incurable as well as fatal. So, it is needed to increase information, education and communication system to prevent the disease. There is no evidence based treatment available to treat the fatal disease. Some evidence based herbal drugs like *Echinacea purpurea*, *Allium sativum*, *Dacus carrota*, *Camellia sinensis*, *Panax ginseng*, *Cimicifuga recemosa*, *Linum usitatissimum* can be used to treat the disease in early stage and prevent progression of the disease.

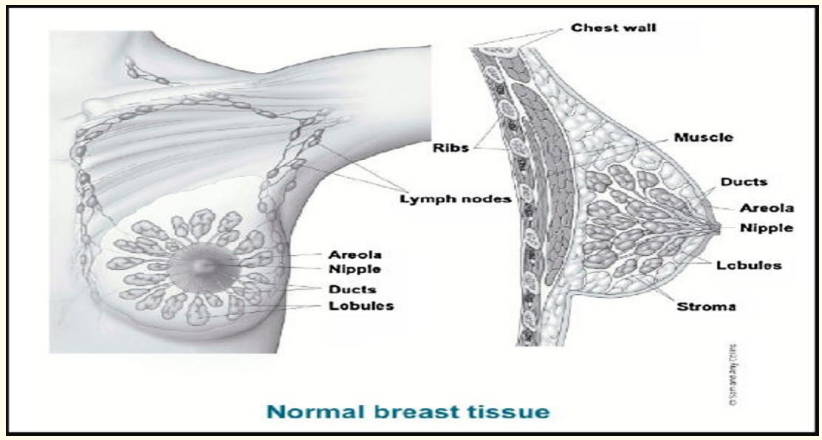
Introduction

Breast cancer is a disease in which abnormal growth of breast cells and form tumors. Initially, cancer cells begin inside the milk ducts and/or the milk-producing lobules of the breast. Each breast consists of 15-20 sections, known as lobes, which are further divided into lobules. Small "ducts" are there to connect the lobes and lobules. Therefore, general form of breast tumor is ductal cancer. Ductal tumor occurs in duct's cells and invades in both breasts as compared to other types of cells. Other classes of breast cancer are invasive (Cancer cells can spread into nearby breast tissue) and noninvasive. Noninvasive cancer means, type of tumor that does not range past in the zone where it originally formed. Invasive breast tumor is metastasize cancer, it has the tendency to spread in surrounding tissues other than the area where it originally produced. It can also be classified as inflammatory breast tumor and an invasive breast tumor or mucinous cancer, developed by mucus generating tumor cells, and tube-like cancer (WHO, 1981). Metastasis can be fatal.

It is the second foremost cause of the death in worldwide. It was observed that the average incidence of breast cancer in Europe was 80.3 per 100 000, in the US it was 92.9 per 100 000 and the world average incidence rate was 43.1 per 100 000. It was also estimated that breast cancer caused 685000 deaths globally in 2020.

Historical evidence showed that breast cancer mortality changed little from the 1930s through to the 1970s when surgery alone was the primary mode of treatment (radical mastectomy). Improvements in survival began in the 1990s when countries established breast cancer early detection program that were linked to comprehensive treatment programs including effective medical therapies.

Certain factors increase the risk of breast cancer including increasing age, feminine sex, obesity, harmful use of alcohol and tobacco, low bodily movement, race/origin past and family history of breast tumor, premature age at menarche, menopause at oldness, old age at first full-term pregnancy, stoutness after menopause, never having been pregnant, having one and only pregnancy rather than various, after pregnancy no breast feeding, usage of postmenopausal estrogen substitution treatment or women's body produces high level of estrogen during reproductive years (Dite et al., 2003) or postmenopausal hormone substitution treatment etc.



It is assumed that the above mentioned factors are assicated with development of breast cancer but till now, it is not idenfied that which specific factors are played pivotal role for formation of breast cancer. Some reverse data also showed that half of breast cancers develop in women who have no identifiable breast cancer risk factor and most women diagnosed with breast cancer do not have a known family history of the disease. Certain inherited high penetrance gene mutations greatly increase breast cancer risk, the most dominant being mutations in the genes Breast Cancer gene 1 (BRCA1), BRCA2 and Partner and localizer of BRCA2 (PALB-2). Women found to have mutations in these major genes may consider risk reduction strategies such as surgical removal of both breasts.

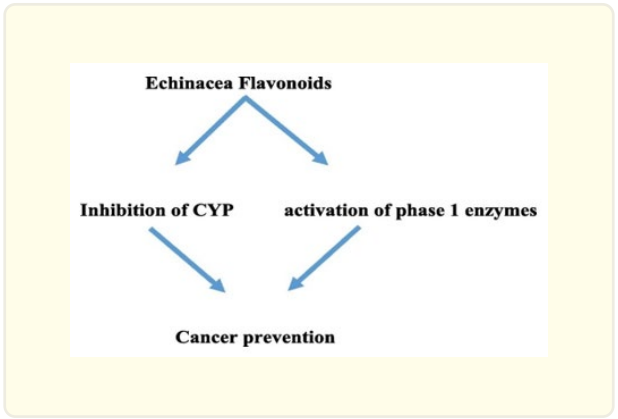
Clinical Breast Examination is a technique for identifying breast tumor for benefit of public health. It is easy to execute, economical and it can be freely qualified by healthcare suppliers (Parkin et al., 1997). In developing countries, due to unavailability of mammography for routine screening, breast cancer is usually identified at late periods therefore, women get insufficient and less cure, pain assistance and comforting care. Breast cancer has important effect on society and life quality of women; so, it becomes life threatening condition such as premature death and reduced productivity (Ferlay et al., 2001).

Ladies are at a higher danger of breast tumor since they have generously more breast tissue than men. Furthermore, estrogen advances the improvement of breast tumor growth. Women of middle age have high risk of breast tumor (Wu et al., 2002, Edwards et al., 2002).

Evidence based effective herbal drugs for management of early stage of breast cancer: Active phyto-chemicals such as carotenoids, flavonoids, ligands, polyphenolics, terpenoids, sulfides, lignans and plant sterols can stimulate glutathione transferase enzyme which helps to prevent the cell proliferation. It is also proved that *Echinacea purpurea*, *Allium sativum*, *Dacus carrota*, *Camellia sinensis*,

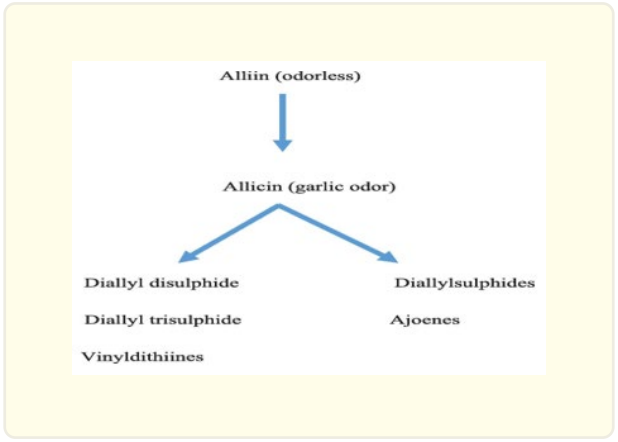
Panax ginseng, *Cimicifuga recemosa*, *Linum usitatissimum* extracts and juices are having anti-breast cancer properties. The volatile oils and extracts of these herbs and plants may inhibit the synthesis of mevalonate kinase that lessen the tumor growth and cholesterol synthesis (Tyler V. Haworth Press; New York: 1994. Herbs of Choice. The Therapeutic Use of Phytomedicinals).

Echinacea: It is belongs to a family Asteraceae. Three types of species are most commonly found, named as *Echinacea purpurea*, *Echinacea angustifolia*, and *Echinacea pallida* for herbal remedies. Researchers have revealed that *E. purpurea* raises the number of natural killer cells in the investigational mice (Steffani, 2005).



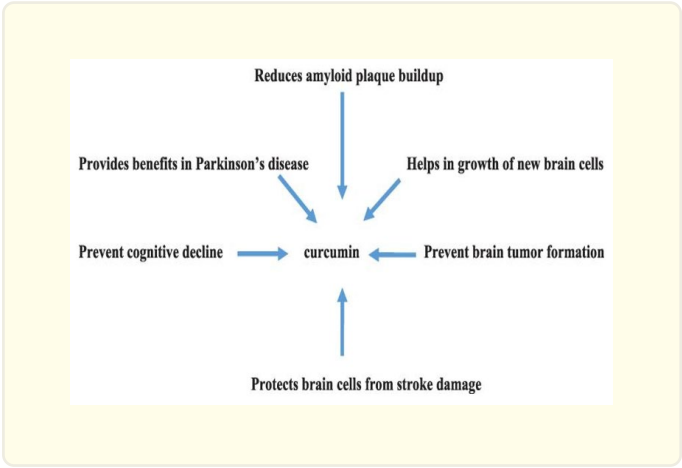
In Echinacea, active Flavonoids are present which act as an immune-stimulant. It flavonoids promote the lymphocyte's activity that increases the phagocytosis by macrophages and the action of natural killer cells and prompting interferon assembly, and it has also lessen the harmful consequence of radiotherapy and chemotherapy. It also helps the patients in prolonging the survival time with progressive stage of cancer. *Echinacea* juice helps to produce Cytokines by macrophages. It has less clear effects on T-cell and B-cell stimulation and propagation effect. Several ingredients of *Echinacea* are reflected to show a role in its special sound effects on the immune system (Luettig et al., 1989).

Garlic: Anti-cancer activity of garlic is due to presence of organic sulfides and polysulfide's. Mechanism behind anti-tumor activity stimulating the lymphocytes and macrophages is that they kill the cancerous cells and interferes with tumor cells metabolism.



Researchers have found that the ripened extract of garlic is also helpful to shield the propagation of several types of cancers such as colon, stomach, breast, lungs and bladder. Complications of chemotherapy and radiotherapy could be lessening with garlic extract.

Curcumin: Curcumin is known to have anti-cancerous activity due to its phenolic substances. Propagation of lung, breast, skin and stomach cancer is limited by curcumin (Winston, 1999).



Eicosanoids, for example prostaglandin E-2 (PGE-2), production is altered by curcumin, an antioxidant agent. It has also anti-inflammatory action in human. Curcumin has been revealed to have inhibitory action in all phases of cancer growth which are initiation, promotion, and propagation. Nitrosamine production is inhibited by turmeric; it results in increase natural antioxidant action of the body. Amount of glutathione and other non-protein sulphahydryls is increased by curcumin, and they act directly on different enzymes.

Carrot: Intake of carotenoids through diet also decreases the occurrence of tumor (Donaldson, 2004). The carotenoid substances are potent antioxidants and show numerous therapeutic activities, such as searching of free radicals, protecting against oxidative damage to cells, improvement of gap intersections, stimulation of immune system and enzyme's activity regulation contributed in cancer production and encourage the activity of immune system of the body (Freudenheim et al., 1996).

Green tea: It is scientifically proved that *Camellia sinensis* is having Anticancer activity. It is also attributed by polyphenolics compounds. Epigallocatechin (EGGG), a polyphenol is present in small amount in *C. sinensis*. Researchers have revealed that green tea possesses antitumor and anti-mutagenic activity. Cells are protected by EGGG from DNA damage produced by oxygen reactive species (Lambert and Yang, 2003). Studies on animal showed that green tea polyphenols restricts the cancer cells division and stimulate the necrosis and apoptosis of tumor cells (Zaveri, 2006). While function of immune system is stimulated by tea catechins, they also inhibit the metastases and angiogenesis in tumor cells. Some studies have shown the protective results of green tea in counter o colon and stomach cancer. Tea and their primary catechins reduce the risk of tumor in number of organs of the body. Harmful effects of radiation can be lessened with green tea. All beneficial effects of tea are due to its antioxidant activity (Keum et al., 2000).

Ginseng: *Panax ginseng* is a plant mainly grows in China, Korea, Japan and Russia. Part used of this plant is dried root. It has many therapeutic uses including cancer. Active substances of ginseng have shown that it reduces or blocks the development of tumor necrosis factor in the skin of mouse, blocks the propagation and metastases of cancerous cells, stimulate cell differentiation, and level of interferon. Other type of cancerous cells stages may also hindered by ginseng's ingredients. An investigation was also carried out in Korea, recommended that ginseng reduces the cancer risk in human. As related to fresh sliced ginseng, its juice or tea, the most potent and active type of ginseng is its extract and dried powder for prevention of cancer threat. By interrupting the DNA synthesis ginseng retains the tumor development. Beneficial effects of active compound of *P. ginseng* include restart of natural killer cells impaired

during chemotherapy and radiotherapy, induces macrophages and enhances antibodies formation.

The ginsenoside Rh2 is a significant bioactive constituent of red ginseng and the main active anti-cancer saponin in extracts. Lee et al., investigated the inhibitory effect of Rh2 on the growth of breast cancer cells in vitro by using MCF-7, a breast cancer cell line. They reported that Rh2 retarded the proliferation of the MCF-7 human breast cancer cell line in a dose-dependent manner by inducing changes in hypo-methylated genes involved in tumorigenesis with the upregulation of ST3GAL4, C1orf198 and CLINT1. A similar mechanism by which Rh2 exerts in anti-cancer activity involves the suppression of C3orf67-AS1, a novel noncoding RNA via promotor methylation.

One of the most studied ginsenosides, Rg3, suppressed breast cancer via several intertwined biological pathways related to cell division and protein synthesis, such as by inhibiting Akt-mediated self-renewal signaling in MCF-7 breast cancer cells (Oh J et al., 2018; Zou M et al., 2017) . Additionally, Rg3 can inhibit the growth of breast cancer cells by downregulating NOX4 and upregulating KDM5A via altering epigenetic methylation (Ham J et al., 2018). Similarly, Rh2-modulated epigenetic methylation of immune response-related genes can hinder cancer cells growth (Lee H et al., 2017). Rd also suppressed metastasis by downregulating miR-18a-mediated Smad2 expression and inhibiting angiogenesis-related vascular endothelial growth factor- (VEGF-) induced Akt activation in cultured or mice xenograft model of MDA MB-231 and 4T1 cells (Zhang E et al., 2017). Similar to the blocking of breast cancer metastasis by halting Akt-activated cell proliferation by Rg3 and Rd, CK ginsenoside repressed Akt1 signaling to promote apoptosis in SKBR3 cells (Choi E et al., 2019). Moreover, CK, Rg5, and Rk1 suppressed tumor growth in mice xenograft models by inhibiting cyclin D1, phosphatidylinositol-3-kinase (PI3K)/Akt, and reactive oxygen species (ROS)/PI3K/Akt signaling pathway, respectively (Liu Y et al., 2019) . The activation of the PI3K/Akt pathway, a key regulator of survival, results in the inference of the control of cell growth and survival, ultimately leading to metastatic competence, angiogenesis, and therapy resistance (Porta C et al.,2014).

Black cohosh: *Cimicifuga recemosa* is a shrub, found in the eastern forests of North America. Patients of breast cancer most commonly used Black cohosh during radiotherapy and chemotherapy. It has been used by Native American since many centuries for the treatment of menopausal signs, pre-menstrual discomfort and dysmenorrhea. It also induces the abortion-like problems. It was also found in 19th century's pharmacopeia. A large range of preparation of black cohosh is present in drug stores. Herbalists have shown that they are safe and effective therapy for menopausal indications. Females, who have been suggested to escape the Hormonal Replacement Therapy (HRT) by their physician, it has been used by those women. Most of the studies have shown the herb's effects on menopausal indications. Although the vigorous principles of black cohosh have not been known, there is assumption of triterpene glycosides to be a vital component, but trace amount of resins and caffeic, isoferulic and fukinolic is also present. Ambiguities are found about the estrogenic and anti-estrogenic activity of black cohosh. In the literature it is revealed that black cohosh has synergistic effects for breast cancer patients when given in combination with other chemotherapeutic agents (Rockwell et al., 2005).

The herb black cohosh (*Actaea racemose*) formerly known as *Cimicifuga racemosa* is a flowering plant belonging to the family Ranunculaceae. Black cohosh root consists of more than 42 triterpene glycosides, 11 phenolic acids, and more than 70 alkaloids and tannins. The triterpene glycosides such as actein, 23-epi-26-deoxyactein and cimiracemoside, as well as phenylpropanoids such as phenylpropanoid isoferulic acid are the major secondary compounds and biologically active components of black cohosh. The alkaloids, tannins and flavonoids in the rhizome are regarded as possibly biologically active compounds. Chemical research described approximately 15 polyphenolic components including fukiic acid, piscidic acid, caffeic acid and their derivatives. Studies have also identified an isoflavone, formononetin, in black cohosh. Remifemin, an extract of the rhizome is commercially formulated and along with other varieties of black cohosh though not standardized are available in the United States.

Flax Seed: Flax seeds are rich source of dietary fiber, omega 3 fat, and lignans. Estrogenic activity is present in flax seeds due to metabolism of lignans to enterodiol and enterolactone, and metabolism occurs in digestive tract. As compared to soy products, flax seeds have more potent phytoestrogens, while intake of flax seeds causes a huge change in the elimination of 2-hydoxyesterone than soy protein (Brooks et al., 2004). A research group of Lilian Thompson at university of Toronto has shown that ground flax seeds have powerful anti-cancer activity. An experiment was conducted on mice; firstly cancer is induced in mice by administering carcinogens, in

one group, anti-cancer activity of flax seed was identified by mixing the lignin in diet of mice. This experiment has results in reducing the tumor load. Flax seeds and secoisolariciresinol diglycoside reduced the malignancies. Recently, this 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 (Chen et al., 2002). Mammary glands morphogenesis in mice is improved by flax seeds. Researchers examined the female mice fed with 10% flax seeds diet, and they found the 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 mammary tissues of mouse, prevention of malignancies, reduction of tumor development are possible by flax seeds in female offspring, making less vulnerable to carcinogens (Tan et al., 2004).

It is needed to conduct clinical trial in different countries and generate evidence based data for preventing breast cancer related mortality in near future. It is an attempt to give attention to the scientific community to identify the new therapeutic metabolities for combating the breast cancer.

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