Review Paper:

Safer herbs are better than bitter medicines in the battle against breast cancer

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Abstract

Breast cancer is a significant public health concern worldwide and is the second most common diagnosed cancer and is also a leading cause of death among women all over the world. Hormone therapy, surgery, chemotherapy and radiotherapy are currently being used to handle breast cancer. Owing to extreme side effects and multidrug resistance, such treatment approaches have become increasingly inadequate. Novel and innovative ways of battling breast cancer are now being enforced. Over a multitude of reasons such as safety, negligible toxicity, no adverse effects, optimized ability and multiple molecular targets, bioactive derivatives from herbs seem to be massively preferred for breast cancer treatment.

According to pre-clinical and mechanistic reports, use of such herbal therapeutic products as potential multi-target preventive or therapeutic agents against breast cancer was firmly implicated. The intent of this review is to promote a view of the usage and efficacy of herbal remedies in the management of breast cancer.

Keywords: Herbs, Breast cancer, Phytochemicals, Dietary supplements.

Introduction

Cancer persists as a major public health crisis and is one of the most deleterious disease with countless deaths worldwide[34]. Among various types of cancer, breast cancer (BC) is currently the most prominent and is the second leading cause of cancer related death among women[48]. Several therapeutic approaches exist including hormonal therapy, surgery, radiation therapy and chemotherapy, which relies on multiple attributes such as cancer level, hormone receptor status, metastatic potential and molecular profiling[2].

Unfortunately, these therapeutic modalities have limited clinical dimensions, culminating in some of the short-term and long-term detrimental effects that have a drastic impact on the health of BC patients, which raises morbidity and mortality[39]. Arising solutions should include attempting to find specific drug targets that are really efficacious in impeding BC cell proliferation, significantly with zero adverse consequences. Traditional herbal pharmaceutical supplements have become popular due to their cost-effectiveness, better availability and no side effects[15]. Such herbal therapeutics have earned tremendous attention in BC treatment due to their selective cytotoxicity and can therefore be used as potential chemotherapeutic agent. Meanwhile, a broad range of herbal products have now been reported to curtail the negative effects of existing BC conventional treatments as well as boost the quality of patient's life and ease stress[28].

Current studies have indicated that natural herbal compounds might target a broad range of BC-specific mechanisms which provide positive feedback towards cancer cell progression and it can also play a pivotal role in controlling BC prevalence[36]. Regular intake of sufficient amounts of such herbal medicines will facilitate BC prevention and treatment via cell cycle arrest, programmed cell death activation, suppression of cancerous metabolic processes and oncogenic transcription, inhibition of cell adhesion, replication and migration and also by blocking major signalling pathways which are necessary for BC maturation[28,30].

Moreover, women have always been the high consumers of herbal medicinal products and therefore BC patients are now strongly willing to buy such remedies. Most of these formulations are based on ancient myths and still have not been clinically evaluated for drug therapy authorization[9]. Hence, this review is attempting to compile the potential of most promising herbal dietary supplements which are worth effective in suppressing one or more of the mechanisms which provoke BC and thereby become a reliable solution for treating BC.

Herbal medicine myths: Herbalism is a cultural medicinal practice focused in the use of plants and their extracts. The earliest recorded history of herbal medicines emerged in China dating back to 2800 BC. It has continued to climb over the last 5000 years at most and develops till today as a potent therapeutic wonder[40]. Along with its continual tradition usage, herbs and herbal derived products are becoming increasingly attracted over the global market as dietary supplements, health-care products, cosmetics etc. At present, the acceptance rate of herbal therapeutic products is growing not only in Asian countries (49% in Japan, 45% in Singapore, 70% in China and 80% in India), but also in western countries[46].

Herbal therapy to fight BC: Medicinal herbs and their derived phytocompounds are continually becoming accepted as valuable complementary cancer medications[54]. Due to the high prevalence rate of metastatic BC, the pre-clinical BC

research program was primarily focused on investigating the potency of herbal medicines[55]. Herbal supplements showed potential anti-BC behavior via modulating biochemical pathways and amplifying immune responses to diminish the inflation of malignancies. They ignite immune cells including Natural Killer (NK) cells, cytotoxic T cells, chemokines and tumor necrosis factor-α attributing to its therapeutic qualities. Herbal products are considered to be the promising alternative / adjuvant option for therapeutic or preventive BC strategies[33].

Herbals active constituents and its tactic mechanism of action against BC: BC treatment is now being tied with phytonutrients derived through various herbs. Moreover, this review concentrates over some of the significant herbs as a medicinal agent to combat BC.

***Azadirachta indica*:** *Azadirachta indica*, commonly referred to as neem, which has been well-known in Indian subcontinent for more than 2000 years being one of the most multipurpose medicinal herbs with such a multitude of biomedical activities. In traditional medicine, all sections of the neem tree-leaves, flowers, seeds, roots and bark were being used as herbal remedies towards various human diseases[50]. Countless studies on the pharmacology of neem tree substances were carried out. The neem leaf is particularly a 'reservoir' of organic compounds. Effective chemically diverse and structurally complex compounds such as azadirachtanin, azadirachtanin-A, beta-sitosterol, hyperoside, isoazadirolide, nimbaflavone, nimbandiol, nimbinene, nimbolide, quercitrin, rutin and vilasanin were isolated from the neem leaves[42].

It has been stated that neem leaf formulations exhibit varied anticancer properties, especially more vigorously against BC. Arumugam et al[4] stated that the ethanolic fractions of Neem leaf (EFNL) blocks the proliferation of mammary carcinogenesis caused by chemical carcinogen in rat models. EFNL therapy has been highly effective in controlling mammalian tumor burden and in deterring tumor development even after therapy was halted. EFNL therapies potentially upregulated proapoptotic genes and proteins including p53, B cell lymphoma-2 protein (Bcl-2)-associated X protein (Bax), Bcl-2-associated death promoter protein (Bad) caspases, phosphatase and homologous tensin gene (PTEN) and c-Jun N-terminal kinase (JNK).

In addition, EFNL medication induce downregulation of angiogenic proteins (angiopoietin and vascular endothelial growth factor A [VEGF-A], cell cycle regulatory proteins (cyclin D1, cyclin-dependent kinase 2 [Cdk2] and Cdk4) and pro-survival signals such as NFκB, mitogen-activated kinase 1 protein (MAPK1)[4]. Periodic use of neem oil at a dosage of 3 mL / kg (2 or 4 days a week) drastically reduces tumor incidence (80%), burden and mass. Neem intake rescued the rats from breast hyperplasia caused by DMBA[56]. Sharma et al[49] reported neem oil's anticancer effects on positive receptor-ER+ (MCF-7) and ER– (MDA-MB-231) BC cells with 10 µl / ml CC50 and 20 µl / ml CC50 respectively. The neem oil mediated apoptosis and cell cycle arrest in each of these cell types at the phase G_0/G_1.

***Spinacia oleracea*:** Spinach (*Spinacia oleracea L.*), a dark green, leafy vegetable, belongs to the *Amaranthaceae* family which includes beets and chard. The earliest known record of spinach was made in 647 A.D. by the Chinese, where it was called Persian herb. Vitamins A (from β-carotene), C, K and folate and the minerals calcium, iron and potassium are the predominant micro nutrients in spinach. It also supplies fiber. Carotenoids, β-carotene, lutein and zeaxanthin and phenolic compounds are the most significant phytochemicals. Recent studies have proven powerful antioxidant activity in spinach due to high levels of antioxidant compounds such as phenolics and carotenoids contents.

Antioxidant activity is essential, because many chronic diseases and age-related health problems are thought to arise from excess oxidative stress[19].Spinach-isolated carotenoids and glycolipids have been seen to elicit dose-dependent inhibition of BC cells proliferation. Numerous studies have also demonstrated that regular spinach intake was associated with decreased BC risk[31].

The anti-cancer effects of red spinach (*Amaranthus gangeticus Linn*) were analysed by cytotoxic assay using 3-(4,5-dimethylthiazol)-2,5-diphenyl tetrazolium bromide (MTT) shows that the aqueous spinach extract prevented BC cell line proliferation (MCF-7) with the values in IC50 98.8 µg/ml. These findings also indicate that spinach extracts by induction of apoptosis suppressed development of human BC MDA-MB-231 cells[45].

***Rosmarinus officinalis*:** Rosemary (*Rosmarinus officinalis*) is of the genus of labiates (*Lamiaceae*). Rosemary is an ordinary household herb in several regions around the world which is used for multiple purpose like food flavoring, drinks and beverages as well as cosmetic purposes[37]. This has been historically used to alleviate renal colic, dysmenorrhea, respiratory disorders and to promote hair growth. Phenolic diterpenes and triterpenes are the active constituents of the plant family. Caffeic acid, rosmarinic acid (RA), ursolic acid (UA), carnosic acid (CA) and carnosol are the most active prime compounds of Rosemary[11]. Elevated antioxidant effects of these compounds have anti-cancer and anti-inflammatory properties[3]. Therefore, rosemary extracts and their components hinder the initiation and promotion of cancer cells[21].

Yesil-Celiktas et al[53] had already shown the anti-BC activity of Rosmarinus officinalis leaves extraction. The active compounds, carnosic acid and rosmarinic acid were ultimately tested in different cell lines of the BC including MCF-, MDA-MB-231 by MTT. The extracts expressed countless cytotoxic effects towards different cell lines with comparatively low IC50 values varying from 12.50 to 47.55

µg/ml. The antitumor activity of a supercritical fluid rosemary extract (SFRE) in various BC cells explore its impact on the regulation of ER and HER2 signaling pathways.

Additionally, the most important BC-related mitogenic pathways found that SFRE activates antitumor activity against BC cells from different tumor subtypes and the downregulation of ER+ and HER2+ receptors showed the SFRE's anti-tumor effect on Estrogen-dependent (ER+) and overexpressing (HER2 +) BC subtypes. In addition, SFRE substantially increased the efficacy of BC chemotherapy (tamoxifen, trastuzumab and paclitaxel) to support the possible application of SFRE as a complementary approach in BC treatment[17].

***Echinacea*:** *Echinacea* is a therapeutic herb belonging to the botanical family Asteraceae, commonly used for self-medication in some European countries[18]. The various species of *Echinacea* consist of several herbaceous perennial crops which are native to North America and have historically been used to control various diseases. *Echinacea*, was used for treating snakebites, syphilis, septic wounds, tonsillitis, periodontitis, viral infections, furunculosis and nasopharyngeal catarrh[6]. The active constituents of *Echinacea* are polysaccharides, flavonoids, chicoric acid, alkyl amides, polyacetylenes and essential oils. Polysaccharides and chicoric acid glycosides have strong immunostimulatory function in *Echinacea*[20]. It is widely used for its antioxidant and anti-inflammatory effects. *Echinacea* extracts have already been recommended to support cancer chemotherapy.

In a recent analysis, it was stated that *Echinacea purpurea* extracts preserved noncancerous cells from apoptosis[10]. The interaction of doxorubicin along with compounds from *Echinacea angustifolia* roots preserved the non-cancerous cells. In addition, BC cells were efficiently treated with the *Echinacea* samples and doxorubicin. Cynarine has demonstrated strong antiproliferative activity on cells with MCF-7. *Echinacea* herbal medicines affect the proliferation of BC cells and those herbal medicines require further research with anti-BC medicines in order to authenticate its supplementary effects[22].

***Black cohosh*:** *Black cohosh* is a North American perennial herb in the family (*Ranunculaceae*) which has been widely used in Europe over the last 50 decades as a natural remedy to hormone therapy as well as other gynecological disorders[35]. The rhizome has been used for a multitude of purposes including inflammatory disorders, menstrual flow enhancement, dysmenorrhea, cough suppression, diarrhoea care and rheumatism.

The main compounds are triterpene glycosides and phenolics[25]. Additional chemical work has identified several polyphenolic compounds including caffeic acid, fukiic acid, piscidic acid and its derivatives[23].

Einbond et al[14] found that Black cohosh contains components that suppress the proliferation of human BC cells and may therefore potentially become effective in BC prevention or treatment. In growth inhibition and cell cycle analyses, the ethyl acetate Black cohosh fraction showed the highest potency. This Black cohosh fraction prevents the proliferation of ER+ MCF7 and ER−MDA-MB-453 human BC tumor cells with IC50 values of approximately 20 and 10 µg / ml. It also triggered arrest of the G1 cell cycle when assessed at 30µg / ml and 60µg / ml at G2/M for MCF7 cells. It indicates that the extract contains a combination of the components with the more active causing G1 arrest and the less active causing G2/M arrest.

These fractions and the prevalent actein, 23-epi-26-deoxyactein and cimiracemoside-A, diminish human BC cell growth in MCF7 and induce cell cycle arrest at G1. The first and most promising compound actin reduced the level of cycline D1, cdk4 and the hyperphosphorylated form of the pRb protein and raised the level of p21cip1 in MCF7 cells which may result in G1 arrest[14].

***Oregano*:** *Oregano* is a popular mint herb, from family *Lamiaceae*, commonly used in folk medicine to treat inflammatory diseases, respiratory and digestive disorders, headaches, rheumatism, diabetes and others. Flavonoids and phenolic acids in oregano species are some of the most nutritious and explored phytochemicals[29,41]. Kubatka et al documented that low dose Lyophilized Oregano (ORE) suppressed tumor frequency by 55.5%, 44% tumor occurrence and 44.5% tumor volume compared to controls. Analysis of rat tumor cells showed a decrease in expression of Ki67, VEGFR-2, CD24 and EpCAM and an increase in expression of caspase-3 after treatment with low dose ORE. High-dose ORE further decrease the expression of Bcl-2, VEGFR-2, CD24 and EpCAM and enhance the expression of caspase-3 in carcinoma cells. Moreover, *in vivo* analysis showed a decrease in the high-/low-grade carcinomas ratio in both groups.

Additionally, both MTT and BrdU assays measured the anti-proliferative effect of oregano extract on the MCF-7 cell line. An increase in the percentage of caspase-dependent and apparent non-caspase-dependent apoptotic pathways have been reported in ORE-treated MCF-7 cells. Termination of Bcl-2 anti-apoptotic activity, decline of the mitochondrial membrane potential and stimulation of the mitochondrial apoptosis pathway were also observed[26].

Vanilla planifolia: *Vanilla planifolia* (vanilla) is a well-known herb which is commonly used in various food and medicinal products as a flavouring agent[12]. Vanilla planifolia's key ingredient is vanillin, a methyl protocatechuic aldehyde (4-hydroxy-3-metoxybenzaldehyde) that makes up 85% of the total volatile in vanilla beans. The other constituents addressed are vanillic acid, anisaldehyde, benzoic acid hydroxide, anisic acid, caproic acid, vitispiranes, eugenol, phenols,

phenol ether, carbonyl compounds, acids, lactones, 25% carbohydrates, 15% fat, B complex and mineral salts[7]. Research by Kaliappan et al[24] showed the anti-proliferative effects of vanilla extract on MCF-7 cells. MTT assay clearly establishes potent anti-cancer activity against MCF-7 cells.

The assay detects reduction of MTT salt by mitochondrial dehydrogenase to a blue formazan compound indicating the feasibility of the cells. The cell viability of MCF-7 cells declined as the extract dose increased confirming the extract's anti-cancer property at 31.2µg / ml with an IC50 rating. The IC50 values reported for the above-mentioned alkaloid compounds indicate that the vanilla extract shows significant inhibition in MCF-7 cells compared with other alkaloids. In addition, the presence of DNA fragmentation shown by gel electrophoresis method supports the anti-proliferative effects and the induction of apoptosis of vanilla leaf extract[24].

***Coriandrum sativum*:** Coriander (*Coriandrum sativum L.*), a part of the *Apiaceae* family, was one of the most commonly used medicinal herbs with nutritious as well as therapeutic potential. Throughout the formulation of many household remedies, coriander is used to treat cold, high fever, diarrhea, vomiting, stomach illnesses and is often used as a remedy for constipation, worms, rheumatoid arthritis and muscle pain. Many of coriander's therapeutic qualities can be traced to its unique phytonutrients and is also often referred to as a depository for bioactive compounds[44]. Consequently, coriander herbal oils were strongly explored pharmaceutical activities like antibacterial, antioxidant, hypoglycemic, hypolipidemic, anxiolytic, analgesic, antifungal, antimicrobial, anti-inflammatory, anti-convulsant and anti-cancer activities[27].

The herb expressed anticancer activity in BC cells of MCF-7 by influencing antioxidant enzymes ultimately led to accumulation of H_2O_2, cell cycle arrest during the G2/M process and death by the death receptor and mitochondrial apoptotic pathways. Similarly, ascorbic acid is found in *C. sativum*, a compound well-known for its antioxidant properties and anti-BC[51]. A structure-specific Bcl-2 phosphorylated homoisoflavone molecule from Vietnamese coriander (*Polygonatum odoratum*) has proven its potent anti-BC activity with a biochemical mechanism by targeting the anti-apoptotic Bcl-2 protein phosphorylation, thereby induce apoptosis and G2/M cell cycle arrest in the BC line (MCF-7)[43].

***Mentha piperita*:** Peppermint or mint (*Mentha piperita L.*), a perennial aromatic herb of the *Lamiaceae (Labiatae)* family has gained greater interest on both the nutrition and pharmaceutical companies to its medical benefits to mankind. The generalized use of *M. piperita* in traditional medicine has encouraged exploration of its possible biological activity, admitting that even some recent studies have documented the cytotoxic and anti-inflammatory activity of *M. piperita* essential oil. There is still many evidence that peppermint derivatives play a key role in angiogenesis and metastatic preventative effect[32].The impact of peppermint oil aromatherapy for nausea and vomiting throughout the initial phase of chemotherapy in BC patients is also evident that the peppermint reduces nausea symptoms and act as a strong supplement for BC patients[13]. Vital peppermint oils blocked proliferation of both MCF-7 and MDA-MB-231at 350 and 550 µg/ml. There was also an up-regulation of the apoptotic genes p53 and Bid along with an escalation of the ratio of Bax/Bcl2[47].

***Murrayakoenigii*:** The *Murrayakoenigii (L.) Spreng* is a common herb, popularly known as curry leaf, belongs to the *Rutaceae* genus, which is endemic to India and now made available worldwide[8]. Curry leaf has a mildly pungent, salty, feebly acidic taste and is commonly used in the cooking process.

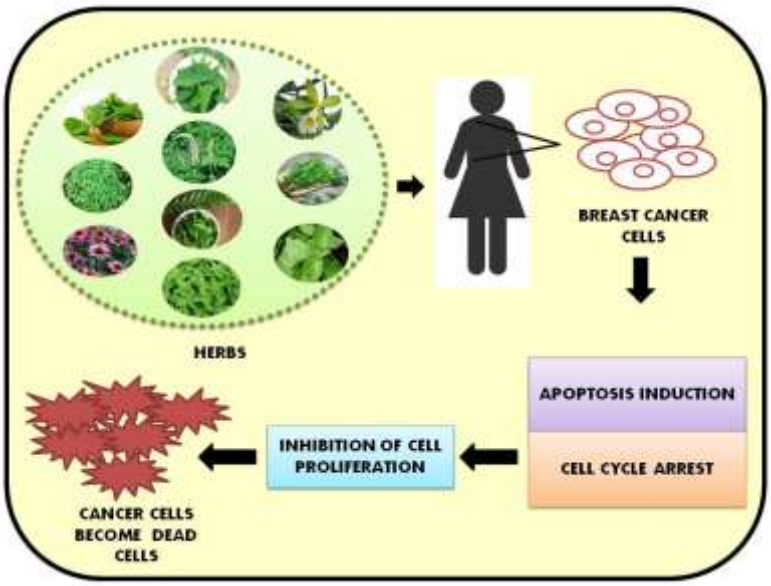

Fig. 1: Therapeutic herbs against Breast Cancer

Table 1
Medicinal herbs in the combat against Breast cancer

S.N.	Medicinal herbs	Common name	Family name	Active constituents	Mechanism against BC
1.	*Azadirachta indica*[4,49]	Neem	Meliaceae	Azadirachtanin, Azadirachtanin-A, Beta-sitosterol, Hyperoside, Isoazadirolide, Nimbaflavone, Nimbandiol, Nimbinene, Nimbolide, Quercitrin, Rutin and Vilasanin	• Upregulated proapoptotic genes and proteins, • Downregulation of angiogenic proteins, • Cell cycle arrest by modifying cell cycle regulatory proteins.
2.	*Spinacia oleracea*[19,45]	Spinach	*Amaranthaceae*	Vitamins A (from β-carotene), C, K and folate and the minerals, calcium, iron and potassium.	• Apoptosis induction
3.	*Rosmarinus officinalis*[11,17]	Rosemary	*Lamiaceae*	Caffeic acid, Rosmarinic acid (RA), Ursolic acid (UA), Carnosic acid (CA) and Carnosol	• Regulation of ER+ and HER2+ signaling pathways
4.	*Echinacea*[18,20,22]	Coneflower	*Asteraceae*	Polysaccharides, Flavonoids, Chicoric acid, Alkyl amides, Polyacetylenes and Essential oils	• Apoptosis induction, • Immunomodulatory effect
5.	*Black cohosh*[14,35]	black snakeroot	*Ranunculaceae*	Caffeic acid, Fukiic acid, Piscidic acid	• G1 arrest G2/M arrest, • Reduced the level of cyclin D1, cdk4.
6.	*Oregano*[26,41]	wild marjoram	*Lamiaceae*	Flavonoids and Phenolic acids	• Decrease the expression of Bcl-2, VEGFR-2, CD24 and EpCAM, • Enhance the expression of caspase-3
7.	*Vanilla planifolia*[12,24]	vanilla orchid	*Orchidaceae*	Vanillic acid, Anisaldehyde, Benzoic acid hydroxide, Anisic acid, Caproic acid, Vitispiranes, Eugenol	• Inhibition of cell proliferatrion
8.	*Coriandrum sativum*[44,51]	Coriander	*Apiaceae*	Linalool, p-cymene, Alpha-pinene, Camphor,Geraniol, Limonene,Fatty oil, Oleic and Linoleic acid.	• Cell cycle arrest during the G2/M process, • Promote death by the death receptor, • Stimulate mitochondrial apoptotic pathways.
9.	*Mentha piperita*[32,47]	Peppermint or mint	*Lamiaceae*	Menthol, Menthone, 1,8-Cineole, Menthyl acetate, Isovalerate, Pinene, Limonene	• Up-regulation of the apoptotic genes p53 and Bid
10.	*Murrayakoenigii*[1,5,52]	curry leaf	*Rutaceae*	Kelantan, Selangor and Johor	• Promoting the development of T cell cytokine (IL-2 and IFN-γ), • Sub-G0 phase arrest, • Induce apoptosis by facilitating cell death-transmitting signals

It is one of the traditional folk medicines containing a variety of potential phytochemicals with health beneficial properties. Distinct sections of *M. Koenigii* were used for the control of cough, asthma, vomiting, influenza, rheumatism, poisonous bites and skin eruptions in ancient Ayurveda medicine. In particular, antitumor, antioxidant, anti-inflammatory, antihyperglycemic and hypoglycemic effects have also been investigated[5]. A preliminary analysis confirmed that curry leaf extracts (Kelantan, Selangor and Johor) seemed to have a massive anti-cancer activity towards MDA-MB-231 cancer cells with such an inhibitor rate of 67.2, 59.8 and 53.6 percent at a dose of 320 µg / mL with IC50 value of 103.4, 149.6 and 194.3 µg / mL respectively[16].

In addition, *M. Koenigii* aqueous extract disrupted BC progression and diminished tumor mitotic divergence by promoting the development of T cell cytokine (IL-2 and IFN-γ) and cytotoxicity[52]. Moreover, Curry Leaf Extract lowered the survival of cells and modified dose-dependent growth kinetics in BC cell lines thereby shows substantial cell arrest in S phase only in cancer cells[38]. Koenimbin, an active compound in *M. Koenigi*, induce apoptosis in MCF7 cells by facilitating cell death-transmitting signals controlling the mitochondrial membrane potential via Bcl2 downregulation and Bax upregulation owing to cytochrome c release from the mitochondria to the cytosol. It has also cause sub-G_0 phase arrest ($P<0.05$) in BC cells[1].

Conclusion

Healing comes only from nature. Herbs instigate their therapeutic impact via its countless targets and are incredibly safe. According to the preceding analysis, it is quite clear that herbal derivatives have a promising potential for both the prevention and treatment of breast cancer. The naturally derived herbal products addressed in this study act as an excellent starting point for plenty of pharmaceutical exploration.

Herbal medicines were not an alternative medicines. they are the only original medicine for breast cancer treatment. Current data to discuss herbal activity against breast cancer is too limited. Sensibly, future scientific studies will have to take initiatives to validate those herbs which hopefully mitigate the financial burden of costly breast cancer therapies.

References

1. Ahmadipour F., Noordin M.I., Syam Mohan A.A., Paydar M., Looi C.Y., Keong Y.S., Siyamak E.N., Fani S., Firoozi M., Yong C.L. and Sukari M.A., Koenimbin, a natural dietary compound of Murrayakoenigii (L) Spreng: inhibition of MCF7 breast cancer cells and targeting of derived MCF7 breast cancer stem cells (CD44+/CD24−/low): an in vitro study, *Drug Design, Development and Therapy*, **9**, 1193 **(2015)**

2. Akram M., Iqbal M., Daniyal M. and Khan A.U., Awareness and current knowledge of breast cancer, *Biological Research*, **50(1)**, 33 **(2017)**

3. Andersson D., Cheng Y. and Duan R.D., Ursolic acid inhibits the formation of aberrant crypt foci and affects colonic sphingomyelin hydrolyzing enzymes in azoxymethane-treated rats, *Journal of Cancer Research and Clinical Oncology*, **134(1)**, 101-7 **(2008)**

4. Arumugam A., Agullo P., Boopalan T., Nandy S., Lopez R., Gutierrez C., Narayan M. and Rajkumar L., Neem leaf extract inhibits mammary carcinogenesis by altering cell proliferation, apoptosis and angiogenesis. *Cancer Biology & Therapy*, **15(1)**, 26-34 **(2014)**

5. Balakrishnan R., Vijayraja D., Jo S.H., Ganesan P., Su-Kim I. and Choi D.K., Medicinal profile, phytochemistry and pharmacological activities of Murrayakoenigii and its primary bioactive compounds, *Antioxidants*, **9(2)**, 101 **(2020)**

6. Barnes J., Anderson L.A., Gibbons S. and Phillipson J.D., Echinacea species (Echinacea angustifolia (DC.) Hell., Echinacea pallida (Nutt.) Nutt., Echinacea purpurea (L.) Moench): a review of their chemistry, pharmacology and clinical properties, *Journal of Pharmacy and Pharmacology*, **57(8)**, 929-54 **(2005)**

7. Belay M.T. and Poole C.F., Determination of vanillin and related flavor compounds in natural vanilla extracts and vanilla-flavored foods by thin layer chromatography and automated multiple development, *Chromatographia*, **37(7-8)**, 365-73 **(1993)**

8. Bhandari P.R., Curry leaf (Murrayakoenigii) or cure leaf: review of its curative properties, *Journal of Medical Nutrition and Nutraceuticals*, **1(2)**, 92 **(2012)**

9. Cassidy A., Are herbal remedies and dietary supplements safe and effective for breast cancer patients, *Breast Cancer Research*, **5(6)**, 300 **(2012)**

10. Chicca A., Adinolfi B., Pellati F., Orlandini G., Benvenuti S. and Nieri P., Cytotoxic activity and G1 cell cycle arrest of a Dienynone from Echinacea pallida, *Planta Medica*, **76(5)**, 444-6 **(2010)**

11. Costa S., Utan A., Speroni E., Cervellati R., Piva G., Prandini A. and Guerra M.C., Carnosic acid from rosemary extracts: a potential chemoprotective agent against aflatoxin B1. An in vitro study, *Journal of Applied Toxicology: An International Journal*, **27(2)**, 152-9 **(2007)**

12. Dignum M.J., Kerler J. and Verpoorte R., Vanilla production: technological, chemical and biosynthetic aspects, *Food Reviews International*, **17(2)**, 119-20 **(2001)**

13. Eghbali M., Varaei S., Hosseini M., Yekaninejad M.S. and Shahi F., The effect of aromatherapy with peppermint essential oil on nausea and vomiting in the acute phase of chemotherapy in patients with breast cancer, *Journal of Babol University of Medical Sciences*, **20(9)**, 66-71 **(2018)**

14. Einbond L.S. et al, Growth inhibitory activity of extracts and purified components of black cohosh on human breast cancer cells, *Breast Cancer Research and Treatment*, **83(3)**, 221-31 **(2004)**

15. Ekor M., The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety, *Frontiers in Pharmacology*, **4**, 177 **(2014)**

16. Ghasemzadeh A., Jaafar H.Z., Rahmat A. and Devarajan T., Evaluation of bioactive compounds, pharmaceutical quality and anticancer activity of curry leaf (Murrayakoenigii L.), *Evidence-Based Complementary and Alternative Medicine*, **1**, 1-8 **(2014)**

17. González-Vallinas M., Molina S., Vicente G., Sánchez-Martínez R., Vargas T., García-Risco M.R., Fornari T., Reglero G. and Ramirez de Molina A., Modulation of estrogen and epidermal growth factor receptors by rosemary extract in breast cancer cells, *Electrophoresis*, **35(11)**, 1719-27 **(2014)**

18. Harbage J.F., Micropropagation of Echinacea angustifolia, E. pallida and E. purpurea from stem and seed explants, *Hort Science*, **36(2)**, 360-4 **(2001)**

19. Hedges L.J. and Lister C.E., Nutritional attributes of spinach, silver beet and eggplant, Crop Food Research Confidential Report **(2007)**

20. Hobbs C., Echinacea: A literature review, *Herbal Gram.*, **30(Suppl)**, 33-47 **(1994)**

21. Huang S.C., Ho C.T., Lin-Shiau S.Y. and Lin J.K., Carnosol inhibits the invasion of B16/F10 mouse melanoma cells by suppressing metalloproteinase-9 through down-regulating nuclear factor-kappaB and c-Jun, *Biochemical Pharmacology*, **69(2)**, 221-32 **(2005)**

22. Huntimer E.D., Halaweish F.T. and Chase C.C., Proliferative activity of Echinacea angustifolia root extracts on cancer cells: Interference with doxorubicin cytotoxicity, *Chemistry & Biodiversity*, **3(6)**, 695-703 **(2006)**

23. Jacobson J.S., Troxel A.B., Evans J., Klaus L., Vahdat L., Kinne D., Lo K.S., Moore A., Rosenman P.J., Kaufman E.L. and Neugut A.I., Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer, *Journal of Clinical Oncology*, **19(10)**, 2739-45 **(2001)**

24. Kaliappan V. and Kumaravelu P., Antiproliferative effects of Vanilla planifolia leaf extract against breast cancer MCF-7 cells, *International Journal of Basic & Clinical Pharmacology*, **8(1)**, 51 **(2019)**

25. Kronenberg F. and Fugh-Berman A., Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials, *Annals of Internal Medicine*, **137(10)**, 805-13 **(2002)**

26. Kubatka P. et al, Oregano demonstrates distinct tumour-suppressive effects in the breast carcinoma model, *European Journal of Nutrition*, **56(3)**, 1303-16 **(2017)**

27. Laribi B., Kouki K., M'Hamdi M. and Bettaieb T., Coriander (Coriandrum sativum L.) and its bioactive constituents, *Fitoterapia*, **103**, 9-26 **(2015)**

28. Laskar Y.B., Lourembam R.M. and Mazumder P.B., Herbal Remedies for Breast Cancer Prevention and Treatment, Medicinal Plants-Use in Prevention and Treatment of Diseases, Intech Open **(2020)**

29. Leyva-López N., Nair V., Bang W.Y., Cisneros-Zevallos L. and Heredia J.B., Protective role of terpenes and polyphenols from three species of Oregano (Lippia graveolens, Lippiapalmeri and Hedeoma patens) on the suppression of lipopolysaccharide-induced inflammation in RAW 264.7 macrophage cells, *Journal of Ethnopharmacology*, **187**, 302-12 **(2016)**

30. Liao G.S., Apaya M.K. and Shyur L.F., Herbal medicine and acupuncture for breast cancer palliative care and adjuvant therapy, *Evidence-Based Complementary and Alternative Medicine*, **1**, 1-17 **(2013)**

31. Longnecker M.P., Newcomb P.A., Mittendorf R., Greenberg E.R. and Willett W.C., Intake of carrots, spinach and supplements containing vitamin A in relation to risk of breast cancer, *Cancer Epidemiology and Prevention Biomarkers*, **6(11)**, 887-92 **(1997)**

32. Loolaie M., Moasefi N., Rasouli H. and Adibi H., Peppermint and its functionality: A review, *Arch. Clin. Microbiol*., **8(4)**, 54 **(2017)**

33. Ma H., Carpenter C.L., Sullivan-Halley J. and Bernstein L., The roles of herbal remedies in survival and quality of life among long-term breast cancer survivors-results of a prospective study, *BMC Cancer*, **11(1)**, 222 **(2011)**

34. Ma X. and Yu H., Cancer issue: global burden of cancer, *The Yale Journal of Biology and Medicine*, **79(3-4)**, 85 **(2006)**

35. McKenna D.J., Jones K., Humphrey S. and Hughes K., Black cohosh: efficacy, safety and use in clinical and preclinical applications, *Alternative Therapies in Health and Medicine*, **7(3)**, 93 **(2001)**

36. Mitra S. and Dash R., Natural products for the management and prevention of breast cancer, *Evidence-Based Complementary and Alternative Medicine*, **1**, 1-23**(2018)**

37. Moran A.E., Carothers A.M., Weyant M.J., Redston M. and Bertagnolli M.M., Carnosol inhibits β-catenin tyrosine phosphorylation and prevents adenoma formation in the C57BL/6J/Min/+(Min/+) mouse, *Cancer Research*, **65(3)**, 1097-104 **(2005)**

38. Noolu B., Ajumeera R., Chauhan A., Nagalla B., Manchala R. and Ismail A., Murrayakoenigii leaf extract inhibits proteasome activity and induces cell death in breast cancer cells, *BMC Complementary and Alternative Medicine*, **13(1)**, 7 **(2013)**

39. Odle T.G., Adverse effects of breast cancer treatment, *Radiologic Technology*, **85(3)**, 297M-319M **(2014)**

40. Pan S.Y., Litscher G., Gao S.H., Zhou S.F., Yu Z.L., Chen H.Q., Zhang S.F., Tang M.K., Sun J.N. and Ko K.M., Historical perspective of traditional indigenous medical practices: the current renaissance and conservation of herbal resources, *Evidence-Based Complementary and Alternative Medicine*, **1**, 1-20 **(2014)**

41. Pascual M.E., Slowing K., Carretero E., Mata D.S. and Villar A., Lippia: traditional uses, chemistry and pharmacology: a review, *Journal of Ethnopharmacology*, **76(3)**, 201-14 **(2001)**

42. Puri H.S., Neem: the divine tree Azadirachta indica, CRC Press **(1999)**

43. Rafi M.M. and Vastano B.C., Identification of a structure specific Bcl-2 phosphorylating homoisoflavone molecule from

Vietnamese coriander (Polygonatum odoratum) that induces apoptosis and G2/M cell cycle arrest in breast cancer cell lines, *Food Chemistry*, **104(1)**, 332-40 **(2007)**

44. Rajeshwari U. and Andallu B., Medicinal benefits of coriander (Coriandrum sativum L), *Spatula DD*, **1(1)**, 51-8 **(2011)**

45. Sani H.A., Rahmat A., Ismail M., Rosli R. and Endrini S., Potential anticancer effect of red spinach (Amaranthus gangeticus) extract, *Asia Pacific Journal of Clinical Nutrition*, **13(4)**, 396-400 **(2004)**

46. Sewell R.D. and Rafieian-Kopaei M., The history and ups and downs of herbal medicines usage, *Journal of HerbMed Pharmacology*, **3**, 1-3 **(2014)**

47. Seyedeh Zeinab Taheri Rouhi, Proliferation inhibitory effects of peppermint oil on human breast cancer cell lines, *Journal of Cancer Science and Therapeutics*, **6(10)**, 1 **(2014)**

48. Sharma G.N., Dave R., Sanadya J., Sharma P. and Sharma K.K., Various types and management of breast cancer: an overview, *Journal of Advanced Pharmaceutical Technology & Research*, **1(2)**, 109 **(2010)**

49. Sharma R., Kaushik S., Shyam H., Agarwal S. and Balapure A.K., Neem seed oil induces apoptosis in MCF-7 and MDA MB-231 human breast cancer cells, *Asian Pacific Journal of Cancer Prevention: APJCP*, **18(8)**, 2135 **(2017)**

50. Subapriya R. and Nagini S., Medicinal properties of neem leaves: a review, *Current Medicinal Chemistry-Anti-Cancer Agents*, **5(2)**, 149-56 **(2005)**

51. Tang E.L., Rajarajeswaran J., Fung S.Y. and Kanthimathi M.S., Antioxidant activity of Coriandrum sativum and protection against DNA damage and cancer cell migration, *BMC Complementary and Alternative Medicine*, **13(1)**, 347 **(2013)**

52. Yeap S.K., Abu N., Mohamad N.E., Beh B.K., Ho W.Y., Ebrahimi S., Yusof H.M., Ky H., Tan S.W. and Alitheen N.B., Chemopreventive and immunomodulatory effects of Murrayakoenigii aqueous extract on 4T1 breast cancer cell-challenged mice, *BMC Complementary and Alternative Medicine*, **15(1)**, 306 **(2015)**

53. Yesil-Celiktas O., Sevimli C., Bedir E. and Vardar-Sukan F., Inhibitory effects of rosemary extracts, carnosic acid and rosmarinic acid on the growth of various human cancer cell lines, *Plant Foods for Human Nutrition*, **65(2)**, 158-63 **(2010)**

54. Yin S.Y., Wei W.C., Jian F.Y. and Yang N.S., Therapeutic applications of herbal medicines for cancer patients, *Evidence-Based Complementary and Alternative Medicine*, **1**, 1-15 **(2013)**

55. Yue G.G., Lee J.K., Chan B.C., Kwok H.F., Hoi S.W., Sze D.M., Fung K.P., Leung P.C. and Bik-San Lau C., An innovative anti-cancer Chinese herbal formula exhibited multi-targeted efficacies in metastatic breast cancer mouse model, *Chinese Medicine*, **13(1)**, 64 **(2018)**

56. Zingue S., Kamga Silihe K., FoubaBourfane I., Boukar A., Tueche A.B., Njuh A.N. and Njamen D., Potential of Regular Consumption of Cameroonian Neem (Azadirachta indica L.) Oil for Prevention of the 7, 12-Dimethylbenz (a) anthracene-Induced Breast Cancer in High-Fat/Sucrose-Fed Wistar Rats, *Evidence-Based Complementary and Alternative Medicine*, **1**, 1-13 **(2019)**.

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