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EDITORIAL

Natural cures for breast cancer treatment

KEYWORDS

Herbal medicines;
Anti-tumor;
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Immune-suppressive;
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Cancer;
Phytochemicals

Abstract For centuries, herbs and plants have been used for medicinal purposes and as food as well. This review concerns about different types of plants that retain the immune stimulating and anti-tumor properties. Large variety of active phytochemicals such as carotenoids, flavonoids, ligands, polyphenolics, terpenoids, sulfides, lignans and plant sterols has been identified in different types of herbs. These phytochemicals have different mechanisms of action. They either stimulate the protective enzyme like glutathione transferase or prevent the cell proliferation. This review has centered on the biochemical properties of *Allium sativum*, *Echinacea*, *Curcuma longa*, *Arctium lappa*, *Camellia sinensis*, *Panax ginseng* and *Flax* seed. Extracts and juices of *Withania somnifera*, *Amoora rohituka*, *Dysoxylum binectariferum* and *Vaccinium macrocarpon*, respectively also used as anti-breast cancer. The volatile oils and extracts of these herbs and plants inhibit the synthesis of mevalonate that lessen the tumor growth and cholesterol synthesis.

1. Introduction

Worldwide, the second foremost reason of the death is breast tumor. In UK, on an average, one woman out of nine will progress this disease in their lifespan. There are several factors associated with the breast tumor, for example gender, diet, use of alcohol, body movement, family history, lifestyle and endocrine aspects as well including both exogenous and endogenous. There are some other important factors that lead to breast cancer, like previous benign and mammographic density. However, still it is not clear, which factor is most important in breast cancer's pathogenesis (Abdulkareem, 2013). So, breast cancer for woman has converted into the 2nd foremost reason of the death. The chemotherapeutic agents used for its treatment are derived from the plant origin, particularly fruits, leaves, flowers, lichens and fungi. "Herb" is a botanical term means plants producing fruits, seeds, with nonwoody stems. These plants and herbs have played very important role in maintaining the human health. Today public has more interest in herbal remedies than synthetic medicines because herbals contains natural active compound that can support the human health (Dmitri et al., 2015).

An office of alternative medicine was recognized in 1993 by National Institute of Health, to support the competent investigators that want to study the unconventional therapy systemically. A survey has shown that more than one out of three Americans utilized nonconventional treatment per year for at least once, and this report was published by Eisenberg in 1993. People want the solution without any harmful effects such as anxiety, depression, insomnia and headache (Eisenberg et al., 1993). These herbal remedies are used by self-prescription for management of common disorders for example fever, infections, insomnia, colds, cough, anxiety, arthritis, premenstrual syndrome, weakness and cancer. There are some examples of plants that are used in breast cancer, for example ginko, goldenseal, ginseng, garlic, *Echinacea*, aloe vera and saw palmetto. For medicinal purposes, many types of native herbs are used in Americans Indians for example black cohosh, goldenseal, ragweed, and snakeroot. Herbs contain aromatic ingredients and essential oils that provide flavor to foods such as culinary herbs (Tyler, 1994). In this review, an attempt has been made to characterize the plants and their extract that may be utilized in breast tumor treatment in Pakistan and in other countries as well. Evidence on the existence of plants, their scientific names, active principals and origin of these plants has been taken from the literature.

2. Breast cancer

Cancer is defined as uncontrolled cell division in our bodies, and it ultimately results in death. Normal body cells are

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destroyed by cancer cells. Cancer may be caused by unevenness in the body and can be treated by improving this difference. To find out what exactly cancer is, research has spent billions of dollars. Cancer causes deaths of millions of people. Worldwide, 2–3% annual deaths occur because of cancer, and this was surveyed by American Cancer Society. So, all over the world there are about 3500 million people annually die from cancer. There are many treatment options like chemotherapeutic but they have resistance as well as many adverse effects that prevent their usage. Every year more than one million women, worldwide, are diagnosed with breast tumor. 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).

For breast cancer, on an average in advanced countries survival rate is 73% and 57% in unindustrialized countries. Rates of breast cancer have dropped in developed countries due to early detection and screening. Therefore, there are three approaches to control breast cancer: professional and public knowledge, practice and attitudes. These approaches are readily available in unindustrialized countries than in developing countries. In terms of both costs and survival, measure to reduce the breast cancer at diagnostic stage is possible to have overall benefit (Ziegler et al., 1993). Clinical Breast Examination is a technique for identifying breast tumor for benefit of public health; it was shown by indirect evidence from studies. It is easy to execute, economical and it can be freely qualified by healthcare suppliers (Parkin et al., 1997). Ladies are at progressively great danger of breast tumor, as a result of changing acquaintances to conceptive and nourishment related factors after some time period, with occurrence rates expanding in many countries and world's region in the previous couple of decades. The quickest developments are found in unindustrialized nations, where breast tumor growth hazard has verifiably been little with respect to industrial countries (Ziegler et al., 1993). Today herbal remedies are mostly used by self-prescription for management of common ailments for example, anxiety, arthritis, colds, coughs, constipation, fever, headaches, infections, insomnia, intestinal disorders, premenstrual syndrome, stress, ulcers, and weakness. Some of the more common herbs in use today are *Echinacea*, garlic, ginseng, goldenseal, ginkgo, saw palmetto, aloe vera, and feverfew (Tyler, 1994).

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 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. General inflammation of breast refers a less severe form of tumor, called inflammatory breast tumor. Other forms of breast tumor are medullary cancer, defined as "an invasive breast tumor that produces a separate border among cancerous tissue and regular tissue" mucinous cancer, developed by mucus generating tumor cells, and tube-like cancer (WHO, 1981) (see Fig. 1).

Each lady is at danger for developing breast malignancy. A few moderately solid danger components for breast malignancy that influence vast extents of the all-inclusive commu-

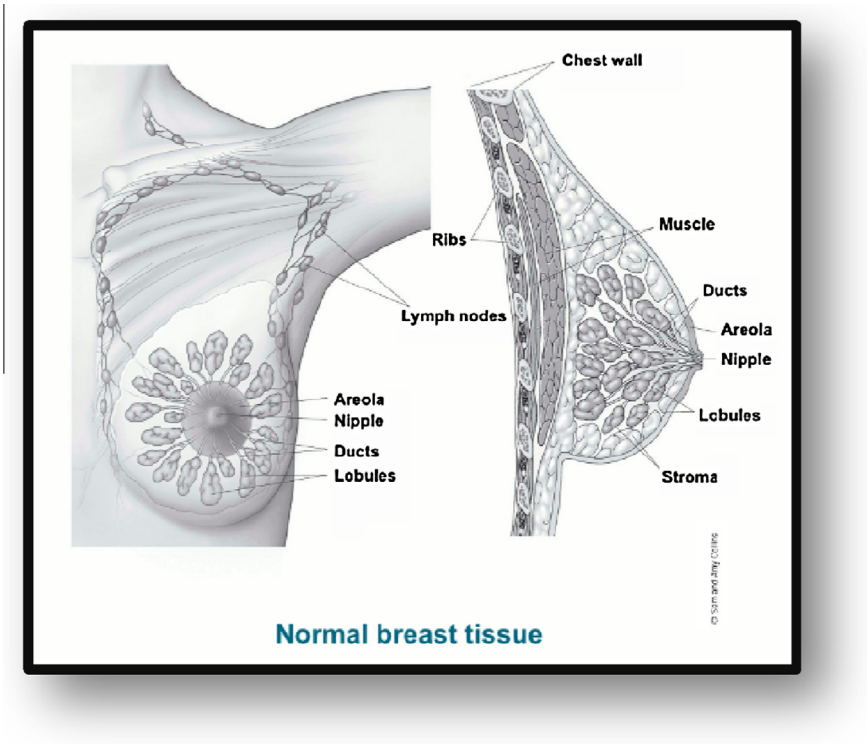

Figure 1 Normal breast tissue.

nity have been known for quite a while. Be that as it may, most breast tumor cases happen in ladies who have no recognizable danger other than their sex. The "well-known" danger elements for breast tumor are feminine sex, oldness, past breast tumor, a type of breast infection, inherited components (history of family with breast tumor), premature age at menarche, menopause at oldness, old age at first full-term pregnancy, stoutness after menopause, low bodily movement, race/origin and high-measurements presentation to radiotherapy in life. The "estimated" danger components for breast tumor includes, never having been pregnant, having one and only pregnancy rather than various, after pregnancy no breast feeding, usage of postmenopausal estrogen substitution treatment or postmenopausal hormone substitution treatment, orally intake of contraceptives, some specific dietary habits like high intake of fat and less intake of fiber, characteristic items, and vegetables, low measure of phytoestrogens, liquor use, smoking of tobacco, and untimely conception. Disregarding the way that men can and do have breast tumor harm, the disorder is 100 times more inclined to happen in a woman as compared to man (Wu et al., 2002). Ladies are at a higher danger of breast tumor since they have generously more breast tissue than men do. 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).

This risk increases as the age of women increases especially after 40 years of age. At the age of 50 or older, women have more than three-fourths of breast tumor in United States (Helmrich et al., 1983). The danger of breast tumor is greater in ladies who have nearby blood relations (mother, sister, or girl) who have had the ailment. If any relatives have developed the breast tumor before the age of 50 years, or in both breasts, the risk of expansion will be higher (Claus et al., 2003).

Nonetheless, most ladies who developed breast malignancy (around 80%) have no such family history of the cancer. The impact of family history on breast disease danger is accepted to be because of hereditary variables. Maximally 5–10% of all breast growth cases are inferable from particular acquired single-quality transformations, and numerous different cases have some hereditary part. The proof from individual families that have breast growth happens much of the time and from expansive epidemiological studies has demonstrated that a few ladies have a familial inclination to breast growth. Some families have hereditary breast tumor which is inherited in an autosomal dominant manner. Hereditary breast tumor spread due to germ line mutation in BRCA1 and BRCA2 genes are reasons for propagation of cancer. Autopsy findings and histopathological results are used to diagnose this hereditary cancer. There are some unidentified genetic defects that put the women on risk of breast tumor except mutations in BRCA1 and BRCA2 genes. Women who touch menarche timely at the age of 12 years or less than 12 and those who have menopause at old age of 55 years, they have more risk of breast tumor than the other women. Estrogen production is responsible for this relationship. Women's body produces high level of estrogen during reproductive years (Dite et al., 2003).

Ladies who begin to bleed at younger age and/or touch menopause at a late age are presented to large amounts of estrogen for a larger number of years than are ladies who have a late menarche or premature menopause. Women's age at 1st pregnancy is additional part of conceptive history that is related with breast growth hazard. Ladies who have their 1st full-term pregnancy at a moderately premature age have a lower danger of breast tumor than the individuals who never have kids or those who have their 1st kid generally at old age in lifespan (Helmrich et al., 1983).

Obesity has become reliably connected with an expanded danger of breast tumor growth between postmenopausal ladies (Brown and Allen, 2002; Hirose et al., 2001). This relationship might be intervened for a second time by estrogen generation. Fat cells create some estrogen and stout postmenopausal ladies, subsequently, have a tendency to have more levels of estrogen in blood as compared to thin ladies. Research has reliably demonstrated that the danger of breast tumor growth is less in actually dynamic premenopausal ladies as compared to inactive ladies (Friedenreich et al., 2001). Body movement in puberty might be particularly defensive, and the impact of body action might be most grounded among ladies who have no less than one full-term pregnancy. Investigations of cultural attributes of breast tumor growth uncover that non-Hispanic white, Hawaiian, and dark ladies have the most elevated amounts of breast tumor growth hazard.

High risk of breast tumor was found in women who have presented to high doses of radiation during puberty. This relationship was found both in atomic bomb stayers and women who had high doses of radiations for some therapy (Preston et al., 2002). There are other endogenous hormonal factors for example age of women at first pregnancy and having child, these affect the breast cancer. Females that have no child are at more danger for breast tumor development. Breast cancer risk becomes low if first pregnancy occurs after the age of 30–35 years. The long term utilization of postmenopausal estrogen treatment or joined estrogen/progestin hormone substitution treatment might be connected with an expansion in breast tumor hazard (Porch et al., 2002).

The relationship among the utilization of oral contraceptives and breast malignancy has been contemplated. Numerous studies attempting to connect oral contraceptives with expanded breast tumor growth have been uncertain. In any case, these studies have demonstrated that oral contraceptives try not to affect breast tumor growth hazard (Marchbanks et al., 2002). The utilization of postmenopausal estrogen therapy or in combination with therapy, both may be related to breast tumor factor. It was also studied that there is association among oral contraceptives usage and breast tumor although they do not have prolonged effect on breast tumor. It has been studied that relationship exists between breast tumor and diet, low rates of disease were found in Asia and high rates in Western industrialized nations. An inclusive result was found between vegetarian and non-vegetarian. A link was found in alcohol, cigarette smoking and breast tumor (Atkinson, 2003; Chen et al., 2003). Breast cancer will spread more rapidly in females who have already been identified with breast tumor. Incomplete pregnancy and premature termination of pregnancy have been linked with breast cancer risk. High estrogen level in incomplete pregnancy is responsible for breast cancer.

3. Geographical worldwide variations

All over the world, the total of women identified with breast tumor is higher than one million. Over one-fifth of expected 4.7 million diagnosed tumor in women, neoplasm is most com-

mon. In both sexes, in developing and developed countries, breast cancer is the 2nd greatest tumor after lung cancer (Ferlay et al., 2001). Generally, a good survival was shown in 2000, when number of deaths is considerably lower about 375,000 deaths in females with breast cancer. However, death rates depend upon the stage of disease. By stage, there is difference in survival that is also very valuable in developing countries. In Sweden, survival rates differ from 83% to 61% in Slovaki. Survival and prevention from cancer is possible only by effective treatment either by antibiotics or by natural products obtained from different plant origins (Coleman et al., 2003).

4. Globally some common herbs that are used for the treatment of breast cancer

4.1. Echinacea

Echinacea, belongs to a family Asteraceae. It is uninhabited aromatic plant that cultivates mainly in the Great Plains and eastern regions of North America and also produced in Europe. For herbal remedies three types of species are most commonly found, named as *Echinacea purpurea*, *Echinacea angustifolia*, and *Echinacea pallida*. But for research and treatment *E. purpurea* is most commonly used. There are some common names that are linked with *Echinacea* are purple coneflower, Kansas snakeroot and black Sampson. Researchers have revealed that *E. purpurea* raises the number of natural killer cells in the investigational mice. In future *E. purpurea* could be a potential therapy for anti-cancer treatment (Steffani, 2005).

Flavonoids act as an immune-stimulant, they are present in *Echinacea*. It was supported by Winston et al., and 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. Cytokines production by macrophages has shown to increase by Commercial preparations of *Echinacea* juice. Less clear effects on T-cell and B-cell 7 stimulation and propagation are found. Several ingredients of *Echinacea* are reflected to show a role in its special sound effects on the immune system (Luettig et al., 1989) (see Fig. 2).

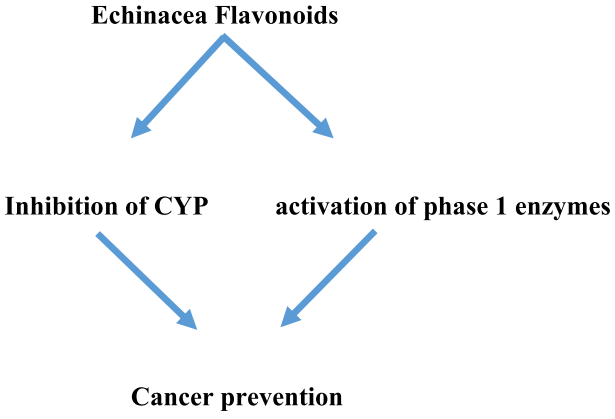

Figure 2 Action of flavonoids for cancer prevention.

4.2. Garlic

Garlic (*Allium sativum*), for hundreds of years it has been used for treating many illnesses. It involves hundred or more than hundred therapeutically useful secondary metabolites, for example, alliin, alliinase, and allicin. Alliin, an amino acid, is present in garlic oil that is transformed to allicin after its rhizomes are crumpled. An originator of Sulfur comprising compound is allicin, which is responsible for odor and its therapeutic properties. Garlic oil contains another Sulfur holding substance, Ajoene. Ajoene delays the cancer production while selenium as antioxidant. Bioflavonoids, cyanidin and quercetin, are also found in garlic with antioxidant properties (Galeone et al., 2006; Yang et al., 2001). Anti-cancer activity of garlic is due to high amount 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 (Winston, 1999) (see Fig. 3).

Studies have shown that the number of suppressor T cells is increased by garlic and converts the lymphocytes in that form which is cytotoxic to cancerous cells. Metastases are prevented by altering the adhesion and attachment of cancerous cells, circulating in the blood vessels. Harmful effects of carcinogens to DNA are prevented by ripened garlic extract; it improves the immune system of the body, increases the removal of carcinogens from the body, and enhances the detoxifying enzyme's activity. 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 lessen with garlic extract.

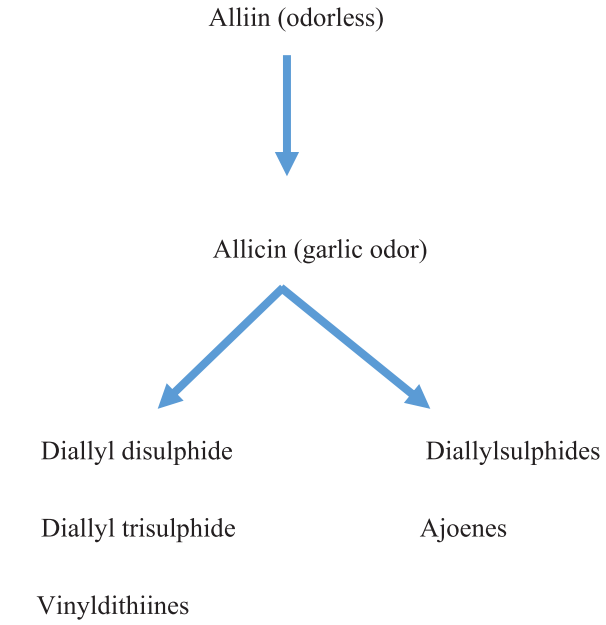

Figure 3 Action of alliin on tumor.

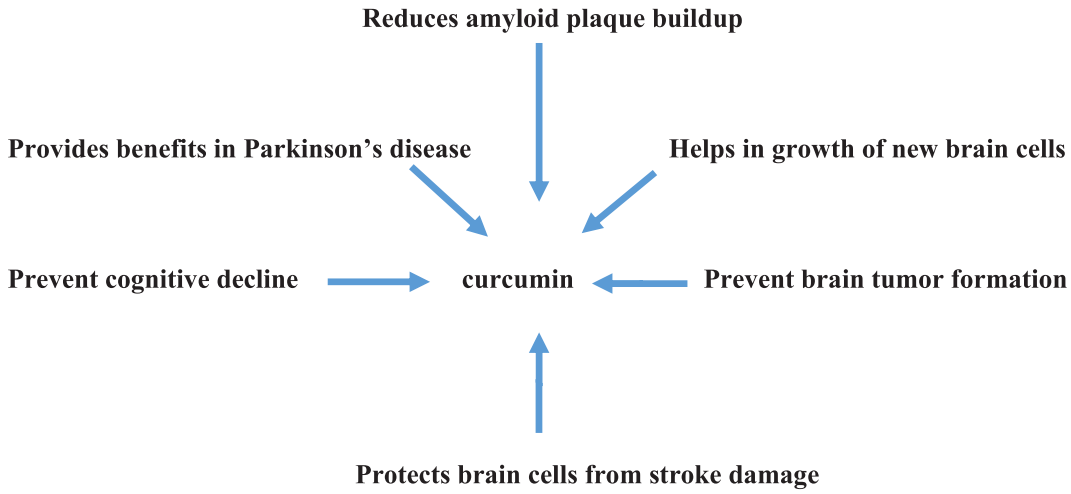

Figure 4 Activities of curcumin.

4.3. Turmeric

Scientific name of turmeric is *Curcuma longa*. Turmeric gives dark yellow color to food. Curcumin, the active ingredient of turmeric, is present in its rhizome and rootstock. Curcumin is known to have anticancerous activity due to its phenolic substances. Propagation of lung, breast, skin and stomach cancer is limited by turmeric (Winston, 1999) (see Fig. 4).

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 (Sakkara et al., 2011).

4.4. Burdock

Scientific name of Burdock is *Arctium lappa*. Its root is found and used in Europe and Asia. There are many therapeutic uses of burdock in herbal remedies. Its root has gummy texture and sweet taste. In old times burdock was useful in arthritis, tonsillitis and measles, but nowadays it has been found that burdock has antitumor activity. It contains some active ingredients that alter the changes in oncogenes. Burdock has been utilized in treatment of breast tumor, ovary, bladder, malignant melanoma, lymphoma and pancreatic cells. It relieves the pain, lessens the tumor size and enhances the survival phase. To withstand the fast propagation and division of cells, a huge amount of nutrients is required during cancer. But cancer cells can live in stressed circumstances for example with low oxygen and less amount of carbohydrates, because tumor cells have high tolerance to stressed conditions. Burdock seeds contain an active ingredient called Arctigenin. Arctigenin, has shown the ability to remove the tumor cells with low nutrients (Tamayo et al., 2000). Burdock root consists of flavonoid type and polyphenol anti-oxidant, and they may have oppressive effect on tumor development. Normal body cells are protected from toxic substances and lessen the cells mutation, by extract of root. Burdock contains the most important active ingredient that is known as, Tannin, a phenolic compound. It stimulates macrophages action, limits cancer propagation and retains immune-modulatory properties (Potter, 1997).

4.5. Carotenoids

An active compound known as "carotenoids" possessed by green, herb with leaf, rose hips. These aromatic plants are used as dyeing agents for example saffron, annatto and paprika. Consumption of vegetables and fruits has been linked with less expansion of different forms of tumor. 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).

4.6. Green tea

Scientifically green tea is known as *Camellia sinensis*. Anticancer activity is 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 were performed resulted 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).

4.7. Ginseng

Scientific name of ginseng is *Panax ginseng*. It is lasting 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.

4.8. Black cohosh

Scientific name of black cohosh is *Cimicifuga recemosa*. It is a shrub, found in the eastern forests of North America (Rockwell et al., 2005). 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. A patent medicine Lydia Pinkham's Vegetable Compound was famous, and this herb was principle component of this medicine. 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. Various research studies have contradictory results, some studies have shown that it enhances or lesson the cancer cell production in culture. 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).

4.9. Flax seed

Flax plant has small brown and golden hard-coated seeds. These small seeds contain all active components. 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 (J. Chen et al., 2002; W. Y. 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).

4.10. Vitamin D

Vitamin D is produced by sun exposure of skin. Large amount of vitamin D is produced by simple contact of hands, arms and face in summer. Even standing in sunshine on the beach until pinkness of the skin is equal to a 20,000 IU oral dose of vitamin D_2. Minimal amount of vitamin required by our body is 1000 IU/day, to maintain the sufficient level. Oral uptake of vitamin D is only source to maintain its level in the absence of sunshine. In one day 4000 IU can be taken safely with other benefits. Kidneys are responsible to maintain the active hormonal form of vitamin D in blood. Anti-cancer activity is possessed by this active type of vitamin D. The capability to change the chief circulating form of vitamin D 25(OH) D, into hormonal form, 1, 25(OH) 2D, vital organs of the body performed their functions. All these organs have local mechanism by which they convert the circulating form into hormonal form, and this mechanism is stimulated by exposure to sunshine (Barreto et al., 2000).

5. Conclusion

Multi-factorial factors are involved for breast cancer; many factors act independently or may be in combination, especially in high risk individuals. It is important to know the pathogenesis of this common disease which is associated with high mor-

tality and morbidity especially if not detected early. So the role of early screening in high risk individuals as well as proper surveillance of treated case in order to detect recurrence at early stages has been advocated.

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