ARTICLE

BREAST CANCER AND PHYTOCHEMICALS: THE CURRENT PERSPECTIVE

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ABSTRACT

Breast cancer affects one in eight women during their lives with higher mortality rate. The risk factors are age, older women possess higher risk, genes - there are two genes, BRCA1 and 2 (Breast Cancer Gene 1 and 2) that greatly increase the risk; women with family history of breast or ovarian cancer, personal factors - beginning periods before age 12 or going through menopause after age 55, overweight, using hormone replacement therapy, taking birth control pills, drinking alcohol, not having children or having children after age 35 or having dense breasts. Phytochemicals are compound that are produced by plants and they protect the cells from damage that could lead to cancer. The anticancer efficacy of phytochemicals such as flavonoids, flavanols, catechins, epicatechins, anthocyanins, anthocyanidins, isoflavones and polyphenols have been discussed in this article in regard to breast cancer especially focusing on quercetin, green tea phytochemicals ans soy bioactives. Reported studies indicated that consumption of phytochemical rich foods in early part of life decreases the cancer risk. Phytochemicals mostly exhibit anticancer activity against the breast cancer by arresting cell growth and inducing apoptosis. This article emphasizes how phytochemicals exert their impact in prevention and therapy of breast cancer.

KEY WORDS
Breast cancer, quercetin, green tea, soy phytochemicals, anticancer.

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INTRODUCTION

Breast cancer is one of the leading cancers that cause death of a huge population worldwide [1]. The common type of breast cancer is ductal carcinoma, that begins in the lining of the milk ducts and lobular carcinoma, which begins in the lobules of breast. Breast cancer occurs in both women and men, although male breast cancer is rare. Estimated new cases and death from breast cancer in the U.S. in 2014 are new cases in female is 232,670 and in male is 2360 whereas the number of death in cases of female is 40000 and in case of male is 430 [2].

For the past two decades, the major cause of breast cancer in women is due to the hormone therapy after menopause. In recent years, incidence rate is slightly low in white women whereas the rate increases slightly in African American women. Breast cancer in female is higher in developing countries than in developed countries. Breast cancer tumours show expression of HER2 which is directly linked to deregulate the activation of intracellular mitogenic pathway. This results in aggressive tumor behaviour and resistance to chemotherapy. Several studies have demonstrated that polyphenolics from pomegranate, green tea, and cranberry are the potent inhibitors of cancer cell proliferation and induces apoptosis [3].

Consumption of fruits and vegetables has been consistently associated with a reduced risk of human cancers. Flavonoids are a group of potentially chemo protective compounds widely distributed in vegetables, fruits and beverages and have structures that consist of phenolic benzene rings linked to a heterocyclic pyre or pyrone. Flavonoids of 6 principal subgroups - anthocyanidins, catechins, flavonols, flavones, flavanones, and isoflavones, are relatively common in human diets. Flavonols (e.g., kaempferol, quercetin, and myricetin) are the abundant flavonoids in plant foods and are mainly present in apples, onions, leafy vegetables, broccoli, and berries. Flavones (e.g., apigenin and luteolin) and anthocyanidins are present in relatively small quantities in grains, leafy vegetables, and herbs. Catechins (e.g., catechin and epicatechin) are abundant in tea, grapes, apples, chocolate, and red wine. Flavanones (e.g., naringenin and hesperetin) are predominantly contained in citrus fruits and their juices. Isoflavones (e.g., daidzein and genistein) are mainly found in soybeans and soy-based products [4]. Flavonoids have many biological effects that may play a role in cancer prevention, including antimutagenic free radical scavenging, and anti-proliferative properties, regulation of cell cycle and cell signaling, and inhibition of angiogenesis.

Phytochemicals are compounds that are produced by plants and are found in fruits, vegetables, beans, grains, and other some plants. Some of the phytochemicals are believed to protect cells from damage that could lead to cancer. It is deducted that cancer risk can be reduced by as much as 40% by eating more fruits, vegetables, and plant foods that have certain phytochemicals in them. Some phytochemicals help to stop the formation of potential cancer-causing substances (carcinogens), helps stop carcinogens from attacking the cells, help cells stop and wipe out any cancer-like changes. In this article, an effort has been made to highlight the anticancer efficacies of phytochemicals mainly quercetin present in different fruits and vegetables, green tea phytochemicals and soy bioactives in amelioration of breast cancer.

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BIOEFFICACY OF PHYTOCHEMICALS AGAINST BREAST CANCER

Phytochemicals are non-nutritive plant chemicals that have disease prevention properties. The activity of phytochemicals against breast cancer against have been studied in different experiments. The phytochemicals that show potential is quercetin, present in cranberry and tea-polyphenol epigallocatechin. The major anthocyanidin are galctosides and arabinosides of cyaniding and peonictin. It is found that anthocyanidin inhibits the oxidative process that is linked with the tumour growth. The proanthocyanidin contains two linkages, the 4β→B which is a B-linkage that is common and others between 4β→8 and 2β→0→7 [5] which is an A-linkage that inhibits the tumour growth and has anti-proliferative effect in the selected cell line. The peel of cranberry fruit contains ursolic acid in a low concentration that induces apoptosis at high concentration and the inhibition is more in micromolar concentration. Cox 2 promotes the growth of cancer which is been inhibited by anythocyanidin.

Quercetin

Flavonoids, one of the remarkable phytochemicals remove the carcinogen by increasing the transcription of detoxification of enzymes. The flavonoids in different fruits and vegetables especially quercetin reduce the risk of different cancer [6]. Breast cancer tumours show overexpression of human epidermal growth factor receptor 2 [HER 2] which is directly linked to the deregulation of intracellular mitogenic pathway that results in aggressive tumour behaviour and resistance to chemotherapy. Quercetin is a flavonoid present in most of the fruits and vegetables. Lapatinib is an oral molecule that inhibits the growth of EGFR and HER2. When the activity of quercetin is studied on a two cancer cell line the one that is resistant to lapatinib (SK-BR-3-Lap R) and the other sensitive to lapatinib (SK-BR-3], it is found that quercetin suppressed the growth of both the cell line and the colony formation of lapatinib sensitive cell [SK-BR-3],but not the resistant cell [SK-BR-3-Lap R]. The inhibitory effect of phosphorylation on Akt and ERks on the SK-BR-3 cell line was low when treated with quercetin and it had a strong inhibitory effect on the cell line treated with lapatinib. The accumulation of cell in G2/M phase and the reduction of G1 phase in SK-BR-3-Lap R and SK-BR-3 had a significant result on quercetin but when treated with lapatinib the cell accumulated in G1 phase only as found in SK-BR-3 cell line [7]. Apoptosis is induced on both cell lines by quercetin whereas lapatinib has no impact on the resistant cell. The volume of tumour in the breast cancer can be reduced by pomegranate extract (Pg), since it has cytotoxic and anti-inflammatory properties. The cancer cell line contains a specificity protein (Sp) transcription factors (Sp1, Sp3, Sp4) where Sp1 is involved in the regulation of NF-κB. The Sp transcription factors mediate the growth of cell. The up regulation of genes, overexpression of Sp causes the cell to survive. The cytotoxic activities of Pg is studied in cancer cell line [BT474 and MDA-MB-231] and on non-cancer cell line (MCF-10F and MCF-12A). It has been found that the Sp is increased in the cancer cell line (BT474 and MDA-MB-231) by Micro-RNA-27A. When the cancer cell line becomes transfected with an antagomir of Micro-RNA-27a, it increases the zinc finger mRNA [ZBTB-10-Mrna] expression [8]. As a result, it suppresses the Sp and Sp dependent m-RNA in the cancer cell line. When the cancer cell line (BT474) is treated with Pg, it decreases the luciferase activity, which is been transfected with pNF-kb-Luc and mi-RNA-27a activity is decreased by the antagomir that suppress the tumour cells [8]. Pg also increases the expression of SHIP [which is a 14kDa protein and it is a regulator of p13K] by the down regulation of mi-RNA-155, which is regulated by binding to the 3'UTR region of SHIP-1. The cell transfected with anti-miRNA-155 decreases the activity of NF-κB in concentration dependent manner. Pg also decreases the mi-RNA-155 level that plays an important role in anti-inflammatory and cytotoxic efficiency. The hydroxyl radical that damage biomolecules and hypochlorous acid are harmful free radical. DPPH is also one such thing. PRME has a great scavenging activity on these free radicals. It also has a scavenging activity on nitrous oxide and peroxynitrite anion. When, lung and breast carcinoma cell line and non-malignant cell lines were pre-treated with PRME and it showed anticancer activity against breast carcinoma but not against lung. PRME arrests the G2/M phase and S phase of breast cancer both in dose dependent and time-dependent manner and it increases the apoptosis. PRME inhibited almost all cell cycle protein, but cdk1 and cyclin A1 was not inhibited, which suggest that there is a transition from G2-M phase and S-G2 phase. When DNA is damaged, p53 which is a tumor suppressor is activated and it arrests the cell cycle and induce apoptosis. The initiation of caspase cascade is by two pathway. Once caspase 8 is activated, it releases cytochrome c from mitochondria which activates caspase 9 and induces apoptosis [9]. Similarly Bcl2/Bax protein ratio is also important apoptosis. When the breast carcinoma cells were treated with PRME, the ratio of Bcl2/Bax increases in a time dependent manner and induces apoptosis.

The human breast cancer resistance protein BCRP / ABCG2 which is a member of G subfamily of the large ATP-binding cassette (ABC) transporter family. This is known as efflux pump. BCRP is a half transporter with only six transmembrane helices (TMs) [10]. Glucuronidation is a significant metabolic pathway that facilitates efficient elimination and detoxification of numerous endo and xenobiotics. Targeting this feature, works are going on towards improving the efficacy of synthetic drugs and plant based bioactives for treating breast cancer.

Green tea polyphenols

It is evident from several studies that there is convincing risk reduction effects of green tea against mammary tumors. Overall data derived from case-control studies also show a dose-dependent, statistically

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significant association between green tea intake and breast cancer risk reduction [3]. Moreover, differences in the green tea-breast cancer association by menopausal status (a beneficial effect mainly in premenopausal women) has been suggested in some studies though some studies showed no differences in results by menopausal status [11-14]. Regular intake of green tea might be a relevant factor for the lower incidence of breast cancer in Asian populations having multifarious beneficial properties; and there are supportive evidence of its protective effects in some epidemiological studies [15-17] while black tea intake, in contrast, appears to be unrelated to breast cancer risk in Asian and western populations [17]. Green tea is rich in tea catechins, namely epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin (EC), and epicatechin gallate (ECG), which possess several cancer chemo preventive characteristics including anti-oxidation, anti-inflammatory, anti-proliferative, and anti-angiogenic [18]. Few of the epidemiologic studies have investigated the relationship between green tea and breast cancer risk by hormone receptor status although in vitro studies show cytotoxic effects of EGCG toward breast cancer cells regardless of estrogen receptor status [19].

The bioavailability of tea polyphenols in human might also possess some influence in their efficacy against breast cancer [3]. Variations in genes involved in the metabolism of tea polyphenols may also amend the green tea-breast cancer association [3]. One of the most imperative conjugation reaction of the tea catechin is O-methylation by the catechol-O-methyltransferase (COMT) [20, 21]. Genetic polymorphisms of methylenete trahydrofolate reductase (MTHFR) and thymidylate synthase (TYMS) genes in the folate pathway and angiotensin converting enzyme (ACE) in the angiotensin-II pathway have been found to influence the green tea-breast cancer association in respective studies [22, 23].

The risk of breast cancer is also associated with the concentration of circulating estrogens and androgens. The cross-sectional studies revealed that green tea intake lowers the circulating estrogens in pre and post-menopausal stage [24, 25]. The green tea intake did not differ the concentration of the estrone, estradiol and sex hormone binding globulin (SHBG) whereas testosterone concentration differed significantly when compared to non-green tea drinkers [24, 25]. IGF-1 is a peptide that stimulates mitosis and inhibits apoptosis. IGF-1 binds to a binding protein known as IGFB-3. They may influence the risk of breast cancer development. Green tea infusion influence it and inhibits the growth of breast cancer [26-28]. Adiponectin is a hormone secreted in adipocyte that is been up-regulated by catechin expressions. But it did not decrease the level of expression of adiponectin. Studies say that adiponectin level increases by the daily uptake of green tea among the Asian women [29, 30].

Green tea or EGCG did not have any effect on post-initiation stage. But oral admiration of polyphenon E in the drinking water can delay the tumour growth than the normal water [31]. The dosage of green tea also play an important role. Low dose delays the cancer. Green tea in combination with tamoxifen is more useful in suppressing the tumor. EGCG enhance the tamoxifen that induces apoptosis [32, 33]. Studies say that better understanding of EGCG only reduce the risk of cancer but also green tea before carcinogen can delay the breast cancer [32, 33]. SV40 mouse model proposed the chemopreventive effect of green tea [31] but the results are inconclusive and a better understanding of the mechanisms by which green tea reduces the risk of cancer is needed.

Catechins

Metastasis is the main cause of death in patients with breast cancer. The process of metastasis involves a series of cellular events in which cell motility of breast cancer cells takes place regulated by some factors referred as motility factors. During the process, autocrine motility factors (AMF) and Cry61 become activated upon stimulation by heregulin-β1 (HRG) [34]. HRG activates the epidermal growth factor receptor-related protein B3 (ErbB3)/ErbB2 hetero-dimerization and its phosphorylation. (-)-Epigallocatechingallate (EGCG) and (-)-epigallocatechin (EGC) are major catechins in green tea. They are also found in other sources such as apples, plums, onion, hazelnuts, pecans etc. It has also been demonstrated that EGCG suppresses the growth of breast cancer cells including the MCF-7 human breast carcinoma cell line by inhibiting the overexpression of tumor-associated fatty acid synthase (FAS)[35]. It has been reported that while MCF-7 cells were incubated with either EGCG or EGC (each 30μM) for predetermined periods prior to treatment with HRG, EGCG blocked the ErbB2/ErbB3 heterodimerization incrementally with time [1]. Migration/invasion is an important step in the metastasis of breast cancer cells. Activation of ErbB3/ErbB2 heterodimers by HRG can contribute to metastasis by enhancing tumor cell invasion. HRG is capable of promoting the tumorigenicity and metastasis of MCF-7 cells in vivo [36]. EGC inhibited the migration/invasion of MCF-7 cells to the same extent as EGCG in the assay using Boyden chambers. However, EGC suppressed the phosphorylation of erbB2 and ErbB3 at a low cell confluence and did not activate Akt at either a low or high cell confluence [1]. EGCG inhibited the migration/invasion through down-regulation of ErbB2/ErbB3/P13K/Akt signaling, whereas EGC did so through pathways involving the disruption of the HRG-stimulated activation of ErbB2/ErbB3 but not Akt [1]. EGCG and EGC may have potential as anti-metastasis drugs against breast cancer to be used with/after anti-cancer drugs. Tumour-associated macrophages (TAM) play an important role in tumour microenvironment. Especially, M2 macrophages contribute to tumour progression depending upon the expression of NF-κB. Tumour-derived exosomes can modulate tumor microenvironment by transferring miRNAs to immune cells. Exosomes are circular fragments of membrane released from the endosomes, and they are shed from the surface membranes of most cell types [37]. Macrophages populate the microenvironment of most tumors. EGCG has significant influence on tumor-derived exosomal miRNAs and TAM. Study using murine breast cancer cell line 4T1, used for ex vivo and in vivo experiments where tumor cells or TAM isolated from

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murine tumour graft were incubated with exosome, derived from miR-16 inhibitor-transfected and/or EGCG-treated 4T1 cells [38]. It has been found that cytokines with high (IL-6 and TGF-β) and low (TNF-α) expression in M2 macrophages and chemokines for monocytes (CSF-1 and CCL-2) and molecules in NF-κB pathway (IKKα and Iκ-B) showed diffenrential expression when evaluated by RT-qPCR or western blot [38]. Expression of chemokines for monocytes were low in tumour cells from EGCG-treated mice and cytokines of TAM was skewed from M2- into M1- like phagocyte by EGCG as evidenced by decreased IL-6 and TGF-β and increased TNFα. Ex-vivo incubation of isolated tumour cells with EGCG inhibited the CSF-1 and CCL-2 expression. It was observed that treatment with EGCG leads to up-regulation of miR-16, which might be transferred by exosome to TAMs and contributes to the suppression of NF-κB, and inhibition of TAM infiltration and M2 polarization [38].

Soy bioactives

Soy isoflavanones can cause a decrease in the estrone (E1) and luteal phase estradiol (E2) in women without any significant variation in the pre and post- menopausal phase [39]. It is been found that Asian women who took soy isoflavones have high 2/ 16α hydroxyl, a marker for lower cancer risk. It has also been reported that soy if taken regularly reduces the risk of acquiring cancer along with lower mammographic density, another marker of breast cancer (high density, high risk of cancer), similar to green tea which also reduces the mammographic density because of its anti-proliferative and anti-angiogenc capacity [39].

Higher production of NAF fluid also denotes high cancer risk. Regular consumption of soy causes a reduction of NAF fluid in post-menopausal women [39]. To know the activity of soy in breast cancer, isoflavones is injected directly into the breast tissue by breast reduction surgery, fine-needle biopsies. In the reduction surgery, the isoflavones concentration was low in hydrolysed breast tissue. Due to variation in gene, the effect of soy may differ. The time period of soy food consumption also influences its effect as anticancer agent. It has been found that consumption during the early part of life reduces the risk of cancer than the soy intake during the late life [40, 41]. The intestinal bacteria has the capacity to metabolise the isoflavones into equol, if the soy is taken in the early part of life it can produce equol that has a protective effect against the breast cancer in the later part of life.

Consumption of soy foods during childhood, in adolescence and during puberty may reduce mammary cancer risk in women [42]. Studies have also examined whether an exposure to genistein or soy protein isolate (SPI), either in utero or prepubertally, or a combination of both, affects later mammary tumorigenesis [42]. Moreover, in addition to genistin (the glucoside conjugate of genistein) and genistein (the aglycone), SPI contains daidzin (the glucoside conjugate) and daidzein (the aglycone), the other main IFs in soy. It has been found that daidzein has weaker oestrogenic properties than genistein. The third isoflavone of soy protein isolate is glycitin and its aglycone glycitein, but they are present only at low levels. Susceptibility to malignant transformation may increase due to exposure of Genistein/Soy protein isolate in utero, if the exposure continues to adulthood a reduction in risk may occur [42]. If an early life exposure to genistein, or other estrogenic compounds, alters breast cancer risk by targeting progenitor cells or epithelial stem, changes in apoptosis and cell proliferation are expected to be seen. Hereditary mutation in BRCA1 not only increase the risk of breast cancer but also risk for ovarian and prostate cancer. BRCA 1 interacts with RAD51 protein and, as a result, BRCA 1 is capable of acting as a gatekeeper in maintaining genomic integrity by preventing DNA damage and inducing DNA repair [43]. Dietary exposure to genistein can be protective in absence of functional BRCA1. Moreover, inactivating mutations or deletions of the PTEN gene are among the most common changes found in human cancers, especially breast cancer. The PTEN protein is a lipid phosphatase and has been suggested to act as a tumor suppressor [44]. Genistein promotes apoptosis in mammary epithelial cells by inducing PTEN [45]. The changes were accompanied by a decrease in mammary tumorigenesis. However, the focus is on changes in gene expression, especially involvement of genes like BRCA1 and PTEN. The effects on mammary gland morphology and signalling pathways induced by pubertal exposure to genistein mimic those induced by the oestrogenic environment of early first pregnancy [42].

Dietary exposure to soy foods is associated with lower mammary tumor risk and reduced body weight and adiposity in humans. Obesity is an independent risk factor for the development of hormone receptor-positive breast cancer in postmenopausal women. The level of pro-inflammatory cytokine interleukin-6 increases with body mass [46], and is considered to constitute a viable marker for poor prognosis in breast cancer patients. Soy protein isolate (SPI) and GEN-fortified casein (CAS) decreases mammary adipocytes cell size when they were exposed in limited amount [47]. Dietary SPI and GEN exposure reduce mammary adipocyte cell size which was accompanied by increased expression of tumor suppressors PTEN and E-cadherin in mammary tissue. MSF cells cultured in a differentiation medium with 40nM GEN showed reductions in mature triglyceride accumulation, adipocyte numbers, and PPAR-γ and fatty acid synthase transcript levels [47]. Adipose differentiation by GEN inhibition was accompanied by increased estrogen receptor β (Erβ(Esr2)) gene expression and was modestly recapitulated by ERβ-selective agonist 2,3-bis-(4-hydroxyphenyl)-propionitrile (DPN). Reduction of ERβ expression by siRNA targeting increased Pparγ transcripts levels and stromal fibroblast differentiation into mature adipocytes; the latter can be was reversed by GEN but not DPN [47]. Therefore, it is evident that dietary factors may have mammary tumor-preventative effects independent of their effects on body size and adiposity by inhibiting local adipogenesis in the mammary fat pad.

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Phytoestrogens

Phytoestrogens are a group of plant-derived substances that are structurally or functionally similar to estradiol [48, 49]. Phytoestrogens, especially soy, has been fuelled by epidemiologic studies that have suggested low incidence of breast cancer in countries with high soy intake. Isoflavones are the most common form of phytoestrogens and are found in all the plants variety, soy being the greatest dietary source [50]. The tumorigenicity has been found to be reduced in MCF-7 breast cancer cells with genistein treatment [50].

Polyphenols

Resveratrol, a polyphenol form of grapes and red wine has many health beneficial effects. They have neuro protective, anticancer, anti-inflammation, anti-ageing, anti-microbial and cardio properties. Resveratrol is mainly important for breast cancer since it has been shown to exert both estrogenic or ant estrogenic effects (depending upon the concentrations used) and binds to estrogen receptors ERα and ERβ with comparable affinity [51]. Resveratrol has been shown to inhibit cell migration / invasion and metastasis in several types of cancer, especially breast cancer. Resveratrol at 50μM acts in an anti-estrogenic manner to reduce cell migration while, resveratrol at 5μM acts similar to estrogen which induces invasion, cell migration and formation of lamellipodia on ERα (-), ERβ (+) MDA-MB-231 breast cancer cell line. Lamellipodia are actin structures found at the leading edge of migrating cells that are under Rac regulation [52]. Rac activity is decreased by 50μM resveratrol, whereas estrogen and 5μM resveratrol increases Rac activity in breast cancer cells. Higher concentrations of resveratrol inhibits Akt and MAPK activities and lower concentrations of resveratrol promotes proliferation in human cancer cells and induces Akt and MAPKs, among other tumorigenic signalling proteins. Therefore, the growth and metastasis of breast cancer are induced depending upon the dose of resveratrol.

CURRENT PERSPECTIVE

In recent times, several breast cancer studies going on targeting breast cancer genes, proliferation, apoptotic induction, inflammation, metastasis arrest etc. involving phytochemicals such as curcumin, oregano, apigenin, sulforaphane, lutein, sesamin, beta-sitosterol etc. in pre-clinical trials [53, 54]. A combination of synthetic and natural drugs or two or more natural drugs working in synergy targeting breast cancer is a likely futuristic approach.

CONCLUSION

From the studies it is been inferred that any flavonoids should be taken at early stage of life for better result, since the breast cancer is been suppressed by dose and time dependent manner. Among the different flavonoids studied quercetin plays a major role in cancer treatment. It has good inhibitory effect against cancerous growth and induces apoptosis. Since it has good anti-cancer properties it can be used as adjuvant or a drug to treat the cancer. Adjuvant is used to remove the secondary tumour growth. Most of the adjuvant used in the cancer treatment have their own side effect. But quercetin would not have much side effect as others since it is naturally obtained from the plants. Some amount of quercetin can used in the chemotherapy drug for better result. But studies should be conducted to prove it. It was also inferred that consumption of soy foods during childhood and adolescence in women reduces mammary cancer risk. Genistein/SPI exposure limited to the prepubertal period appears to reduce later mammary cancer risk but the effect is mostly lost if the exposure remains risk. It was also established that early first pregnancy (before 20 years of age) reduces breast cancer risk, while women undergoing first pregnancy after 35 years of age are at increased risk. Obesity also increases breast cancer in women. Consumption of grapes, pomegranate and cranberry also reduces the risk of breast cancer. Green tea phytochemicals especially EGCG also possess significant beneficial effect in breast cancer. However, further studies including clinical trials are needed to validate the potential of these phytochemicals as an alternative but effective measures in amelioration of breast cancer.

CONFLICT OF INTEREST

There is no conflict of interest among authors.

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