

Promising Anticancer Potential of Herbal Compounds against Breast Cancer: A Systemic Review

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Abstract

Breast cancer (BC) exhibit a high level of mortality rate and incidence but a comprehensive treatment is unavailable, which can successfully eradicate this fatal disease. Novel therapeutic strategies have been intensively studied to eradicate BC, including the use of traditional medicines and phytochemical (herbal compounds). These compounds have been studied in many aspects, such as targeting cell cycle and key tumor-associated metabolic pathways. In this study, we reviewed the literature for the potential therapeutic application of herbal compounds against breast cancer. Several terms, including "Herbal compounds", "Breast Cancer" and "Traditional medicines", were searched in PubMed and Web of Science databases. The search results were narrowed down using many filters and the resultant literature was critically analyzed. The enormous number of articles showed the promising potential of herbal compounds as anticancer therapy. The comprehensive evaluation of the literature suggested the anti-angiogenic, anti-proliferative, anticancer stem cells, anti-inflammatory/antioxidant, anti-metastatic, and epigenetic effects of herbal compounds as anticancer effects against BC. Despite this enormous data, there is lack of sufficient demonstration of the consumption of herbal compounds in a regular as anticancer strategy in clinical trials. Therefore, given its promising anticancer potential, focus should be shifted towards the regular use of herbal compounds in anticancer strategies.

Keywords: Anticancer Strategy, Breast Cancer, Herbal Compounds, Traditional Medicines

1. Introduction

Cancer is known to be the major cause of mortality worldwide along with cardiovascular diseases, despite of advancement in research and diagnosis. In the whole world, breast cancer is considered to be the second most occurring neoplasia among women¹. According to an estimate, nearly 500,000 deaths of the total 2 million breast cancer patients are recorded per year. This rapidly increasing number of breast cancer patients in the 21st century implies the epidemic status of this disease¹. Cancer chemoprevention is considered to be an effective tool to minimize the threat of cancer development. This chemoprevention is known to target both the

epigenetic changes that are responsible for sporadic breast cancer and genetic factors of breast carcinogenesis. Epigenetic modifications leading to sporadic breast cancer is responsible for 90% of all cases¹. Moreover, the chemoprevention is regarded as effective, less toxic and cost effective in comparison to the therapy done to treat breast cancer.

Phytochemicals are abundantly present in the eatable parts of plant which reduces the occurrence of human disease particularly cancer^{2,3}. Epidemiological, preclinical, and clinical trials proposes that plants containing phytochemicals, such as phenolic compounds, terpenoids and flavonoids etc. exhibit anticancer and other significant biological effects, including anti-allergic, anti-

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aggregatory, anti-inflammatory and neuro-protective, effects⁴. The phytochemicals are known to target the varied molecular pathways in cancer development such as angiogenesis, cancer stem cells, proliferation, inflammation, cell infiltration, apoptosis, or epigenome, without causing detrimental effects in cells. Research in this area firmly proposes that the synergistic or additive effects of phytochemicals found in the foods derived from whole plant might be linked with their substantial anticancer and pleiotropic properties⁵. It is assumed that the single molecule derived from plants does not cause the same biological activity as the molecules derived from whole plant. It means that the effect of a single molecule is much weaker as compared to the synergistic effects produced by the molecules derived from whole plant^{2,6}. Alternative medical care systems e.g., Chinese, Ayurvedic belonging to traditional medicine have been widely used over thousands of years as a potent source in suppressing cancer growth. The plants, spices and herbs derived molecules and their combined formulas are used in traditional medicine and could contribute as an anticancer

agent and chemoprevention in carcinogenesis without producing harmful effects. Thus, the use of traditional medicine owing to their boundless benefits has gained prime importance in the area of cancer research^{6,7}. The combined effects of numerous phytochemicals derived from various plant substances in traditional medicine poses significant tumor suppressive effects. They target the cell signaling pathways that considered being effective in reduction of carcinogenesis in high-risk individuals. Consequently, the use of traditional medicine should be considered an effective therapeutic approach in oncology research.

In this study, we searched different databases for mining the literature related to potential anticancer effects of herbal compounds and their mechanism of actions were critically studied and reviewed.

2. Methodology

A workflow of the methodology adopted is presented in Figure 1.

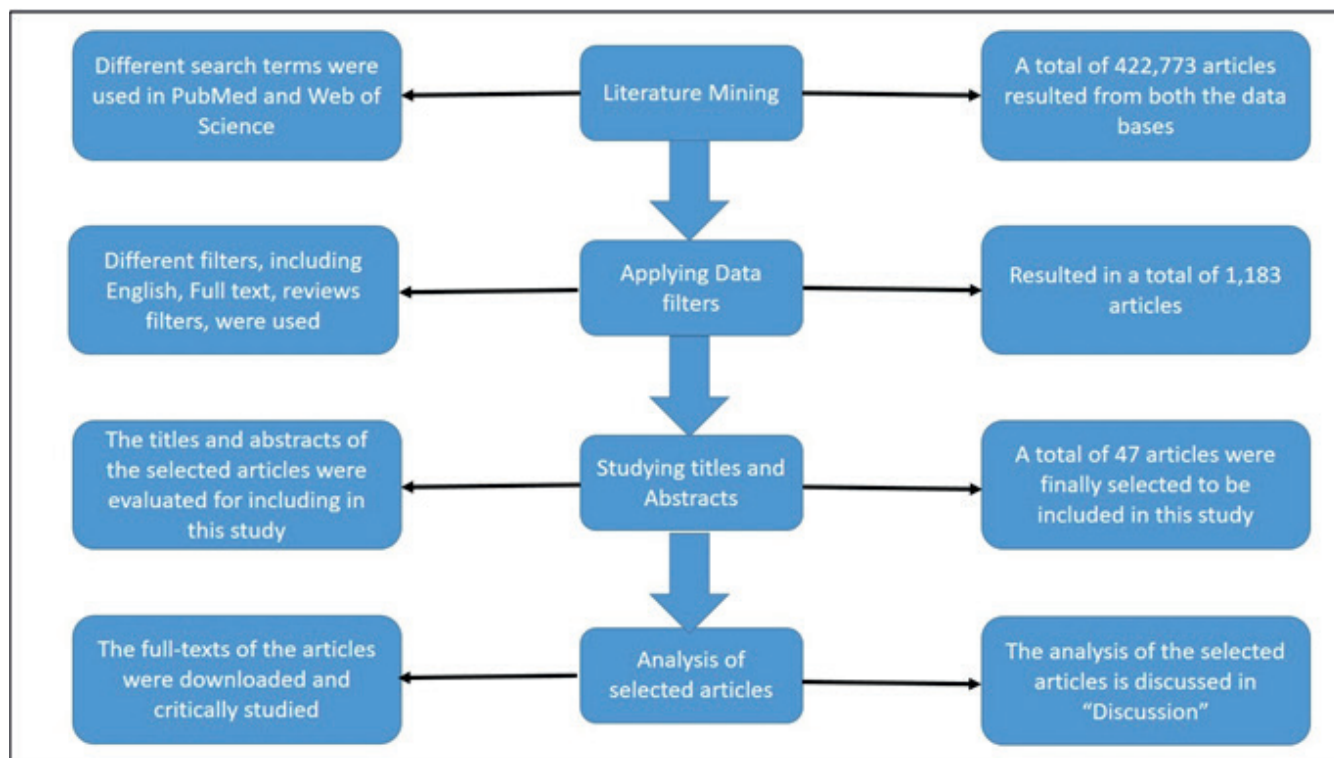


Figure 1. Workflow of the study.

2.1 Data Mining

The articles were searched and retrieved from PubMed and Web of Science databases. Different search terms were used, which included “Cancer”, “Herbal compounds” and

“Anticancer effects of herbal compounds”. The resulted articles in both of the databases were in a very huge number. Therefore, many filters were used to narrow down the search results. First, the search results were

filtered for full-text articles, followed by filtering for English language. The resulted data was still huge, which was then filtered to skip the review articles, including narrative reviews, systemic reviews and meta-analysis. Then, the search results were filtered for “Breast Cancer” and “Traditional medicines”, which narrowed down the search results to a number which could be studied.

2.2 Data Assessment

The assessment of the search results were carried out in two steps. In the first step, the titles of the articles were studied and those did not match the requirements of this study were excluded. In the second step, the abstracts of the selected were studied and if the article fulfilled our requirements were selected. The full texts of the selected articles were downloaded and critically analyzed.

3. Results

3.1 Data Assessment

From the initial data search, the results from both the databases included 422,773 articles. To study this huge number of articles was out of our capacity. Therefore, the filters, including full-text, English and reviews filters, were applied, which narrowed down the results to 344,983 articles, 334, 213 articles and 290,271 articles, respectively. The addition of more filters to narrow down data to those related to breast cancer only surprisingly lowered the number of articles to a total of 1,183. The year-wise distribution of all articles from both the databases is presented in Figure 2.

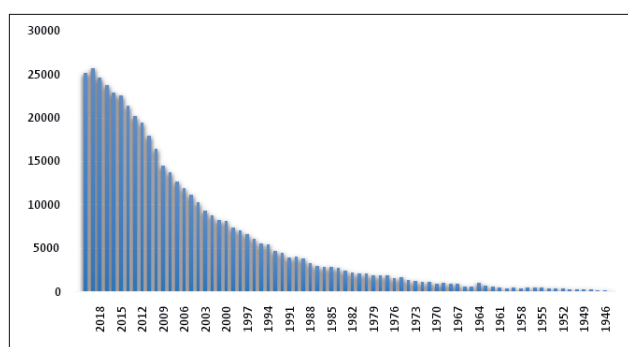


Figure 2. Year-wise distribution of all the articles from PubMed and Web of Science.

3.2 Assessment of the Data

The titles of all the selected 1,183 were studied. It was found that some of the articles did not fit our requirement,

which were, therefore, skipped. The abstracts of the selected articles were studied and their full texts were downloaded. Finally, a total of 47 articles were included in the study (Table 1-3).

3.2 Analysis of the Potential Anticancer Herbal Compounds

The full-text articles were critically studied and the articles were divided into two categories. The first categories included the anticancer effects of the herbal compounds against all cancer types (Table 1-3). The second category included articles that focused on the potential anticancer effects of herbal compounds against breast cancer. The articles from the second category were then critically analyzed.

4. Discussion

4.1 Targets of Herbal Medicinal Compounds

4.1.1 Targeting the Cell Cycle

The phytochemical given to the cancer cell lines cause changes in cell cycle. Phytochemicals alters the cell signaling pathways and modulates the apoptosis, proliferation and survival of cancer cells^{51,52}. The interaction of Cyclin-Dependent Kinase Inhibitors (CDKIs) and cyclin which are the two subunits of Cyclin-Dependent Kinases (CDKs) is necessary for its activity. The CDKs can be regulated to arrest the cell cycle at any stage⁵³. The reduced expression of Cyclin D1 and E, down regulation of CDK4/6 and CDK2, by various phytochemicals in particular flavonoids or curcumin is due to their ability to arrest the cell cycle at g1 phase in cancer cell^{54,55}. Various phytochemicals causes increase in the synthesis of CDK1 and it is binding with CDK which inhibits the activity of CDK, known to be responsible for the transition from G1 to S phase⁵⁶. Numerous phytonutrients exhibited a strong inhibition and arrested the cell cycle at G2 phase^{57,58}. During the G2-M transition-linked cellular changes, a fundamental role was demonstrated by Cdc2 kinase activity and the modulations in chk1/2, cdc25 and cyclin B1, along with p21/cip1 and p53, were effected significantly. The phytochemicals of soy and garlic such as curcumin and isoflavones have been reported to reduce the activity of CDC2 kinase and arrest the cell cycle at G2-M checkpoint, resulting in the inhibition of the proliferation of tumor cell⁵⁸⁻⁶⁰.

Table 1. Evaluation of articles, reporting the anticancer potential of plants-derived compounds in cancer models

Plants specie	Dose of compounds for cancer induction	Model organism	Mechanism of Action of cancer induce diet	Anticancer effects	Refs.
Rosemary	Mammary carcinogenesis was induced with DMBA in rats	200 mg/kg of bodyweight of organism	Activation of genetic pathway for tumor formation by mutations in Hras codon that is supposed to involve in carcinogenic activity	Antioxidant, Anti-inflammatory	8
Blueberries	Mammary carcinogenesis was induced with Estradiol-In rats	5% of diet contain estradiol	Activation of ROS, Interfere with estrogen generation of oxidative stress RESULT TUMOUR FORMATION	increases antioxidant activity, Prevent damaging of DNA	9
Blueberries	Tumor was induced in mice with MDA-MB-231	5% to 10% of diet contain MDA-MB-231	Tumor formation result metastases, proliferation, and apoptosis	Increases antioxidant activity in the blood	10
Blue or black berries	Mammary carcinogenesis was induced with Estrogen in rats	Supplied 5% as diet	Stimulate cell proliferation and expression of CYP1A1 and ER α	Increases antioxidant activity in the blood	11
Caraway	Mammary carcinogenesis was induced with Estrogen in rat	7.5% of diet contain estrogen	Formation of tumor, activation of apoptosis pathway, expression of cyclin D1 cytochrome c, expression of ER β and ER α	Having anti-inflammatory activity	10
Cyclopia	orthotopic	100g-300g of diet contain orthotopic	Tumor formation		11
Subternata	Mammary carcinogenesis was induced in LA7 cells	500 mg/kg of body weight	Tumor formation		12
Dunaliella	Mammary carcinogenesis was induced with DMBA in rats	1000 mg/kg of body weight	Tumor formation cell proliferation,	Induce apoptosis	13
Taraxacumofficinale	Mammary carcinogenesis was induced with DMBA in rats	500 mg/kg of body weight	Trigger the formation of cancer by activating the apoptotic pathway, higher Akt1, Map3k1, Erbb2, Pdk1 expression	inhibit the proliferation melanoma cells	14
Chlorella	Mammary carcinogenesis was induced with NMU in rats	3 g/kg to 30 g/kg of body weight	Induce tumor formation and latency by apoptosis	Having cytotoxic activity	15
Barley grass	Mammary carcinogenesis was induced with NMU in rats	Chow of 3 g/kg to 30 g/kg	Regulation of tumor formation result from oxidation, proliferation and Apoptosis	Inhibit tumor growth	16

Mixture of polyphenol and fruit peel	Mammary carcinogenesis was induced with NMU in rats	Chow of 3 g/kg to 30 g/kg	Histopathological tumor, proliferation, sign of apoptosis, angiogenesis	Having anti-carcinogenic activity	17
Origanum vulgare L	Mammary carcinogenesis was induced with NMU in rats	Chow of 3 g/kg to 30 g/kg	Signs of tumor, cell division, Apoptosis and angiogenesis and improve tumor histopathology by this plant species, lipid oxidation, anti-BCSCs effects	Having antioxidant activity	18
Syzygium aromaticum. L	Mammary carcinogenesis was induced with NMU in rats	Chow of 1g/kg to 10g/kg	Tumour formation, apoptosis sign, and improve epigenetic modulation, modulation of lipid	Having lot of antioxidant content	19
Pomegranate	Mammary carcinogenesis was induced with DMBA in rats	0.2–1.0–5.0 g/kg of body weight	induction of apoptosis pathway cytochrome c		12,13

Table 3. Studies reporting the inhibition of pathways in breast cancer studies by plants-derived compounds

Natural compound	Chemotherapeutic drug	Signal pathway	Refs.
Curcumin	Rhtrail	FEN1 DR5/IAP	36, 37
Quercetin	Rhtrail	c-FLIP/DR5	38
Emodin	Tamoxifen	Ras/ERK	39
Resveratrol	Doxorubicin	HSP-27	40
Resveratrol	Doxorubicin	Carbonyl reductase 1	41
Formononetin	Metformin	ERK1/2/Bcl-2	7
Crassin	Doxorubicin	Apoptosis-ROS	42
Enterolactone	+	Apoptosis	43
Secoisolariciresinol	+	Antiproliferative, pathway ROS production pathway.	43
Nordihydroguaiaretic acid	Cisplatin	ROS	44
Trans-nerolidol	Doxorubicin	Doxorubicin accumulation	45
Wogonin	Doxorubicin	Nrf2	46
Biochanin A	Daunorubicin	Not investigated	47
Glabridin	Doxorubicin	Not investigated	48
Ursolic acid	Doxorubicin	Not investigated	49
Mangiferin	+	p-Glycoprotein,	50

Table 2. Clinical and epidemiological studies, reporting the correlation of plants-derived compounds with breast cancer

Plants specie	Study design	Volunteer	Results	Refs.
Cruciferous	Meta-analysis	18673 volunteer of breast cancer	Lower breast cancer risk	20
Peach and Berries	population study	75929 postmenopausal women as volunteer	Proved to effective so low risk of postmenopausal	21
Soy, Fruit and Vegetable	Population study	629 Breast cancer women patients	Protective role in breast cancer	22
Soy	KOHBRA study	2271 breast cancer patients	Lower the risk of breast cancer in the carrier of mutations in BRCA	23
Green tea	Referent study	Control of 434 and 439 breast cancer patients	Reduced the risk in premenopausal breast cancer	24
Tea	Referent study	4501 controls and 5082 breast cancer patients,	Reduced of BC risk in young women	25
Diet rich in fiber	Referent study	2571 controls and 2135 breast cancer patients,	Reduced BC risk in ER-PR	26
Allium vegetable	Referent study	310 control and 285 breast cancer patients	Lowers the breast cancer risk	27
Mediterranean rich diet	Referent study	1017 control and breast cancer patients,	Reduced the risk in breast cancer	28
Mediterranean rich diet	Longitudinal study	2381 breast cancer patients	Reduced breast cancer risk	29
Diet rich in Phytochemicals	Referent study	175 Control and 100 BC patients	reduced breast cancer risk	30
Salad and Fruit	Longitudinal study	815 breast cancer patients	reduced breast cancer risk	31
Scutellariabarbata Extract	Clinical study	21 breast cancer patients	Antitumor activity	32
Scutellariabarbata Extract	Clinical study-phase	27 breast cancer patients	Promising clinical result	33
Chinese herbal Barbata	Clinical study	182 breast cancer patients	Metastatic Breast Cancer patients survive Long time	34
Preparation of Omega-3 fatty acid	Clinical study	266 post-menopausal individuals	Reduced the density of breast risk associated with obesity in breast cancer	35

4.1.2 Causing Cell Apoptosis

It has been reported that the programmed cell death of cancer cells due to various phytochemicals is because of their ability to arrest the cell at G1-S and G2-M transition. Antioxidant effects and chemoprevention against cancers are exhibited by several phytochemicals^{61,62}. Phyto nutrients affects both the intrinsic and extrinsic pathways of apoptosis mediated by their anticancer properties, activating caspase-3 which is downstream effector proteases (caspases)^{63,64}. Quercetin, curcumin, tea flavonoids and genistein, have been shown to down regulate the signaling pathways of EGFR, ERK and Akt and activates JNK signaling which exhibits pro-apoptotic and anti-proliferative effect^{65,66}. In addition to antioxidant properties majority of the phytochemicals are known to induce oxidative stress as well. Poly-phenolic compounds behave as both antioxidants and pro-oxidants depending upon the cellular concentration of ROS⁶⁷. Usually, phytochemicals causes disproportion in the redox status of the cell by the production of ROS, which modifies the pathways of apoptosis through mitochondria and p38 MAP kinase^{68,69}. As a result, the ROS generated by phytochemicals damages the DNA that leads to programmed death of tumor cells⁷⁰. This clearly suggests that several extracts of plant and phytochemicals exhibits inhibition of signal proteins or molecules associated with the survival, stress and death pathways of the cell.

4.1.3 Angiogenesis

Tumor growth results in the formation of new blood vessels from the pre-existing ones by angiogenesis. It is a critical step in the progression of tumor. Thus, angiogenesis has gained an attention as an important target in the treatment of several cancers. A monoclonal antibody known as Bevacizumab is the first FDA approved antiangiogenic drug. This drug targets the Vascular Endothelial Growth Factor A (VEGF-A), which is an essential factor for angiogenesis. There are more than 10 antiangiogenesis drugs which are in clinical use nowadays. There are few natural compounds which have been reported as antiangiogenic compounds. Previous reviews by Mirossay *et al.* (2018) and Mojziset *al.* (2008) have discussed chalcones and flavonoids as the inhibitors of angiogenesis^{71,72}. Moreover, some other phenolic compounds, including resveratrol, Gallic acid and curcumin also show antiangiogenic effects^{73,74}. Several marine-derived compounds were reported to inhibit angiogenesis after extensive experimental research against cancer⁷⁵. Acquired resistance results in the failure of treatment procedures in most of the cancer

patients. In tumor mass a group of cells are present known as Cancer Stem Cells (CSC). These cells having aggressive phenotypes are thought to be responsible for the failure of cancer treatments such as chemotherapy, radiotherapy and immune therapy^{76,77}. The maintenance and progression of tumor, recurrence of cancer and metastasis are due to the resistance in cancer treatment. Chemo-resistance can be overcome by targeting these cancer stem cells. This can be an effective strategy to treat cancer. The reported literature demonstrated that the signaling systems in CSCs which are involved in the self-renewal and proliferation of CSCs can be intervened by phytochemicals⁷⁸⁻⁸⁰. The use of phytochemicals poses a great strategy to eradicate CSCs. Thus, these molecules may help the researchers to develop novel drugs that can target and eradicate breast CSCs⁸¹.

4.1.4 Epigenome

According to the research, the sporadic breast cancer can be initiated and spread by epigenetic modifications. The risk of cancer development in an individual can be predicted, which is the fast growing field within clinical medicine. Research in oncology outlines the specific epigenetic aberrations, such as methylation status of tumor activating and suppressing genes, histones modification, and regulation noncoding RNA-linked genes^{82,83}. Epigenetic alterations and mutations in enzymes responsible for the regulation of chromatin may results in the unusual chemical modification of histones and alter the synthesis of histone modifying enzymes. Phytochemicals efficiently causes epigenetic changes and thus can play role in cancer chemoprevention⁸³. Various *in vivo* and *in vitro* studies demonstrated the role of phytochemicals in the acetylation and methylation of histone proteins. Isolated phytochemicals or their combination alters the oncogenic or tumor suppressive miRNAs expression as demonstrated by numerous preclinical and few clinical studies on breast cancer cells^{84,85}. The malignant related genes may get silenced by methylation. Hyper methylation of the promoter region of tumor suppressor genes plays a crucial in the development of cancer⁸⁶. The miRNA expression and DNA methylation along with better understanding of pathways involved in cancerous cellular signaling could serve in the establishment of effective chemo preventive and therapeutic approaches. For this purpose, several phytochemicals showed potential source to alter the epigenetics⁸³.

4.2 Plant-derived Compounds Potential in Preclinical Breast Cancer Studies

The anticancer activity of phytochemicals and their mode of action is evaluated by several preclinical and few clinical studies. Numerous plant derived compounds were assessed to describe their potential role in treating neoplastic disease, which findings may start a new potential site in cancer therapy research.

4.2.1 In-Vitro Studies

Phytochemicals could serve as a potential source to prevent and treat breast cancer and several other types of cancer. *Origanum vulgare* L., *Chlorella pyrenoidosa*, *Syzygium aromaticum* L., young barley grass, and fruit peel polyphenols were evaluated for their anticancer activities using an in-vitro model of breast carcinoma. The antioxidant, antiviral, antimicrobial, anti-inflammatory properties of phytochemicals present in chlorella makes it an important functional food^{87,88}. The in vitro study in human breast adenocarcinoma cells showed proapoptotic and anti-proliferative effects of *Chlorella pyrenoidosa*. The extract of *Chlorella pyrenoidosa* causes the ROS accumulation in MCF-7 cells. Results demonstrated that the proapoptosis caused by chlorella extracts is due to the production of ROS¹⁵. Another vitro study conducted by Kunte and Desai (2018) revealed that the extracts of *Chlorella minutissima* involved in the inhibition of MMP-1, -2, and -9 synthesis by interfering at both mRNA and protein level and causes inhibition of the active forms of MMP-2 and -9 in breast cancer model⁸⁹. The extract of young barley, which is domesticated crop, contains many phenolic compounds such as leucoanthocyanidins, catechins, and flavones including 2-O-glucosylvitexin saponarin, coumarins and luteolin⁹⁰. Evidence shows the anticancer activities of extracts of young barley^{91,92}. Another study conducted on in vitro breast cancer model demonstrated that the young barley causes caspase-dependent proapoptosis¹⁶. This effect is due to the arrest of cell cycle at S phase, resulting into apoptosis. Furthermore, it was shown that the apoptotic activity of barley extracts is due to the accumulation of ROS in the breast cancer cells⁹³. These results suggested that young barley could serve as a safe dietary agent in the cancer chemoprevention in BC models. Researchers are still trying to find out the possible mechanisms.

The volatile oil of an aromatic plant known as *Origanum vulgare* L. contains excessive amounts of phenolic compounds and monoterpenoids that exhibit antioxidant and antimicrobial activities^{94,95}. Recently,

the in-vitro cancer lines were used to evaluate the antiproliferative effects of oregano crude extract⁹⁶. Kubatka *et al.* demonstrated that oregano activates caspase-7 and induces apoptosis in MCF-7 cells. Moreover, oregano induces apoptosis by the deactivation of protein Bcl-218. Several studies showed interesting results in in vitro breast cancer model using *Origanum majorana* MDA-MB-231 BC cells were also assessed to determine the cytotoxic effects of *O. majorana* extracts⁹⁷. Al Dhaheeri *et al.* demonstrated the effects of *O. majorana* in the triple negative MDA-MB-231 cells⁹⁸. They demonstrated that the cytotoxic activity is dependent on the concentrations of crude extract used. Low concentration of oregano crude extract induces mitotic arrest by damaging DNA and increases the expression of p21 and survivin which are CDK inhibitors.

Conversely, major apoptosis caused by the activating TNF-alpha extrinsic pathway was induced by high oregano concentrations. It is accompanied by the activation of caspase-8, high levels of the damage to DNA, depletion of p53 mutations, and, interestingly, deficiency of surviving proteins. *Majorana* also has anti-invasive and anti-metastatic effects against the cell line of breast cancer. Importantly, these effects are mediated by controlling cell migration, adhesion or invasion by modulating the activities or expression of proteins, such as MMP-9, E-cadherin, uPAR, MMP-2, VEGF and ICAM-1 at least in part by inhibiting the signaling pathways of NO and NF- κ B⁹⁹. Owing mainly to his antioxidant and antimicrobial activities, Clove attracted attention¹⁰⁰. The anti-proliferative properties of the extracts of clove or eugenol have also been studied in the last decade. The strong anti-proliferative effect of these extracts was observed. The clove extract treated MCF-7 cells have been shown to contribute to cell aggregation in the S process shortly after 24 hours. In addition, major cell augmentation in the sub-G0/G1 fraction was also detected. In addition, the dysregulation of mitochondria was associated with activation of caspase, inhibition of Bcl-2 activity, thus leads to the programmed death of the cell¹⁹. The anti-proliferative efficacy in five separate cancer cell lines was studied¹⁰¹. Later, in both cancer cell lines the growth inhibition by the extracts of clove was confirmed by Aisha *et al.*¹⁰²

The anticancer effects of single flavonoids have been tested by several in vitro studies^{103,104}. However, flavonoid combination has higher anticancer efficacy compared with a single flavonoid as shown by several studies. The polyphenols (Flavin 7) present in the fruit peel also inhibits the growth of MCF-7 cell by arresting the cell cycle at G1 phase¹⁷. Later it was found that the

dysfunction of mitochondria accompanied by caspase-dependent apoptosis was caused by Flavin-7. In addition, modulation was also demonstrated for signaling pathways. In addition, the role of ROS in cell death induced by Flavin-7 was also clearly established¹⁰⁵. More recently, Kim *et al.* and Shanmugapriya *et al.* have also reported that ROS production in breast cancer cells by phenol rich plant extracts induces apoptosis of these cell^{104,106}. In MCF-7-treated cells, both authors revealed that cell death is associated with the increase in the production of ROS. Thus, many other functional plant foods with reported in vitro anti-cancer activities against breast cancer are also available^{107,108}.

4.2.2 In Vivo Studies

In in vivo breast cancer models, plant-derived foods have proven anticancer properties. Several animal studies have shown that plant derived foods minimize the threat of experimental BC significantly. 7,12-Di-methyl-Benz(a) Anthracene (DMBA)-induced rat mammary carcinogenesis was inhibited effectively by the extracts of rosemary and its isolated component carnosol. Rosemary reduces the tumor frequency in each rat by 74% and carnosol did the similar reduction by 65% compared with controls. Moreover as compared to controls, rosemary as well as carnosol efficiently decreased the in vivo development of rat mammary DMBA-DNA adducts by 44% and 40% respectively⁸.

In other findings, it has been reported by Jeyabalan *et al.* that blueberries minimizes the occurrence of tumor of estradiol mammary carcinoma in female rats by 48% and 58% and also have therapeutic and chemopreventive mode⁹. Anticancer effects were due to the down-regulation of expression of genes ER- α and CYP1A1 and change in level of miRNA in mammary tissues. Adam *et al.* worked on xenograft model of MDA-MB-231 cells in female nude mice to evaluate the effects of blueberry powder in two different concentrations (5% and 10%)¹⁰. As a result blueberries showed significant reduction of tumor volume in which 5% showed 75% reduction and 10% exhibited 60% reduction as compared to controls. However, 25% less lymph node metastasis as compared to control was developed by the mice fed with 5% of the blueberries powder. After a high dose of therapy, blueberries showed significant anti-proliferative activity in treated groups. It also altered the expression of IL-13, IFN γ and Wnt thrombospondin-2. The anticancer properties of black and blue berries were compared by Ravoori *et al.* in rat mammary oncogenesis mediated by estrogen¹¹. Both significantly prolonged the expectancy of tumor by 24 and

39 days, respectively. Moreover, blueberries significantly reduced the tumor frequency and proliferation of mammary tissues. Blueberries down-regulate the CYP1A expressions while blackberries down-regulate the ER α expression meritoriously. Isoflavone-rich soy germ effectively reduced the development of mammary cancer in rats induced by PhIP. Histopathologically, it has been verified that less malignant and non-fibrous features of carcinoma treated with soy germ¹⁰⁹. Another study revealed that by 17 β -estradiol of caraway significantly delayed and prevented tumorigenesis in rat. It has been described that with caraway in diet reduced tumor frequency by 40% and tumor volume by 53% in treated animals versus control. Caraway down-regulate the expression of estrogen receptor α , cyclin D1, CYP1B1 and CYP1A1. Bishayee *et al.* demonstrated that pomegranate emulsion showed outstanding chemopreventive activity in induced-DMBA mammary oncogenesis in rat¹³. Different quantities (0.2, 1, 5g/kg) of pomegranate reduced the tumor frequency, tumor weight, tumor burden as compared to controls. Pomegranate specifically enhanced the expressions of caspase-3/-7/-9, Bad, Bax/bcl-2 ratio, cytochrome c and poly (ADP ribose) polymerase, and showed antiapoptotic and anti-proliferative activities in the cancer tissues of rat. In addition, the same authors¹² revealed that pomegranate decreased the expression of intratumor ER- α and ER- β and reduced the ER- α : ER- β ratio. PE silenced the expression of cyclin D1 and Wnt signaling (via β -catenin) in mammary carcinomas of rat induced by DMBA. In another study, the extracts of *Cyclopiasubternata* reduced the volume of mammary tumor at the same rate as tamoxifen in an orthotopic rat model. Notably, in animals no side effects of tamoxifen and letrozole were reported¹¹⁰. The in vivo anticancer effects of plant derived foods against mammary carcinoma were also demonstrated by several recently published papers^{14,111}. Recently, the chemo-preventive efficacy of numerous plant derived foods against rat mammary carcinogenesis was also demonstrated. *Origanum vulgare* L. (0.1%) administered in diet effectively inhibited the tumor frequency by 55.5%, repressed tumor occurrence by 44%, and decreases the volume of tumor mass by 44.5% in comparison to control group¹⁸. The expression of VEGFR-2, CD24, EpCam, and Ki67 has been shown to down regulate in rat cancer cells. On the other hand, same dosage of oregano increased the caspase-3 expression. 3% oregano increased the tumor latency by 12.5 days. Moreover, in in vivo cancer cells the expression of CD24, VEGFR-2, Bcl-2, and EpCam got down-regulated and the expression of caspase-3 has been up regulated. Histopathological analysis showed that the tumor ratio in

comparison to control group was decreased by the use of oragano. In another study, the chemo-preventive effects against mammary carcinogenesis in rats were analyzed by providing 0.1% and 1% of *Syzygium aromaticum* L. in diet¹⁹. According to the results, the tumor frequency was suppressed by 47.5% and 58.5% by administering clove buds in dose dependent manner as compared with control. Immunohistochemical analysis of carcinoma cells demonstrated that high dose of clove administration was linked with the down regulation in expression of Ki67, Bcl-2, and VEGFA, CD24 and CD44.¹⁹

Similarly, the same group showed enhanced expression of ALDH 1, caspase-3 and Bax. Besides, in both clove groups the level of MDA was decreased considerably in mammary tumors. After oregano treatment, the analyses of histone modifications revealed that trimethylations and acetylations of lysine were increased in carcinomas. Clove administration in rats did not show any considerable changes in methylation of promoter of RASSF1A and TIMP3. Our experimental findings (0.3% and 3% in the diet) with dark fruit peels revealed that frequency of tumor decreased by 58% as compared with control. Moreover, it has also been demonstrated that latency was lengthened by 8 days and tumor frequency was also decreased by 24% as compared with control. In higher and low dose group carcinomas, its chemoprevention feature showed significantly decreased in ratio. Additionally, the analysis of rat carcinoma cells demonstrated the increased expression of caspase-3 and decrease in the VEGFR-2, Bcl-2, and Ki67 expression by the intake of dark fruit peels in high-dose¹⁷. However, the same breast cancer rat models were used to test the anticancer efficacy of the two green foods i.e. young barley grass and *Chlorella pyrenoidosa* (doses of 0.3% and 3% in the diet). It was observed that *Chlorella* reduced the frequency of tumor by 61% and extends the tumor latency by 12.5 days as compared with control group¹⁵. Higher dose of *Chlorella* increases the expression of caspase-7 by 73.5% and decreases the expression of vascular endothelial growth factor receptor-2 by 19% in rat tumor cells. Only minute antitumor effect of 0.3% barley was observed in carcinomas and no improvements were detected by increasing the dose of barley. The treated groups showed enhanced expression of caspase-3 and reduced expression of Ki67 as revealed by Immunohistochemical analysis tumor cells in rats.¹⁵

5. Conclusions

The critical assessment of the literature showed a wide range of the anticancer effects of herbal compounds as

synergistic or additive effects against breast cancer that could aid in designing specified treatment strategies. However, there is lack of literature showing the validation of these findings in clinical trials. Therefore, the animal studies and clinical trials are needed to be conducted for the evaluation of these herbal compounds and make them a step closer towards potential therapeutic strategy against breast cancer. The anti-neoplastic efficiency of these herbal compounds is sometimes overlaid by many unidentified high-risk factors in females, which are not considered in laboratory studies. Thus, more elaborative studies, considering well-designed and strictly controlled research conditions and clinical trials are needed in this regard. The adverse effects of herbal compounds in cancer patients could be attributed to the inappropriate use of drugs combination. Additionally, the herbal compounds can also promote tumor or act as carcinogens. Therefore, given the inappropriate interference of herbal compounds in the treatment of cancer, it is highly recommended to be more careful in patients having hormonal or target therapy.

6. Acknowledgements

None

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