Chemoprevention of breast cancer; toward better outcomes
Waleed Hamdi Almaramhy

ABSTRACT
Breast cancer is one of the major burdens that affect women and their life. Many studies showed that many chemopreventive agents have anticancer effect; however, some studies were contrary to them. This article reviewed and summarized the available medical evidences of chemoprevention in breast cancer. An extensive literature search was carried out in the following databases including: Medline (PubMed interface), Scopus, and Google Scholar to identify articles that discussed the role of chemoprevention in breast cancer. The following keywords were used independently and in combination including carcinogenesis, breast cancer, and chemoprevention in the search process. The retrieved articles were further explored in order to find other relevant resources. Although various chemopreventive agents have been investigated in breast cancer and there have been major achievements in this field, more research work and clinical trials are needed to determine the therapeutic efficiencies of these agents in human being.

Keywords: Chemoprevention, breast cancer, carcinogenesis.

Introduction
Cancer chemoprevention is the use of a natural, synthetic, or biological substance over a period of time to delay or prevent the development of cancerous cells [1].

De Flora and collaborators categorized agents of chemoprevention into three types, namely, primary, secondary, and tertiary factors. The primary agents prevent the occurrence of cancer in a healthy person by preventing mutagenesis and carcinogenesis. The secondary prevention agents play role against the early and pre-clinical stages of tumorigenesis by inhibiting the progression of tumors. Activities inhibited during tumor progression include signal transduction modulation, antioxidant activity, immune and hormone modulation, and inhibition of angiogenesis. In cancer patients, tertiary prevention is achieved by avoiding metastasis and invasion, especially after treatment. This also entails modulation of the cell’s adhesion molecules, prevention of proteases that degrade the extracellular matrix and exerting anti-metastatic genes activation [2,3]. For an ideal chemoprevention agent, it should have the following vital requirements including effectiveness against at least one carcinogenesis process, safe for short and prolonged use, easy to use and with less cost. In order to choose the susceptible patient, the pharmaco-genetical features of the agent should be explored extensively [4].

The effective applications of various chemopreventive agents are dependent on the action of mechanism at the cellular, molecular, tissue as well as the entire organ and system levels. Carcinogenesis entails a number of stages of molecular and biochemical alteration within the tissue cells where cancer develops. Also, it entails the gradual accumulation of the primary agent alterations that result to malignancy upon multi-step cellular transformations, proliferation, mutation, propagation, angiogenesis, invasion as well as metastasis.

Figure 1 demonstrates the major stages in multi-stage carcinogenesis. These stages are interlinked by a number of chemical, biological, physical, or psychological stressors via epigenetic or genetic alterations [5].

Materials and Methods
An extensive literature search was carried out in the following databases including Medline (PubMed interface), Scopus, and Google Scholar to identify articles that discussed the role of chemoprevention in breast cancer in the period between 2001 to 2020. The
following keywords were used independently and in combination including: carcinogenesis, breast cancer, and chemoprevention in the search process. The retrieved articles were further explored in order to find other relevant resources. Irrelevant and duplicated articles were excluded, and we included the others.

Discussion

This review focuses on several potential pathways that facilitate the anti-neoplastic properties in these compounds, thus inhibiting the progression of breast cancer. Examples of such compounds are discussed below:

**The dietary elements of chemoprevention**

**Dietary blueberry**

Currently, berries are gaining popularity for their therapeutic and chemopreventive potential against cancerous cells. These berries are rich in a component known as anthocyanins, which are good for inhibiting cancer development by protecting cells from damage that comes as a result of reactive oxygen species. The core structure of anthocyanins composed of six anthocyanidins including malvidin, delphinidin, cyanidin, peumidin, peonidin, and pelargonidin [6]. These anthocyanins have di-, tricyclic, and mono-sugars attached to the core structure of anthocyanidin and they have high antioxidant characteristics. A lot of attention has been shifted toward berries lately owing to their potential for cancer chemoprevention. The anthocyanins trigger phase II enzymes (that metabolize xenobiotics and carcinogens), induce apoptosis, and demonstrate anti-inflammatory, antiproliferative, and anti-angiogenic features [6].

In a recent study, five main anthocyanidins were mixed to form an equimolar mixture and then used to explore the effects of anthocyanins on lung cancer cells. The findings from the study demonstrated that anthocyanidins have a great potential to inhibit proliferation of cancerous cell lines both in vivo and in cell culture [7].

Also, previous studies have demonstrated that a diet that is supplemented by blueberries has the potential to protect human cells against mammary tumorigenesis that is mediated by 17β-estradiol (E2). A study was conducted to test the therapeutic and preventive activities of blueberry powder supplemented diet (i.e., 50:50 mixture of Rube and Tifblue). The animals under study were given a diet with 5% blueberries, either 3 months after or 2 weeks before E2 treatment for therapeutic and preventive groups, respectively. From the study, the two interventions minimized tumor latency for mammal tumors for a period of 37 and 28 days, respectively [6].

In both modes, the multiplicity and volume of the tumor was significantly reduced. Such an effect on the mammary tumorigenesis is due to Estrogen receptor (ER)-α gene...
expression and Cytochrome P450 Family 1 Subfamily A Member 1 (CYP) 1A1 down regulation which are suitable modulations for the microRNA levels. Based on these data, it is evident that blueberries are effective in preventing mammary tumorigenesis mediated by E2 in both therapeutic and preventive modes [6].

**Vitamin D**

Based on many research studies, there is growing evidence showing vitamin D, as well as its metabolites could exert immune modulatory, pro-differentiating, and anti-proliferative effects on the neoplastic cells both in vitro and in vivo via delaying the growth of a tumor. Various clinical and experimental results propose that vitamin D as well as its analogues could be appropriate to inhibit malignant transformation, and/or malignant progression of many different tumors including the breast cancer. Based on these observations, there is a likelihood that vitamin D might be used as a potential anticancer and chemopreventive agent [8].

In addition, these studies also demonstrated that vitamin D exerts specific receptors that have a higher affinity for the growth inhibitory agents [i.e., 1, 25(OH)2 D3]. To supplement these findings, other in vitro studies suggested that antisense oligonucleotides, which minimize the intracellular levels of vitamin D receptors are able to minimize tumor sensitivity to anti-proliferative impacts of the 1, 25(OH)2 D3 [9].

On the other hand, overexpression of vitamin D receptors leads to potentiation of cellular developmental arrest [9]. According to previous studies, 1, 25(OH), D3 inhibits the proliferation of ovarian cancer cells by inhibiting the human telomerase reverse transcriptase mRNA via a small non-coded RNA [7].

Equally, the potential of 1, 25(OH)2 D3 to minimize human telomerase reverse transcriptase mRNA via as well as to inhibit the growth of ovarian cancer cells was compromised when miR-498 was absent. This came as a result of cell line depletion and tumor-bearing mice. Lastly, some studies suggested that vitamin D fosters a number of malignant cells in the human body to undergo differentiation to become mature phenotypes. Vitamin D also induces cell death through apoptosis depending to the type of cells [8].

**Chemopreventive phytochemicals**

The process of carcinogenesis could be affected by phytochemicals. This is because some of the phytochemicals inhibit procarcinogens’ metabolic activation to their final electrophilic species. Also, they inhibit procarcinogens from interacting with DNA. Therefore, these agents block the initiation of tumors. Moreover, the dietary blocking agents trigger carcinogens detoxification, which results in their excretion from the body. Some of the other phytochemicals inhibit the final stages of carcinogenesis process such as progression [10].

All these natural compounds have anti-metastatic, anti-inflammatory, anti-angiogenic, anti-proliferative, and anti-neoplastic features that inhibits breast cancer [8]. This article reviewed and summarized the available medical evidences of chemoprevention in breast cancer.

**Chemopreventive natural compounds**

**Green tea**

There are various publications with controversial findings regarding the intake of green tea. A recent Cohort study done by Zhang et al. [11] suggested that green tea consumption of five cups or more per week might be linked to a lower incidence of breast cancer. Moreover, an updated meta-analysis involved findings from 14 studies found that green tea drinkers were shown to have a lower risk of breast cancer [12].

This is due to the fact that it has anti-oxidative polyphenolic compounds such as epigallocatechin-3-gallate (ECG) which interferes with several cell signaling pathways as well as several targets in the cells, that might interact with one another, thus reducing the chances of carcinogenesis [13]. This is achieved through various mechanisms including prevention of phase one CYP enzymes, induction of antioxidant and phase II detoxification enzymes, inhibition of cell cycle progressions, anti-inflammatory effect, metastasis process mediation, and control of the pro-apoptotic properties [14]. Moreover, the anti-carcinogenic effects might come as a result of indirect and/or direct interaction with various molecular targets like Activator protein 1, NSAID activated gene (NAG-1), Platelet-derived growth factor (PDGF), and 5α-reductase. Also, the growth inhibitors of the ECG have demonstrated to sensitize the cancerous cells only rather than the normal ones [14].

Contrary to the constant findings of inhibitory effects of green tea and tea polyphenols toward the development of tumors induced by carcinogens in various experimental animal models, the findings from the human population is often mixed. Green tea drinking has been shown to have a protective effect in the development of digestive duct cancer as well as an inhibitory role in the development of precancerous lesions of the oral tract in a number of interventional and observational studies. There are a number of publications with controversial findings regarding the intake of green tea. A recent meta-analysis study involved findings from eight different epidemiological studies that were conducted on the intake of green tea and breast cancer risks [15]. The summary on the risk of breast cancer that was based on three case controls intake as well as cancer risks at different organ sites. The data neither excludes nor confirms a particular role of green tea on cancer prevention. These findings are contrary to the relatively constant evidence derived from other experimental researches.

There are various reasons to explain the inconsistent findings from published epidemiological studies. First, the
Chemoprevention of breast cancer

exposure of human beings to green tea and tea polyphenols is limited, a range of one to two orders compared to those applied in vivo and in vitro experiments [15].

Alcohol consumption and residual cigarette smoking effect contributes a lot to these different results among various studies. Also, the severe effects of hot tea beverages might mask or complicate the association between green tea and cancer risks given the varying tea consumption differences among human populations. In addition, heterogeneity of the amount of tea consumed and the nourishments in various populations is also likely to contribute to varying results in the association of tea consumption to cancer risks [15].

More extensive prospective observational studies were conducted. It was concluded that phase three intervention experiments provided definitive data while assessing the deleterious or beneficial effects of tea consumption on the development of cancer across human populations [10]. Since the factors that cause cancer are likely to vary across various populations, green tea intake might influence carcinogenesis in specific situations rather than triggering broad effects in various cancers across the whole population. Therefore, the population that is likely to benefit from the consumption of green tea is required to be identified. These interventional studies across different populations are likely to come up with vital information regarding the protective role of tea polyphenols and green tea on cancer of specific organs or particular populations. Provided that green tea is allowed in moderate doses and it could be administered safely with no observed adverse effects, then green-tea and tea polyphenols could be recommended for human consumption [10].

Curcumin

Curcumin refers to dietary pigments naturally derived from plant turmeric roots (Curcuma longa linn). It possesses anti-inflammatory, anti-metastatic, and anti-neoplastic properties that prevent the development of tumors. Curcumin is considered as a cancer growth inhibitor and cancer chemotherapeutic and chemopreventive agent. This dietary pigment exerts in vitro anti-neoplastic properties through regulation of B-cell lymphoma, matrix metalloproteinase (MMP), Bax, nuclear factor (NF)-E2-related factor-2, flab endonuclease as well as protein kinase B signaling/phosphoinositide-3-kinase [16].

There are various studies conducted on chemotherapeutic and chemopreventive properties of curcumin on breast cancer risks. Curcumin controls the activity of the metastasis-facilitating enzyme, MMP-2 doses and regulates the invasive phenotype induced in the Michigan Cancer Foundation-10A (MCF10A) breast epithelial cells by the oncogene H-Ras [17]. Curcumin triggers cytotoxic effects on the cells of H-Ras induced MCF-10A. It could also induce the cells apoptosis through downregulation of Bel-2 and upregulation of Bax, which are two main apoptosis-linked genes products [18]. The same observations had been made in other cancerous cell lines of the human breast like MCF-7 and MDA-MB-231 cells [14,19]. In addition, F-box S-phase related proteins are highly involved in the progression of breast cancer, particularly Human epidermal growth factor receptor 2 (HER2)/ER-negative breast cancers [17]. Curcumin inhibits cell growth by inhibiting Skp2 and induction of p27 in MDA-MB-231 human breast cancer cells. Altogether, curcumin limits the growth of cancer cells, especially the HER2 or ER negative breast cancers.

Contrary to the consistent findings of curcumin as anti-cancer agent, one study has demonstrated that the effect of curcumin in cancer risk is limited [20]. Moreover, this study demonstrated that a mixture of Berberine and Curcumin synergistically inhibits the development of both MDA-MB-231 and MCF-7 cancerous cells as compared to when these compounds are used separately. Further studies revealed that the breast cancer suppressing properties of the two compounds were due to apoptosis induction as well as autophagic death of cells. This co-treatment induced significant apoptosis that was dependent on caspase and Extracellular signal-regulated protein kinases (ERK) pathways [20].

Sauchinone

This is a compound that has anti-cancer properties in MCF-7 human breast cells [21]. Sauchinone (SC) downregulates the proliferative and angiogenetic properties by minimizing Bel-2, cyclin D1, Vascular endothelial growth factor (VEGF) gene properties [22]. It also activates the caspase-3 compounds that perform a significant role in activation of apoptosis. SC could be utilized as a chemopreventive and chemotherapeutic agent in breast cancer [22].

Lycopene

This is another main carotenoid found in vegetables and fruits. It inhibits the development of different malignancies such as prostate and breast cancer [16,23]. The anti-cancer properties of Lycopene functions by suppressing the growth signaling factor, inducing apoptosis and changing antioxidant or phase II detoxifying enzymes [24]. Moreover, Lycopene regulates the invasion of tumor cells, angiogenesis, metastasis, thus inhibiting the growth and development of cancer [24].

Such anti-cancer properties reduce the chances of DNA damage from reactive oxygen species. There is a correlation between ERKs and Lycopene as well as protein kinase B (Akt) or mammalian target of rapamycin (mTOR) signaling pathways in breast cancer cells [16]. Moreover, Lycopene inhibits metastasis, invasion as well as proliferation of invasive breast cancer cells e.g., H-Ras-induced-MCF-10A breast cancer cells and MDA-MB-231 human breast cancer cells.
Lycopene inhibits Akt and ERKs activation. In breast cancer cells, it inhibits invasion, migration, and proliferation via activating ERKs and Akt signaling pathways [16].

Lycopene has anti-proliferative activities in the triple-negative breast cancer cells, in which estrogen receptors, progesterone receptors, and HER2 protein are all negative. It often induces apoptosis via Bax proteins through Akt phosphorylation inhibition, which serves a significant role in the process of apoptosis, cell survival as well as the down streaming of mTOR. Thus, apoptosis is induced by Lycopene through the prevention of Akt/mTOR signaling pathways in breast cancer [25]. In addition, Lycopene reduces cell viability and arrests cell cycles at various stages, which inhibits cell proliferation [26]. Another way through which Lycopene inhibits cancer cell development is by down-regulating the Skp2 signaling pathway. Skp2 plays a significant role in the progression of breast cancer, especially the ER/HER2 negative ones [10]. In G1 phase, cyclin D1 is highly overexpressed. Lycopene suppresses insulin-like growth factor (IGF-1)-induced cell cycle progression to S phase from G1 and minimizes the levels of cycline D1, thus inhibiting the development of the MCF-7 cells of the breast cancer [16].

**Denbinobin**

This is a substance that is generated from *Ephemerantha lonchophylla*. It is also referred to as 5-hydroxy-3, 7-dimethoxy-1, and 4-phenanthra-quinone. This compound is extracted from *Dendrobium moniliforme* stems [27]. Denbinobin has anti-angiogenesis, anti-inflammatory, apoptosis-inducing and anti-cancer properties to various types of human cancers. These properties are particularly relevant to NF-κB, Src kinase, as well as IGF-1 receptors of breast cancer cells. There is increased Src kinase activity within breast cancer cells, and it is linked to an invasive disease with poor prognosis. Denbinobin inhibits metastasis by inhibiting the activities of Src kinase within [27].

Moreover, Denbinobin prevents cancer metastasis by controlling Src-induced signaling pathways in breast cancer cells. Denbinobin could be used as a therapeutic factor for breast cancer. Cyclooxygenase-2 (COX-2) and nitric oxide synthase (iNOS) plays a critical role in many inflammatory illnesses. For instance, Denbinobin reduces the COX-2 and iNOS activity in a concentration-dependent manner by suppressing the activation of NF-κB. Denbinobin has anti-inflammatory features that serve as therapeutic agents of various inflammatory diseases [16].

The tumor inhibition and anti-angiogenic properties are linked with improved activities of the IGF-1R. Signaling of IGF-1 receptors results in enhanced proliferation of cells and apoptosis, which facilitates the development of cancer in human body [28,29]. Also, Denbinobin inhibits IGR-1 receptors activation as well as its down-streamed signaling pathway, thereby inhibiting angiogenesis [16].

**Drug chemoprevention**

Both raloxifene and tamoxifen are reported to prevent breast cancer in those women vulnerable to the disease. However, raloxifene was reported to have more favorable side effects since it causes less uterine cancers as well as thromboembolic activities. Another alternative for prevention of breast cancer in the near future are the aromatase inhibitors. This is based on their promising outcomes observed in a number of trials. Recently, a study conducted to test the use of aromatase inhibitors in chemoprevention yielded very promising results which were later published [4,30].

**Tamoxifen**

The risk of getting breast cancer was reduced by 20%-43% owing to the use of tamoxifen. However, the impact of tamoxifen on breast cancer has not been fully established. Tamoxifen minimizes the chances of ER-positive cancer of the breast by 62%, but it never affects the chances of individuals getting ER-positive breast cancer. Such risk reductions are more common in women with estrogen-induced high-risk pre-neoplasia like lobular carcinoma in situ and atypical hyperplasia that stands causes about 75% reduction of breast cancer. The risk for women who have strong breast cancer family backgrounds could significantly be reduced by tamoxifen. However, tamoxifen increases the chances of stroke, endometrial cancer, cataracts and venous thromboembolism. Such risks affect mostly older women [4,30].

**Raloxifene**

Raloxifene is a second-generation selective estrogen receptor modulator that was initially reported to decrease the risks of breast cancer by 76% in most osteoporotic women. That was involved in various outcomes of raloxifene evaluation trials. The succeeding clinical trials demonstrated that if raloxifene is taken at 60 mg per day for a period of 5 years, it could minimize the risks of breast cancer by 44% to 77% in postmenopausal women who are not candidates for the breast cancer risks [31].

Raloxifene trial and tamoxifen National Surgical Adjutant Breast and Bowel Project (NSABP) studies have compared both raloxifene and tamoxifen head to head. The most recent results, with an average follow up of about 81 months indicated that invasive breast cancer risk ratios favored tamoxifen. However, that was statistically significant for the non-invasive breast cancers. When these results were compared to the published initial results, it was evident that invasive breast cancer was more significant than non-invasive diseases. This is a clear suggestion that tamoxifen is
likely to become more effective with time. Based on the Study of Tamoxifen and Raloxifene (STAR) trial, raloxifene is considered safer than tamoxifene in women beyond menopause. Raloxifene does not raise risks of endometrial cancer. However, it is linked to increased risk of getting stroke that is same to tamoxifen. In the case of raloxifene, the risk of pulmonary embolism, cataracts and venous thromboembolism are lower [31].

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)

The usage of NSAIDs such as ibuprofen and aspirin, has been linked with reduced breast cancer risks. Takkouche et al. [32] conducted a meta-analysis involving 38 studies among which 16 studies were controlled studies; of which three controlled studies were performed in well-known cohorts and one clinical trial. From the experiment, the results indicated that NSAIDs minimized the chances of breast cancer.

Also, Kwan et al. [33] found out that the NSAIDs minimizes significantly the risk of breast cancer recurrence in individuals previously diagnosed with breast cancer. However, the underlying mechanisms on the effect of the NSAIDs on cancer of the breast are yet to be determined. There is one theory that is widely accepted regarding the effect of NSAIDs on breast cancer. This theory claims that NSAIDs suppress COXs, therefore inhibiting the development of prostacyclin, thromboxane and prostaglandins-induced inflammation [34]. This theory is further supported with experimental findings which indicated the existence of inflammatory response when transforming from intra-ductal proliferation into carcinoma in situ in the model of 7,12-Dimethylbenz[a]anthracene (DMBA)-transformed mammary tumor [35].

Another theory indicated that NSAIDs could induce the production of reactive oxygen species as well as suppressing NF-κB-induced signaling pathways. Nevertheless, it appeared that salicylates as well as other NSAIDs are agents with the ability to modulate various signaling pathways within cancer cells. In spite of the well-known anti-tumor effects of NSAIDs, there is inadequate knowledge on selectivity of the NSAIDs-induced anti-cancer properties [36].

Conclusion

Although various chemopreventive agents have been investigated in breast cancer cells and the major achievements in this field, more research work and clinical trials are needed to determine the therapeutic efficiencies of these agents in human beings.

Acknowledgement

The author would like to acknowledge the supervisor for his guidance all the time. He responded to my questions and queries. The author thank him for his advice and guidance, which had a great impact in completion of this article.

List of Abbreviations

- E2: 17β-estradiol
- COX-2: Cyclooxygenase-2
- ECG: Epigallocatechin-3-gallate
- ERK1/2: Extracellular signal-regulated protein kinases 1 or 2
- iNOS: Inducible nitric oxide synthase
- MMP: Matrix metalloproteinase
- NSAIDs: Non-steroidal anti-inflammatory drugs
- NF-Kb: Nuclear factor-κB
- AKT: Protein kinase B
- SC: Sauchinone

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent to participate

Not required.

Ethical approval

Not required.

Author details

Waleed Hamdi Almaramhy1
1. College of Medicine, Taibah University, Medina, Saudi Arabia

References


