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Medicinal herbs as a treatment for breast carcinoma

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Abstract
Breast cancer is a leading malignancy causing mortality and morbidity among women worldwide. Therefore, finding effective treatment modalities for Breast cancers is of utmost importance. There is a growing interest to search for herbal remedies for breast cancers due to serious side effects caused by chemotherapy and radiotherapy. Fruits and vegetables contain a wide range of phytochemicals with antioxidant, anti-inflammatory and anti-proliferative properties. Some examples for phytochemicals with anticancer properties against breast cancer are polyphenols, flavonoids, tannins, and Ellagic acid. Extracts from green tea, Mango, Pomegranate, Bael fruit, 'Katupila' (*F. leucopyra*), Custard Apple, Berries, Curry leaves, Bitter goud Papaw and Turmeric have been found to be rich sources of these phytochemicals. The phytochemicals found in these extracts act against breast cancer cell lines such as MCF-7, MDA-MB-231 and Hs 578T through different modes including the arrest of cell cycle, apoptosis, modulation of enzyme pathways and anti-inflammatory properties.

Keywords: breast cancer, phytochemicals, antioxidant, anti-proliferative, polyphenols, MCF-7, apoptosis

1. Introduction
Cancer has now become a major cause of death worldwide. According to WHO estimates 8.8 million deaths in 2015 were due to cancer. Breast cancer is the commonest cancer for women worldwide with an increase of 1.7 million new diagnosed cases in 2012 [1]. Breast cancer is also the commonest cause of cancer death among women with 522,000 deaths worldwide in 2012. Due to this high morbidity and mortality effective treatment for breast cancer is essential. Surgery, chemotherapy, chemo-hormonal therapy and radiotherapy play a major role among the available treatments for breast cancer [2, 3]. However, there are substantial short and long-term adverse side effects from these therapies. Hair loss, nail changes, mouth sores, loss of appetite, nausea and vomiting, increased chance of infections, easy bruising or bleeding, fatigue, diarrhea are some short-term side effects. The long-term side effects include; immunosuppression, early menopause and infertility due to ovarian failure, long-term cognitive deficits, dementia, organ dysfunction and hepatotoxicity [4-10]. These serious side effects have motivated researchers to identify novel anticancer compounds with less adverse effects such as herbal remedies. Therefore at present, phyto-chemicals with potential anti-cancer activity and fewer side effects than chemotherapy are been increasingly used for treatment of cancer. As a result plants and other natural sources have provided nearly 60% of anti-cancer agents which are currently in use [11, 12].

2. Plants Rich with Phytochemicals Active against Breast Cancer
Fruits and vegetables contain awide range of phytochemicals with antioxidant, anti-inflammatory and anti-proliferative properties. Several phytochemicals have shown to be capable of causing induction of cell cycle arrest and apoptosis in cancer cell lines [13]. Some examples for phytochemicals with anticancer properties against breast cancer are polyphenols, phenolic compounds, flavonoids, tannins, steroids, reducing sugars, and Ellagic acid. Extracts from green tea, Mango, pomegranate, Bael fruit, 'Katupila' (F. *leucopyra*), Custard Apple, Berries, Curry leaves, Bitter gourd, Papaw and Turmeric have been found to be rich sources of these phytochemicals. According to Dreosti *et al* (1998) [14] Green tea [*Camellia sinesis (L.)*] infusions or the extracted polyphenol fractions from green tea has been proven to be an active against all phases of carcinogenesis [14]. Ediriweera *et al* (2016) who investigated the potential anti-cancer activity of components of *Mangifera Zeylanica* (A species of Mango that is endemic plant in Sri Lanka) found that the hexane extract from the bark of *Mangifera zeylanica* was found to be rich in polyphenolic compounds [15]. Similarly the major phytochemical constituent in Pomegranate (*Punica granatum*) includes the polyphenolic compounds [16]. The *Pomegranate* juice contains flavonoids and the pericarp contains polyphenols, tannins and ellagitannins [17]. High Phenolic compounds have been found the extracts of Bael fruit (*Aegle marmelos*), 'Katupila' (*F. leucopyra*), custard apple

(*A reticulata*) and curry leaves as well. Strawberries and Raspberries (*Rubus sp*.) are rich in Ellagic acid which has been identified as a potent anti-cancer agent. Ellagic acid has shown to strongly inhibit the growth of MCF-7 and Hs 578T breast cancer cell lines [18].

3. Mechanism of Action by Phytochemicals against Breast Cancer

The phytochemicals found in extracts from tea, mango, pomegranate fruit, bael fruit, 'katupila', Custard Apple, curry leaves, bitter gourd, papaw and turmeric act against breast cancer cells such as MCF-7, MDA-MB-231 and Hs 578T through differ rent modes including the arrest of cell cycle, apoptosis, modulation of enzyme pathways and anti-inflammatory properties. It is revealed that (−)-Epigallo catechin (EGC), which is one of the green tea polyphenols, inhibit breast cancer cell growth due to an induction of apoptosis, without any change in cell cycle progression [19]. (-)-Epigallocatechin-3-gallate can induce cell cycle arrest in the G_0/G_1 phase. This occurs through suppression of tumor-associated Fatty Acid Synthase (FAS) which is involved in tumorigenesis and connected to HER2 (Human Epidermal Growth Factor Receptor 2). Suppression of FAS in cancer cells may lead to growth inhibition and cell apoptosis. Pan *et al* (2007), demonstrated that (-)- epigallocatechin 3-gallate (EGCG) and green tea catechin could down-regulate FAS expression by suppressing EGFR (Epidermal Growth Factor Receptor) signaling and downstream phosphatidylinositol 3-kinase (PI3K)/Akt activation in the MCF-7 breast cancer cell line [20]. Ethanolic extract of Mango peel contains quercetin 3-*O*-galactoside, mangiferin gallate, isomangiferin gallate, quercetin-3-*O*-arabinopyranoside and Mangiferin. This extract has been shown to down-regulateanti-apoptotic Bcl-2 expression, with the result of proteolytic activation of caspase-3, 7, 8, and 9 and the degradation of poly (ADP-ribose polymerase) (PARP) protein [21]. Mangiferin, which is a naturally occurring glucosylxanthone, has exhibited anti-cancer potential through inhibition of the activation of β-catenin pathway. It has been proven that inhibiting β-catenin pathway might play a major role in mangiferin induced anti-cancer activity through modulation of matrix metalloproteinase -7, -9 and epithelial mesenchymal transition [22]. Bakar *et al* (2016) showed that the 'kernel crude extract' can induce cell cycle arrest in both MCF-7 (hormone-dependent breast cancer) cells and MDA-MB-231 (non-hormone dependent breast cancer) cells as well as apoptosis. Kernel extract has induced cell cycle arrest in MCF-7 and MDA-MB-231 at the sub-G1 (apoptosis) and G2-M phases respectively. Apoptosis appeared to be dependent on enzymes caspase-2 and 3 for MCF-7 cells and on caspase-2, 3 and 9 for MDA-MB-231 cells [23]. Extracts from different varieties of Mango such as "Ataulfo" and "Haden" extracts have shown moderate anti-oxidant capacity for the oestrogen independent breast cancer cell line, MDA-MB-231 [24]. There are several mechanisms to some explain the probable mechanism of action of Pomegranate on the breast cancer cell lines; MDA-MB-231 and MCF-7. The effect of pomegranate extracts in combination with genistein was investigated on the growth rate and apoptosis induction in human breast cancer cells MCF-7 [25]. Polyphenols from fermented juice has shown nearly twice the antiproliferative effect with compared to fresh pomegranate juice for human breast cancer cell lines MCF-7 and MB-MDA-231 [26]. Adhami, Khan, and Mukhtar (2009), have revealed that there is a 60-80% inhibition in aromatase and 17-β-hydroxysteroid dehydrogenase type 1 enzymes with the polyphenols obtained from fermented juice. Pomegranate seed oil polyphenols inhibit cyclooxygenase-2 (COX-2) which is a Prostaglandin (PG) synthase. Increased PG production may lead to carcinogenesis by increasing PGE1 and PGE2 which stimulate proliferation of mammary epithelial cells [27] PGE2 inhibits T and B cell proliferation and cytokine synthesis and diminishes the cytotoxic activity of Natural Killer (NK) cells which can lead to tumerio genesis [28] and also enhance proliferation by increasing oestrogen biosynthesis [29]. Furthermore, pomegranate seed oil has inhibited the proliferation of MCF-7 cells by 90% [26]. Pomegranate can significantly suppress cyclooxygenase-2 (COX-2) protein expression in cellular inflammatory pathway, which is induced by Tumor Necrosis Factor-alpha (TNF-α). Rocha A *et al* (2012), have shown that pomegranate juice or a combination of its components (luteolin, Ellagic acid, punicic acid) increase cancer cell adhesion and decrease cancer cell migration without affecting normal cells. This leads to reduction pro-inflammatory cytokines/chemokines and therefore reduced risk for inflammation [30]. In menopausal women, elevated serum levels of estrone and estradiol could lead to an increased the risk of Breast Cancer [31]. Pomegranate (*Punica granatum*) seed oil has a greater ability to inhibit β-estradiol biosynthesis catalyzed by 17-β-hydroxysteroid dehydrogenase enzyme, to invade cancer cells and to promote apoptosis. Grover and Yadav (2004), have studied that Bitter Gourd controls G_2 and M phases of the cell cycle via inhibition by incorporation of thymidine, leucine and uridine into DNA. Inhibition of Guanylate Cyclase activity, activation of Natural Killer cells (NK cells) and induction of apoptosis of Breast Cancer cells are also been reported as benefits of Bitter Gourd [32]. Bitter Gourd extract has a significant ability to decrease cell proliferation in cancer cells and induced apoptotic cell death. Apoptosis of Breast Cancer cells were accompanied by increased poly (ADP-ribose) polymerase cleavage and caspase pathway active action. Furthermore, some studies have been revealed that, this extract inhibit survivin and claspin protein expression, which will lead to suppress the Breast Cancer development. Further studies revealed that, this extract enhanced p53, p21 and pChk1/2 proteins and inhibited cyclin B1 and cyclin D1 protein expression, which will further regulate the cell cycle. These results shows that, Bitter Gourd extract inhibit Breast Cancer cell growth, through signal transduction pathways [33]. Extract of Bael fruit (*Aegle marmelos*) which contains alkaloids, polysaccharides, tannins and carotenoids [34] has shown anti-proliferative activity against MCF-7 and MDA-MB-231 cell lines [35, 36]. This extract has exhibited cytotoxicity against tumor cell lines in brine shrimp lethality assay and Methyl Thiazolyl Tetrazolium (MTT) based assay [37]. According to Kruawan and Kangsadalampai (2006), water extract of Bael fruit has exhibited strong scavenging activity against DPPH radicals, high phenolic compound content and moderate anti mutagens (40%-60%) [38]. The possible mechanism of this extract is not yet clearly identified. The aqueous extract of the 'katupila' (*F. leucopyra*) plant, it is considered as a potential therapeutic agent for the control of oxidative damage due to the high antioxidant activity and phenolic content [39]. Decoction of 'Katupila' *(F. leucopyra)* has indicated significant cytotoxic effects in three breast cancer cell lines MCF-7, MDA-MB-231, SKBR-3. For all three breast cancer cell lines DNA fragmentation and clear apoptotic morphology have been exhibited. In MDA-MB-231 and SKBR-3 cells, caspase 3/7 were significantly activated showing caspase dependent apoptosis while showing caspase independent apoptosis in MCF-7 cells [40]. Custard Apple (*A reticulata*) consist with different phytochemicals; terpenoid,

steroid, flavonoids, cardiac glycoside, tannin, phenol, alkaloid, and reducing sugar. Phenol was the mostly present phytochemical. Custard Appleleaves have shown antiproliferative effect in 7, 12-dimethylbenzeneanthracene (DMBA) induced breast tissues of female albino mice [41]. Organic and aqueous extracts of defatted seeds of Custard Apple have induced apoptosis in MCF-7. With the treatment of organic and aqueous extracts for MCF-7 have been resulted in nuclear condensation, DNA fragmentation, induction of reactive oxygen species generation and reduced intracellular glutathione levels [42]. Noolu *et al* (2013), has demonstrated that hydro-methanolic extract of Curry leaves is a rich source of polyphenols. They have demonstrated that this extract has proteasome inhibitory potential and induces cell death in human Breast Cancer cells and concluded that the leaf extract of Curry leaves can selectively arrest the S phase only in cancer cells. With the help of Annexin V protein, was revealed that the cell death occurred through apoptosis for breast cancer cell lines. Furthermore, they have observed that the extraction inhibited the purified 20S proteasome enzyme and significantly inhibited all the three enzymatic activities associated with the 26S proteasome in living cells according to a dose-dependent manner and revealed that, proteasome inhibitors have selectively inhibited proteasome activity only in neoplastic cells but not in normal cells [43]. Garcia solis *et al.* (2009) found that Papaw (*Carica papaya)* extract which is rich in chlorogenic acid, catechin, catechin conjugates and few quantities of flavonolsis effective in causing inhibition of MCF-7 cell proliferation. They have demonstrated that the cell death occurred through apoptosis [44]. Curcumin, the principal curcuminoid of the Turmeric *(Curcuma longa)* has been shown to have chemo-preventive effect on Breast Cancer, which inhibits the expression of Oestrogen Receptor (ER) downstream genes including pS2 and Transforming Growth Factor (TGF) in ER-positive MCF-7 cells [45]. Ravindran, Prasad and Aggarwal (2009), experimented on mechanism further with relation to curcumin, which modulates growth of tumor cells through regulation of multiple cell signaling pathways including cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1), caspase activation pathway (caspase-8, 3, 9), tumor suppressor pathway (p53, p21), death receptor pathway (DR4, DR5), mitochondrial pathways and protein kinase pathway (JNK, Akt, and AMPK) [46]. Anti-inflammatory mechanisms leading to the anti-carcinogenic activity of curcumin including (1) inhibition of NF-KB and COX-2 [47-50] (2) inhibition of arachidonic acid metabolism via lipoxygenase and scavenging of free radicals [50] (3) decreased expression of inflammatory cytokines IL-lß, IL-6 and TNF-α [51] and (4) down-regulation of enzymes protein kinase C - mediated inflammation and tumor cell proliferation [52]. In addition to the above selected plants, Cabbage (*Brassica oleracea*L. Capitata Group), Broccoli (*Brassica oleracea* L. Botrytis Group), Cauliflower (*Brassica oleracea* L. Botrytis Group), Oranges (*Citrus sinensis* L.), Tomatoes (*Solanum lycopersicum*), Guava (*Psidiumguajava)*, Soybeans (*Glycine max* L.) [53] Carrots (*Daucuscarota subsp. Sativus*), Spinach (*Spinacia oleracea*), Bell pepper (*Capsicum annuum*), Sweet potato (*Ipomoea batatas*) [54] like vegetables and fruits also have been shown the anticancer effect against Breast Cancer according to the literature.

4. Conclusion

After exploring extensive literature reports and research articles we have reviewed the herbs that are used for Breast Cancer. Fruits and vegetables contain vast variety of phytochemicals with anti-oxidant, anti-inflammatory and anti-proliferative properties, induction of cell cycle arrest and apoptosis. Possible biochemical and genetic mechanisms for the anti-cancer effects of phytochemicals can be explained through several actions and pathways.

This comprehensive review will be a guide for researchers and cancer patients and help to broaden their view on management of Breast cancer.

5. Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

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