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MEDICINAL PLANTS FOR PREVENTION AND CURE OF BREAST CANCER: A REVIEW

Engineering

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ABSTRACT

Background: There is a pressing need for the development of some novel anti-cancer agent with potential effectivity and lesser side effects against breast cancer, which is being the major cause of women death world wide. The need for this problem diverted the research towards evaluation of anti-cancer efficacy of phytoconstituents from plants. The results from many in vitro and in vivo studies have suggested the efficiency of many compounds from different medicinal plants against the treatment and prevention of breast cancer **Main body of abstract:** The article is comprised of information dealing with major active phytoconstituents and their mechanism of action, against the major breast cancer cell lines, from Allium sativum, Zingiber officinale, Catharanthus roseus, Curcuma longa, Panax ginseng, Nigella sativa, Camellia sinensis, Echinacea, Linum usitatissimum, and Cimicifuga racemosa. The review presents the information of the in vivo and in vitro clinical studies conducted to evaluate the action and efficiency of the active compounds from these plants on breast cancer cell lines like, MCF-7 and MDA-MB-231. Short **Conclusion:** The information from the article concludes that these medicnial carry some remarkable mechanism for combating infection and have shown a potential anti-cancerous activity. The compounds, for full acceptance and administration, needs to be studied more in context with their bioavailability, toxicity, safety and mode of administration that could bring out their maximum activity.

KEYWORDS

Breast cancer, Phytoconstituents, Apoptosis, MCF-7cell line, Anti-tumor

Background:

Among the countries with low and middle income, in the current scenario cancer causes one in six deaths and about 70% deaths worldwide [1]. This risk can be due to the dietary behaviour risk like the physical inactivity, habit of smoking, alcohol consumption and unhealthy diet. Some other factors that contribute to this are exposure to chemicals, metals for infectious agents and the aging population [2]. Rapid occurrence and high mortality rate has made Cancer to be one of the severe issues for human health that need proper conisderation and require immediate effective prevention and treatment measure. Among the sources for generating effective treatment measures, mother nature has been the best source for some medicinal plants that could provide us with the source of compounds that are effective in treatment of cancer and its corresponding effects. The plant-derived bioactive compounds are vital in treatment of cancer, a publication reports around 3000 plant species that carry the anti-cancer potential [3]. Almost 60% of the drugs used in treatment of cancer are derived from the plant source [4], these plants carry such curative potential due to the presence of a diversity of secondary metabolites called as phytochemicals, that carry effective biological properties. Presence of such bioactive compounds provides the plants with their economic and medicinal importance and some categories of these compounds includes, flavonoids, terpenoids, alkaloids, saponins, tannins, glycosides, phenols, quinones, steroids etc.

An uncontrolled cell divison in our body which ultimately leads to death is referred as Cancer, where the normal body cells are infected or destroyed by the cancerous cells. Two well known Ayurvedic classics, that is “Charaka” and “Sushruta samhitas” describe cancer as a inflammatory or non-inflammatory swelling and regarded as either Granthi or Arbuda that is minor or major neoplasm respectively [5]. Although the treatment measures like chemotherapy and radiotherapy are available, but there adverse effects limit their application and duration of application. Cancer causes millions of deaths world wide and every year around one million women worldwide suffer through breast cancer. The breast cancers are usually identified at very later stages due to the lack of routine screening and mammography. Premature death and reduced productivity are caused due to breast cancer, which adversely affects the life quality of women [6]. Survival rate for breast cancer in developed and developing countries is around 73% while its just 57% in the underdeveloped countries. Womens are at the danger for developing breast cancer, which develop as a result variable acquaintances to the conceptive and unstable nourishment.

Each breast containe lobes, around 15-20 in number and they further seggregrate into lobules, therefore the breast tumor can be referred as the ductal cancer, which develop in the ducts then invades the breast cells. There are several causes for the occurrence and malignancy of breast cancer which include, any breast infection, low bodily movement, inherited components, premature age at menarche, menopause at oldage, and frequent presentation to radiotherapy. Breast cancer is one of the commonest types of cancer and is characterized by some distinguishable pathological types with different outcomes. The different stages of breast cancer include, ductal hyperproliferation that switches to ductal carcinoma *in situ* (DCIS), invasive carcinoma, and metastatic stage. Molecular mechanism of occurrence divides breast cancer into types involving expression and amplification of estrogen receptor (Erα) and progesterone receptor (PR) [7].

The conventional therapies applied for the treatment of cancer carry several side effects as they lack the specificity, hence affect the normal body cells too, there use in the rural settings are also limited [8]. A sturdy resistance shown by the cancerous cells against the cytotoxic and antineoplastic drugs has created a challenging situation to look for the alternate, better and effective option for the issue [9, 10]. Ayurveda, an oldest Indian Indigenous medicine system, that uses plant and their products as the drugs, considered as the natural drugs [11]. The ayurvedic system of treatment is different from the western treatment in terms that it does not intend to carry any aggressive body treatments. Instead the approach stimulates the self healing abilities of body and prioritizes the a side effects free technique [12]. The approach of ehnomedical for the treatment of various ailments including cancer has gain familiarity due to the discovery of active compounds carrying anti-cancerous property that are available in plants at effective concentration. The present review deals with providing the information about the medicinal plants effective against treatement and prevention of breast cancer, their active constituents and the mechanism of action they carry as reported by some in vitro and in vivo studies.

Main text:

Medicinal plants used for treatment of Breast Cancer and their mechanism of action:

1) *Allium sativum*

The herb *Allium sativum* commonly known as garlic is one of the prominently used plant as source of herbal medication in treatment of various ailments. The herb is enriched with diverse therapeutically important metabolites *viz*., allinase, allicin and alliin, an amino acid which is converted to allicin after crumping of its rhizome. These metabolites are prominently found in garlic oil. The therapeutic role and charcetristic odour of garlic is contributed by the compound allicin, which is an originator of sulphur. Ajoene, another sulfur containing compound of garlic is responsible for delaying the production of cancer. Garlic is also enriched with some antioxidants like quercitin, bioflavonoids and cyanidin [13]. High proportion of sulfides and polysulfides in garlic confers the anti-cancerous potential to it. These compounds of garlic carry out the anti-tumor activity by stimulating the lymphocytes and macrophages which in turn engulf

and digest the cancerous cells and also interferes with their metabolic activity [14]. Allicin from garlic possess an anti-tumor activity on the breast cancer and prostate cancer, where the compound induces apoptosis in the cancerous cells [15]. Some studies reports that garlic consumption leads to an increased production of suppressor T-cell that in turn activates lymphotocytes cytotoxic to the cancerous cell. Its is also responsible for preventing metastasis by altering adhesion of the circulating cancerous cells. The extracts prepared with ripened garlic are known to prevent DNA damage and also improves the immunity of body. Garlic extracts could also help to lower the complications generated by chemotherapy and radiotherapy. The mechanism of action carried by compounds of garlic majorily include, apoptosis induction, cell cycle arrest and detoxification of carcinogens by enzyme stimulation [16]. In an in vitro study conducted on breast cancer cell line MCF-7 and MDA-MB-231, natural garlic and its derivatives showed a dose dependent inhibition in growth of cells by induction of apoptosis and cell cycle arrest [17, 18].

2) *Zingiber officinale*

A member of family Zingiberaceae, *Z. officinale* is commonly know as ginger and is among the widely used agents incorporated in traditional medication as anti-cancer agent mainly for the liver, oesophageal and gastrointestinal cancer [19]. The ginger rhizome is used for medicinal preparations and majorily used as poly herbal preparation. Some active compounds of ginger are shogaols, paradols and zingerone, all formed by conversion of gingerols [20]. Its extract follows multiple pathways to exert the anti-cancer effect, as for instance in a study the extract was significant in reducing expression of $NF_{\kappa}B$, a transciption factor responsible in biological processes like inflammation, cellular growth and survival, via suppression of the proinflammatory TNF-α among the rats induced for liver cancer [21]. Another study reports the activity of gingerol, when administered to F344 rats at a dosage of 0.02% for 3 weeks, led to the supression of azoxymethane induced intestinal cancer [22]. Colorectal cancer can be prevented and treated with gingerol compound present in ginger extract. Feeding ginger showed an efficacy in mice who were injected with tumor cells, ginger was given to them before and after tumor cell injection and also after tumor growth [22]. The compound gingerol has also shown anti-angiogenic abilities, which suggest that it could possibly prevent metastasis [23]. The aqueous extract of ginger is found to be effective on MCF-7 and MDA-MB-231 breast cancer cell line. The extract causes morphological changes un the cancer cells as observed under array [24].

3) *Catharanthus roseus*

A member of family Apocynaceae, the madagascae periwinkle has been for a long time for its medicinal concern. A study on human skin cancer cell line A431, reported that the methanolic extract of vinca reduces the proliferation of cancerous cells [25]. The plant is loaded with some potential alkaloids such as vincristine, vinblastin, vindoline, catharantin and vinflunine, present in the aerial parts. Among these alkaloids some are currently being used as anticancer drug [26]. Vinblastine, vincristine and vinorelbineare approved for use in the USA and vinflunine was approved in 2008 in Europe. A study conducted to report the effects of these alkaloids on cancer cell lines including MCF-7, PC3-1C and HeLa of breast, prostate and cervix cancer respectively. The findings suggest that the alkaloids changes the tubular protein linkages to block the cell division in cancerous cells, they prevent the cell from progression [27]. Another study reports the positive effects of these alkaloids in treatment to the patients suffering with breast cancer, leukaemia, lung cancer, hodgkin's lymphoma and testicular cancer [28].

4) *Curcuma longa*

The rhizome belongs to the family Zingiberaceae and is used as poly-herbal preparation against wide variety of cancers. Commonly called as turmeric is a source for a potential metabolite called curcumin, and is evident to inhibit a variety of cancers like breast, colon, renal, prostate, hepatocellular, and B cell lymphoma [29]. The mechanism of action for curcumin to carry its anti-cancerous activity include, downregulation of COX-2 enzyme, anti-oxidant, reduction in DNA adducts level. A study reported curcumin to induce apoptosis via caspase-3 in the colo205 adenocarcinoma cells of colon cancer and is also capable of decreasing ROS and Ca^{2+} level hence leads to apoptosis [30]. A study conducted on MCF-7 and ZR-75 breast cancer cell line reported that a combination of *Curcuma longa*, *Allium sativum* and *Zingiber officinale* and tamoxifen (an oestrogen antagonist) induces apoptosis in oestrogen receptor positive cells of these cell lines [31]. The phenolic compounds in turmeric contribute to its anti-cancerous activity, as its is capable of limiting the propagation of breast, stomach and skin cancer [32]. Curcumin is capable of inhibiting all phases of cancer growth that is initiation, promotion and propagation. Turmeric inhibites the production of nitrosamine which results to increased level of natural antioxidants action in body. Curcumin affects the amount of glutathione and other non-protein sulphahydryls which in turn affect diverse enzyme activity [33]. A study reports turmeric extract's effect on the telomerase activity in breast cancer, where the findings show that it an inhibit the effects of telomerase and also carry anti-proliferative activity [34].

5) *Panax ginseng*

It is a perennial herb of Araliaceae family which include several species out of which the prominent ones are *Panax japonicus, Panax quinquefolius* and *Panax ginseng*, the frequently and widely used species [35]. The roots of *Panax ginseng* are loaded with a numerous bioactive compound out of which ginsenosides is the major active compound [36]. The compound ginsenosides are chemically the triterpene steroidal saponins which differe based on the location, number and type of sugar moieties involved in the structure, which may be arabinose, glucose, xylose or rhamnose. These ginsenosides are of various types among which the most prevalent ones includeRg1, Re, Rd, Rc, Rb3 and Rb1. A study reported the inhibitory effect on growth of breast cancer cells (MCF-7) imposed by Rh2 ginsenosides, obtained from red ginseng [37, 38]. The compound was capable of retarding the proliferation rate by inducing changes in the hypomethylated genes and also upregulated CLINT1 and ST3GAL4 gene [38]. This ginsenoside is capable of mediating the cell cycle arrest in G(0)/G(1) phase in the MDA-MB-231 and MCF-7 cell lines of breast cancer. The arrest is caused by inhibiting the activities of Cdks/cyclin complexes mainly the cyclin D1/Cdk6 and D1/Cdk4 [39]. One more study reported the action of Rh2 on MCF-7 breast cancer cell line, where the compound inhibited cell proliferation by increasing and decreasing expression of p21 protein and cyclin D respectively [40]. The heat processing of ginseng results in production of a chief ginsenoside called as Rg3 which significantlly inhibits proliferation of cancer cells. As reported in an in vitro study Rg3 is capable of inhibiting proliferation in breast cancer cell lines, MCF-7 anf MDA-MB-231, where it decreasing cyclin D1 and A expression and also arrest the cell in G-1 phase [41]. The ginsenoside Rg3 is capable of inducing apoptosis, as reported in a study on MDA-MB-231 cell line via activation of caspase-3 proteolytic cleavage enzyme and production of ROS which in turn degraded the poly (ADP-ribose) polymerase [42]. The breast cancer cell lines express receptor, CXCR4, important for its metastasis property. Rg3 is capable of decreasing its expression, hence decreases the rate of metastasis in bones, lungs and also in lymph nodes [43, 44]. In a mice model study, Rg3 goes well with combination to anti-cancer drug, where it is capable of enhancing the antiangiogenic effect of capecitabine via decreasing density of microvasculature and expression of vasculae edothelial growth factor [45].

6) *Nigella sativa*

Commonly called as Black cumin, *Nigella sativa* is a medicinal herb from Ranunculaceae family [46]. The seeds from the herb is reservoir of numerous active ingredients, and some of the biologically potential ones include; thymol, dithymoquinone, thymohydroquinone and thymoquinone [47]. The member of category thymoquinone are amongst the most biologically active ones viz., carvacrol, p-cymene, 4-terpineol, t-anethole, sesquiterpene longifolene [48]. Several studies support the fact that thymoquinones are capable of inhibiting tumorigenesis via induction of apoptosis in breast cancer cell lines (49, 50). Thymoquinones promotes G(1) phase arrest by inhibiting cyclin D1 and cyclin E to induce apoptosis in T-47D and MDA-MB-468 breast cancer cell line [51]. A study reported that thymoquinone in a time dependent manner can upregulate the expression of p53 gene, a tumor suppressor, in MCF-7 breast cancer cell line to induce the apoptosis [52]. Long term in vitro treatment with thymoquinone inhibits proliferation of MCF-7 cell line via S phase and G2 phase arrest [53]. Methanolic extract of Nigellia seeds is evident to suppress proliferation in MDA-MB-231 and MCF-7 cell line by apoptosis induction via p53 pathway and caspase proteins [54]. Anti-metastatic effects of thymoquinones from *Nigella sativa* have been reported, where it down regulates the expression of CXCR4 chemokine type 4 receptor in MDA-MB-231 breast cancer cell line, in a dose and time dependant manner [55]. A supercritical carbon dioxide extract of *N. sativa* possess the anti-metastatic and pro-apoptotic properties via

inhibition of migration and invasion of MCF-7 breast cancer cell line [56]. Thymoquinones from black cumin seeds showed a protective effect by reducing concentration of breast carcinogens and downregulation of gene expression for Id-1, Bra1, Brac2 and p53 mutations [57]. Although thymoquinones are chemopreventive but lack of its bioavailability due to its hyodrophobic nature limits its access for use [58]. To enhance its delivery, a thymoquinone-encapsulated nanoparticle was synthesized using PEG which aimed on improving its aqueous solubility to enhace its bioavailability. This drug induced apoptosis and inhibited migration in breast cancer cell line through disruption of cytoskeletal actin polymerization [59]. A study conducted on estrogen negative MDA-MB-231 and estrogen positive MCF-7 breast cancer cell line that were treated with a combination of thymoquinones and a conventional drug tamoxifen, imparted a synergistic activity as they decreased the cell viability and induced apoptosis in both cell lines [60].

7) *Echinacea*

A herbaceous aromatic plant endemic to North America, *Echinacea* is a member of Asteracease [61] which covers nine species of *Echinacea* out of which three are traditionally used in phyto-therapeutic products. The part of this plant used in herbal formulation include, roots, rhizomes and flowers [62]. Some of the major compounds reported in the plant via application of HPLC includes, cynarin, flavonoids, echinacin, phytosterols, caffeic, chicoric, and chlorogenic acid [62]. Albiet *Echinacea* is among the commonly used herbal supplements for treatment of cancer patients, there are very few studies related to its use in breast cancer treatment [63, 64]. A study on the balck women's health reported the rapid use of *Echinacea* herb as the herbal medication among the breast cancer survivor and also reports their interaction studies with anastrazole and tamoxifen, used in the adjuvant therapy [64]. The antitumor potential of Echinacea extract has been reported under the in vitro studies, where its extract is significant to reduce growth in BT-549 cell line of mammalian breast cancer [65]. Proliferation of MCF-7 breast cancer cell line was reduced by a root constituent of *E. pallida* that is pentadeca-(8Z, 13Z)-dien-11-yn-Z-one [66]. In a study the MCF-7 cell line was treated with hexane fraction from *E. purperea*, and the extract reduced the proliferation and this was enhanced by the cyanarin which is also helpful in enhancing activity of doxorubicin against the same cell line [67]. Although there are several studies reporting the usage of *Echinacea* extract in treatment of breast cancer both under in vivo and in vitro studies, but the major limitation to its application is its property to inhibit the cytochrome p450 enzyme.

8) *Camellia sinensis*

The leaves and buds of evergreen plant Camellia sinensis is used for the formation of green tea by their exposure to heat or hot steam [68]. The green tea is rich source of polyphenola and caffiene. The polyphenols are comprised of flavandiols, flavonoids, phenolic acids and flavanols [69]. The major class of flavanoids are the catechins that majorily include, epicatechin, epigallocatechin-3-gallate and epichatechin-3-gallate [70] present in different proportions. Quercitin, mycricetin and kaempferol are among the flavones present in the plant extract [71]. The green tea also contains amino and alkaloids such as tryptophan, serine, threonine, aspartic acid and caffeine, theophylline, theobromide respectively [72]. The major component of green tea that imparts the potential biological property is epigallocatechin-3-gallate, which under a study demonstrated a chemopreventive effect against breast cancer development (73, 74]. A study consisting of 45,744 females from USA and Puerto Rica, consuming five or more cups of green tea per week showed a reduced risk of breast cancer [75]. Another study on 1551 patients with breast cancer showed a progression free and better survival, as they were regular consumer of green tea [74]. The synergistic role of green tea compound, Epigallocatechin-3-gallate (EGCG) with anticancer drugs have been reported. In a study, combination of EGCG with 5-aza-2-deoxycytidine showed a significant inhibition of cell proliferation on the MCF-7 and MDA-MB-231 breast cancer cell line [76]. Similarly treatment of the same cell lines with EGCG and quercetin with tamoxifen reduces the cell proliferation rate [77]. In an in vivo study, suberoylanilide hydroxamic acid (SAHA) and EGCG when administered together inhibited the proliferation and hence stoped the grwoth via manipulating the expression of tumor suppressors, PTEN and p27 [78].

9) *Cimicifuga racemosa*

It is flowering plant belonging to the Ranunculaceae family and commonly called as black cohosh [79]. The roots of this plant are rich in the phytoconstituents majorily in triterpene, glycosides, alkaloids, tannins and phenols. The compounds among glycoside category are, cimiracemoside and actein [80, 81], polyphenols are piscidic acid, caffeic acid, fukkic acid and their derivatives too [82], along with isoflavones. Extract of balck cohosh is reported to minimize the symptoms in patients suffering from primary breast cancer [83, 84]. Black cohosh is reported to obstruct the cell proliferation of ER-positive breast cancer cell lines via sevreal mechanisms which may include serotonergic mechanism, estrogenic effect and dopaminergic signalling [85, 86]. Treatment involving the combination of Balck cohosh and tamoxifen adjuvant showed that this decreases the severity and numbers of hot flashes that occur frequently in the post meopausal women when treated with tamoxifen alone [87]. Remifemin, a herbal prepration made with dried black cohosh, when administered to 50 breast cancer patients already being treated with tamoxifen, showed a decreased severity of hot flashe having the baseline value of 17.6 and 13.6 [88]. A study reports the activity of ethanolic and isopropanolic extract of *C. racemosa* as agent to kill estrogen receptor positive and negative breast cancer cell lines that is MCF-7 and MDA-MB231 respectively bu the induction of apoptosis via capases activity [89]. One more study reports that black cohosh extract could causes apoptosis in MCF-7 breast cancer cell line but no estrogenic effect was reported in them [90, 91]. Acetin a potential compound from black cohosh is reported to inhibit the growth of breast cancer cell line via induction of apoptosis [92]. The risk of recurrence of breast cancer is minimized by treatment with black cohosh and it is also used as an adjuvant with many anti-cancer drugs [93].

10) *Linum usitatissimum*

Commonly called as flax seeds or linsed, is a member of family Linacease and is among one of the oldest crops comprised of two species that is brown and yellow that differ in short chain fatty acids and nutritional characteristic [94]. One characteristic feature of flax seeds is that it containes 800 times more amount of lignin than any other plant, which the non-nutritional phenolic bioactive compounds. These compounds mainly includes ecoisolariciresinol diglucoside, lariciresinol, pinoresinol and matairesinol [95]. A study conducted on athymic mice infected with ER positive MCF-7 breast cancer cell line, when administered with dietary flaxseeds, showed a significant inhibition in cell proliferation and also resulted in apoptosis via reduction in cyclin D1 expression [96]. Treatment with 10% flaxseed reduced the tumor growth upto 45% in nude mice infected with breast cancer cell line MDA-MB-435, via decreasing expression of epidermal growth factor receptor and insulin-like growth factor [97]. Enterolactone, a lignin from flaxseed counteracted the angiogenesis in mice infected with MCF-7 human breast cancer cell line, where it inhibuted vascular endothelial growth factor that stimulated the angiogenesis process [98]. Effects of flax seeds in combination with the anticancer drugs have also been reported, where in a study tamoxifen-treated cell when treated with secoisolariciresinol diglucoside and flax seed oil, showed a decreased growth by reducing expression of proteins participating in growth factor mediated signalling pathway and estrogen receptor pathway [99]. Consumption of flax seeds results in the reduced risk for breast cancer as reported by a study on 2999 breast cancer cases and 3370 healthy control (95). The efficiency of flax seeds lignin is determined for its breast cancer reduction potential, as in a review considering some studies, reports that secoisolariciresinol diglycoside when consumed daily decreases the risk of breast cancer through rapid tumor apoptosis reduction in expression of HER2 and cell proliferation [100]. A study conducted on postmenopausal women reported the association of lignin or enterolignan with reduction in breast cancer risk [101, 102]. Intake of dietary phytoestrogen like isoflavones and lignans dusring the adolescence is associated with the decreased breast cancer risk, supported by a population based study conducted with 3024 cases and 3420 control [103].

Conclusion:

The current review documents the chemo-preventive and therapeutic attribute, of bioactive compounds originating from herbal source, against the breast cancer ailment. The practical evidences reported under this depicts the clinical importance of these compounds and their effectiveness alongwith the mechanism of action they carry. The source for these bioactive compounds or can aslo be called as the phytochemical compounds, is from common to rare medicinal plants. These compounds are capable of carrying the anti-tumor activity via vivid mechanisms including apoptosis, inhibition of cellular

proliferation rate, inhibition of metastasis and cell cycle inhibition at different phase. These compounds also capable of controlling the intracellular signalling pathway, the level of gene expression either for any enzyme or factor involved in cell proliferation or metabolism. The active compounds form these medicinal plants have shown a remarkable efficacy in their potential of action as supported by various in vivo and in vitro studies. These compounds not only individually but some are shown to work more efficiently in combination with the anti-cancer drugs, where they even tend to minimize the probability for occurrence of secondary responses generating from chemotherapy. Their bioavailability can be enhanced by the application of nanotechnology and lioposome carriers and their administration can also be improved by this, hence their major drawback can be escaped. The review clearly suggest the potency of these compounds from plants to be used for breast cancer treatment and prevention. For bettter justification and acceptance more clinical studies on human is needed. Further work should also include on deriving the information on their toxicity, quality control and safety profiles for complete acceptance as agent for cancer treatment.

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