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Herbal Medicine: As a Complementary therapy to Traditional Treatment for Breast Cancer-A Systemic review

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ABSTRACT: Herbal remedies have been used for centuries to prevent and treat various health conditions, including breast cancer. Breast cancer is among the most common type of cancer in women around the globe. Second most common cause of breast cancer related deaths in women. Herbal products can be trusted for cancer treatment because of low toxicity. Besides, herbal remedies are easily accepted by the majority of women suffering from breast cancer because of their easy availability and affordability. It focused on the anti-carcinogenic mechanism of the phytocompounds to report their potential chemotherapeutic role. Herbal products have a huge market in medical field. Among herbal supplements which are consumed in the population, Echinacea preparations are very popular. It has immune boosting effects that can suppress tumour growth and invasion. Garlicshows anti-cancerous potential, interfering with the proliferations, motility and malignant progression of both non-invasive breast tumor cells. Curcumin has chemopreventive and anti-tumoral activities against some aggressive and recurrent cancers. Green tea had been shown to have potential beneficial effects on different types of cancer. Korean ginseng is closely associated with its bioactive components including ginsenosides, phenolic acids, flavonoids and polysaccharides. Black cohosh might decrease the effects of Estrogen. Flaxseed reduce the risk of developing cancer due to it is rich in omega-3 fatty acids.

KEYWORDS: Herbal remedies, Low toxicity, Echinacea, Garlic, Curcumin, Green tea, Ginseng, Black cohosh, Flax seed.

I. INTRODUCTION

Breast cancer is a malignant growth that begins in the tissue. It is the second most commonly diagnosed cancer and the number one cause of cancer related death among women with 23% of cancer diagnoses and 14% of cancer death attributable to it. The mysterious histories about breast cancer are ancient Egyptian papyri were the first to describe the disease more than 3000 years ago and labeled it as “untreatable”.

From an imbalance in the body fluids, it is referred to as the humoralism theory in the seventeenth century as the divine punishment; it was only until notable advances in surgical practices came to life in the nineteenth century that breast cancer can be curable. The recent evidence stated that it had surpassed lung cancer becoming now the leading cause of cancer in 2020. The incidence of 2.3 million new cases per year is attributable to breast cancer. In India, the incidence has increased significantly, almost by 50%, between 1965 and 1985. The cancer not well manageable in late stages with only 21% survival rates for stage IV patients with advanced breast cancer (ABC). Also, the survival rates are comparatively poor in India to Western countries due to reasons such as earlier onset of cancer, diagnosis at a lateral stage, delayed initiation of treatments and inadequate treatment if initiated. To mark world cancer day 2021, IARC (International Agency for Research on Cancer) is highlighting some of its key research project, which provide evidence to support interventions to reduce the burden of breast cancer, raise awareness of breast cancer, and provide recommendations on how individuals can reduce their own risk of developing breast cancer disease. In 2022, there were 26% in women diagnosed with breast cancer in India and 2.3 million cases globally according to WHO was released on February 1, 2024.

Breast cancer occurs in every country of the world in women at any age after puberty but with increasing rates in later life. The "assessed" risk parts for breast cancer includes,

- Never having been pregnant,
- Having one and only pregnancy instead of different,

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- After pregnancy no breast feeding,
- Utilization of postmenopausal estrogen replacement treatment or postmenopausal hormone Substitution treatment,
- Orally intake of contraceptives,
- Some Particular dietary habits like high intake of fat and less intake of fibres,
- characteristic items, and vegetables,
- Low proportion of Phytoestorgens,
- Alcohol use,
- Smoking of tobacco, and less than ideal origination.
- The risk increments as the age of women increments particularly following 40years old.

Global estimates reveal striking inequities in the breast cancer burden according to human development. For instance, in countries with a very high Human Development Index(HDI), 1 in 12 women will be diagnosed with breast cancer in their lifetime and 1 in 71 womendie of breast cancer. In contrast, in Countries with a low HDI; while only 1 in 27 women are diagnosed with breast cancer in their lifetime, 1 in 48 women will die from it. Female gender is the strongest breast cancer risk factor. Approximately 99% of breast cancers occur in women and 0.5–1% of breast cancers occur in men. The treatment of breast cancer in men follows the same principles of management as for women.

The common structure of breast consists of 15–20 sections, known as lobes, which are further divided into lobules. Small ‘ducts’ are there to connect the lobes and lobules. Therefore, general form of breast tumor is ductal cancer. Ductal tumor occurs in duct’s cells and invades in both breasts as compared to other types of cells. Other classes of breast cancer are invasive and non-invasive. Non-invasive cancer means, type of tumor that does not range past in the zone where it is originally formed. Invasive breast tumor is metastasize cancer, it has the tendency to spread in surrounding tissues other than the area where it is originally produced. General inflammation of breast refers a less severe form of tumor, called inflammatory breast tumor. Other forms of breast tumor are medullary cancer, defined as ‘‘an invasive breast tumor that produces a separate border among cancerous tissue and regular tissue” mucinous cancer, developed by mucus generating tumor cells, and tube-like cancer (WHO, 1981). There are various stages of breast cancer and as follows,

- Stage 0 - abnormal cells in lining of the ducts or sections of the breast. Results in increased risk of developing cancer in both breasts. It has 100% of survival rate.
- Stage 1 - cancer in the breast tissues tumor less than 1 inch across. It has survival rate of 98%.
- Stage 2 - a cancer in the breast tissues less than 2 inches across. Cancer may also spread to auxiliary lymph nodes. It has 88% of survival rate.
- Stage 3 - a tumor is larger than 2 inches across with extensive spread to auxiliary or nearby lymph nodes. Possible dimpling, inflammation or change of skin colour. It has survival rate of 52%.
- Stage 4 - spread of cancer beyond the immediate region of the breast. It has just 16% of survival rate.

Most people will not experience any symptoms when the cancer is still early hence the importance of early detection. Breast cancer can have combinations of symptoms, especially when it is more advanced. Symptoms of breast cancer are includes,

- A breast lump or thickening, often without pain,
- Change in size, shape or appearance of the breast,
- Dimpling, redness, pitting or other changes in the skin,
- Change in nipple appearance or the skin surrounding the nipple (areola),
- Abnormal or blood fluids from the nipple.

People with an abnormal breast lump should seek medical care, even if the lump does not hurt. Most breast lumps are not cancer. Breast lumps that are cancerous are more likely to be successfully treated when they are small and have not spread to nearby lymph nodes. Breast cancers may spread to other areas of the body and trigger other symptoms. Often, the most common first detectable site of spread is to the lymph nodes under the arm although it is possible to have cancer-bearing lymph nodes that cannot be felt. Over time, cancerous cells may spread to other organs including the lungs, liver, brain and bones. Once they reach these sites, new cancer-related symptoms such as bone pain or headaches may appear.

Treatment for breast cancer depends on the subtype of cancer and how much it has spread outside of the breast to lymph nodes (stages II or III) or to other parts of the body (stage IV).Doctors combine

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treatments to minimize the chances of the cancer coming back (recurrence). These are includes,

- Surgery to remove the breast tumour
- Radiation therapy to reduce recurrence risk in the breast and surrounding tissues
- Medications to kill cancer cells and prevent spreading of cancer cells, including
- Hormonal therapies, chemotherapy or targeted biological therapies.

Treatments for breast cancer are includes,

• Surgery may remove just the cancerous tissue (called a lumpectomy) or the whole breast (mastectomy). Surgery may also remove lymph nodes to assess the cancer's ability to spread.

• Radiation therapy treats residual microscopic cancers left behind in the breast tissue and/or lymph nodes and minimizes the chances of cancer recurring on the chest wall.

• Advanced cancers can erode through the skin to cause open sores (ulceration) but are not necessarily painful. Women with breast wounds that do not heal should seek medical care to have a biopsy performed.

• Medicines to treat breast cancers are selected based on the biological properties of the cancer as determined by special tests (tumour marker determination). The great majority of drugs used for breast cancer are already on the WHO Essential MedicinesList (EML).

• Lymph nodes are removed at the time of cancer surgery for invasive cancers. Complete removal of the lymph node in under arm (complete axillary dissection) in the past was thought to be necessary to prevent the spread of cancer. A smaller lymph node procedure called "sentinel node biopsy" is now preferred as it has fewer complications.

• Medical treatments for breast cancers, which may be given before ("neoadjuvant") or after ("adjuvant") surgery, is based on the biological sub typing of the cancers. Certain subtypes of breast cancer are more aggressive than others such as triple negative (those that do not express estrogen receptor (ER), progesterone receptor (PR) or HER-2 receptor). Cancer that express the estrogen receptor (ER) and/or progesterone receptor(PR) are likely to respond to endocrine (hormone) therapies such as tamoxifen or aromatase inhibitors. These medicines are taken orally for 5–10 years and reduce the chance of recurrence of these "hormone-positive" cancers by nearly half. Endocrine therapies can cause symptoms of menopause but are generally well tolerated.

• Radiotherapy plays a very important role in treating breast cancer. With early-stage breast cancers, radiation can prevent a woman having to undergo a mastectomy. With later stage cancers, radiotherapy can reduce cancer recurrence risk even when a mastectomy has been performed. For advanced stages of breast cancer, in some circumstances, radiation therapy may reduce the likelihood of dying of the disease. The effectiveness of breast cancer therapies depends on the full course of treatment. Partial treatment is less likely to lead to a positive outcome.

The best prevention and control of breast cancer is to check your breast is about a week after your period's ends. It's important you check at the same time every month. There are few steps are involved in the procedure are

• Step 1: lie down on your back with one hand behind your head. Use the pads ofyour opposite hand to examine each beast.

• Step 2: move your three fingers in dime-sized circles. Do tree circles in spot, starting with light pressure, then medium and lastly use deeper pressure. Then "walk" your fingers to next area-do not lift fingers off you're in the armpits.

• Step 3: starting at your breast bone, work your way down breast and back up indimesized circles. Spend extra time in the armpit.

• Step 4: gently squeeze each nipple and look for discharge or pain

• Step 5: call your doctor if you notice anything abnormal.

Chemotherapy is the suggested and viable therapy choice for bosom disease. For quite a long time, herbs and plants have been utilized for restorative purposes and as food also. Herbal products can be trusted for malignant growth treatment on account of their low toxicity. Also, natural remedies are effortlessly acknowledged by most of woman suffering from breast malignant growth due to their simple accessibility and affordability. The plants and herbs have assumed vital part in maintaining the human health. Various sorts of plants that hold the resistant stimulating and anti-tumour properties are Echinacea, Garlic, Turmeric, Burdock, Carotenoids, Green Tea, Ginseng, Black Cohosh, Flax Seed, and Annona muricata. Enormous assortment of active phytochemicals like polyphenolics, carotenoids, flavonoids, Ligands, sulfides, terpenoids, lignans and plant sterols has been distinguished in various kinds of spices. These phytochemicals have various mechanisms of action. They either stimulate the

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protective enzyme like glutathione transferase or prevent the cell proliferation.

II. PLANT PROFILE

Echinacea

Garlic

[1]Echinacea: Synonym: Purple Coneflower; Family Name: Asteraceae; Species: Echinacea Purpurea (L.) Moench.,; Source: Dried Whole Plant; Route Of admistration: Oral; Medicinal Uses: Anti-Cancer, Fighting Inflammation, Antiviral, Antioxidant, Common Cold.
[2] Garlic: Synonym: Ali Blanc, Vitlok; Family Name: Amaryllidaceae; Species: Allium Sativum(L); Source: Entire Bulb; Route Ofadmistration: Oral; Medicinal Uses: Liver Injury, Boost Heart Health, Common Cold, Manage Cholesterol and Blood Pressure.

Green tea

Turmeric

[3] Turmeric: Synonym: Haldi, Manjal and Curcuma; Family: Zingiberaceae; Species: Curcuma Longa L.; Source: Rhizomes; Route Ofadmistration: Oral, Intravenous, Transdermal, Intraperitoneal, Intra Tumoral; Medicinal Uses: Blood Sugar Level, Heart Disease, Immune Boosting, Improve-Digestion, Reduce Inflammation.
[4] Green tea: Synonym: Jade Dew, Matcha, Dragon Well Brew; Family Name: Theaceae; Species: Camellia Sinensis L.; Source: Leaves; Route Of Admistration :Injection, Inhalation, Beverage, Solid Dosage, Transdermal; Medicinal Uses: Anti-Aging, Diabetes, Blood Pressure, Liver Disease, Immune Booster.

Ginseng

Black cohosh

[5] Ginseng: Synonym: Asian Ginseng, Korean Ginseng; Family: Araliaceae; Species: Panax Ginseng L.; Source: Root And Seeds; Route Ofadmistration: Oral; Medicinal Uses: Fatigue, Improve Focus, Flu, Insomnia, Menopausal Symptom.
[6] Black cohosh: Synonym: Black Snakeroot, Bugwort, Karuvachi; Family Name: Buttercup; Species: Actaearacemosa L.; Source: Root And Rhizomes; Route Of Admistration: Oral;Medicinal Uses: Menopause, Premenstrual Syndrome, Painful Menstruation, Weak And Brittle Bones, Sore Throat.

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Flax seed

[7] Flax seed: Synonym: Ali Vidai, Alsi; Family Name: Linaceaespecies: Linumusitatissimuml.; Source: Seed; Route Ofadmistration: Oral; Medicinal Uses: Hair Growth, Relieve Constipation, Ldl, Heart Disease, Lower Blood Cholesterol.

III. MATERIALS AND METHODS:

[1] Echinacea:
Cell viability

MFC-7 cells were treated with different concentrations of Echinacoside (98% (HPLC), 5, 10, 20, and 40 µg/ml) at different times (1-6 days). Cell viability was measured with a 3-(4, 5)-dimethylthiahiazo (-z-y1)-3, 5-di-phenytetrazoliumromide (MTT) kit according to the manufacturer's instructions. Briefly, MFC-7 cells were seeded in 96-well plates (5000 cells/well) and cultured for 1 to 6 days. After treatments, MTT reagent was added to each well and incubated at 37°C for 6 hours. Finally, the optical density value at a wavelength of 450 nm was determined using a microplate reader.

[2] Garlic:
Western blot analysis

Western blotting was performed on ASEE-treated and untreated TNBC cells. In brief, a frozen RIPA lysis solution with a protease and phosphatase inhibitor cocktail was used to obtain cell lysates. Protein samples (40 µg each) were separated by electrophoresis on a 10 %–12 % SDS-PAGE gel and then transferred to a PVDF transfer membrane

[3] Turmeric:
Haemolysis test

Red blood cells from the blood of healthy rats were collected by centrifugation at 3000rpm for 5min. After washing the cells with normal saline, different concentrations (5-400 microgram/mL) of nanoparticles were added to the RBC suspension. RBCs treated with distilled water and NS were used a positive and negative controls, respectively. The samples were incubated at 37 degree C for 2h and then centrifuged for 10min at 3000rpm. The absorbance of the supernatant was measured at 541nm by UV- Vis spectroscopy.

[4] Green tea:
Cell Line

Cell line and culture conditions the cells were cultured in DMEM medium supplemented with 10% fetal bovine serum, 100µg/ml penicillin /streptomycin, and 2Mm I-glutamine. The culture was maintained at 37°c and in an atmosphere containing 5% CO2. The cell culture density was kept to maximum 1×106 cells/ml.

[5] Ginseng:
Cytotoxicity assay

Trypan Blue solution: Trypan Blue is an essential dye, use in estimating number of viable cells present in a population (Kumar et al., 2015). In brief, cell suspension in a fixed volume of cells was made (e.g. 1ml). Cell suspension of 50µl was taken and was mixed with an equal volume of trypan blue (final concentration 0.4%). The solution was mixed well then was transferred to a hemocytometer for counting (in< 5 minutes). Calculate the number of cells per ml, and the total number of cells, using the following formula: % viability = (live cell count/total cell count) *100

[6] Black cohosh:
Search strategy (PSYCHINFO)

According to Psychinfo research on breast cancer, often focuses on the psychological aspects of the disease, including how factors like stress, coping mechanisms social support, depression and anxiety can impact a patient's experience with breast cancer diagnosis, treatment and survivorship, as well as investigating the effectiveness of psychological interventions to manage these challenges.

[7] Flax seed:
Trypan blue cell survival assay

The cell cultures (3×10^5/ml) were plated on 60 mm tissue culture plates on day 0. The cells were treated with 0.3% (v/v, low concentration) or 0.9% (v/v, high concentration) flaxseed oils on day 1 and were maintained without changing the media for the duration of the experiment. Replicate plates were harvested each day for 4–6 days the cell pellets suspended in PBS, pH 7.4 containing

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0.015% trypan blue, and clear (live) cells were counted on a hemocytometer. Cell counts were performed in octuplet, the numbers for each experiment averaged, and the mean ± standard deviation for fold increase reported for 3 independent experiments.

IV. SUMMARY

Breast cancer involves changes in a variety of biological behaviors, as well as abnormalities in multiple signal transduction pathways. Extraction of active components from natural drugs can provide novel ideas for the treatment of tumors. Echinacoside can induce mitochondrial membrane potential imbalance, thus promoting the mitochondrial internal-dependent apoptosis pathway. Through this pathway, it could promote the apoptosis of tumor cells and inhibit the proliferation of human osteosarcoma, breast cancer and rectal cancer cells. These results indicate that Echinacoside has a certain inhibitory effect on the proliferation of tumor cells, indicating that Echinacoside may become an adjuvant drug for the treatment of tumor cells.

We investigated the cell death induced by ASEE in MDA-MB-231 cells, as well as the in silico investigation to analyze the binding interaction of identified components alliin and allicin, through HPLC analysis, with effective cancer markers of breast cancer cells. ASEE reduced the level of p38 and caused cellular apoptosis which indicates that p38 MAPK acts as tumor promoter in MDA-MB-231 cell death.

Curcumin has demonstrated heterogeneous mechanism of action, including antiproliferative effects, modulation of various signaling pathways, regulations of gene transcription, and the ability to disrupt tumors cell divisions. While the oral route offers advantages in non-invationess, cost-effectiveness, and tolerance, it suffers from lower bioavailability than intravenous route.

A statistically significant inverse association between green tea and breast cancer was reviewed. However, a beneficial effect of green tea cannot be excluded, because only case-control studies were analyzed, a statistically significant protective effect was observed. Indeed the importance of case-control studies in defining the causal relationship between exposure and event is well known.

Ginseng is one of the most popular herbs originating from Eastern countries. The present study demonstrated that ginseng had antitumor effects on MCF-7 cells. It disrupted the proliferation, cell cycle, apoptosis and migration of MCF-7 breast cancer cells and promoted apoptosis by interfering with the expression of Bcl-2 in tumor cells.

Black cohosh does not influence circulating levels of estradiol, FSH, or LH appears to extract estrogenic effects on breast tissues. These are mixed evidence regarding the efficiency of black cohosh for the reduction of hot flashes in breast cancer survivors. Based on preliminary observational data, black cohosh does not appear to adversely impact the risk of breast cancer recurrence or incidence in patients with or without a history of breast cancer.

Flaxseed showing a decrease in cell growth after treatment and confirming its potential as an inhibitory agent against cancer cell proliferation. Additionally, the characterization of flaxseed oil's impact on different cell lines, including breast cancer and other types, showed its selective cytotoxicity.

V. CONCLUSION

The present study confirmed that Echinacoside decreased the viability of MCF-7 cells in a dose and time-dependent manner. The cell cycle distribution of MCF-7 cells was significantly disturbed by Echinacoside. Furthermore, Echinacoside promoted the apoptosis of MCF-7 cells, and inhibited the migration and invasion abilities of MCF-7 cells.

Based on both in vitro data and in silico findings, ASEE could be developed as an alternative or complementary therapeutic agent for breast cancer treatment. Based on these reports and their similarity to the architectures of human organs, organoid culture is more advantageous than cancer cell lines. Thus, further organized culture, In-vivo, and clinical studies are needed to understand how a drug candidate may affect cancer cells.

Advancing result on the application of curcumin in breast cancer treatment is essential for improving therapeutic outcomes and quality of life for individual diagnosis with this condition. Additionally, further clinical studies are necessary to establish its role as a reliable breast cancer treatment.

Therefore, further studies are required to confirm these data before any public recommendations can be made. In particular, it is important to conduct studies with greater numbers of people, in different countries, and with a serial

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evaluation of lifetime green tea consumption. Moreover, as tea is one of the most popular beverages in the world and may possess many chemo-preventive qualities, a better understanding of the mechanisms might improve the utilization of green tea in breast cancer primary and recurrence prevention. At the clinical level, results from this systematic review and meta-analysis may be useful to design clinical trials aimed at ascertaining the potential role of green tea as an adjuvant in breast cancer therapy and pave the way to novel preventive strategies for breast cancer.

Our review provide evidence that supports the use of ginseng as an antitumor adjuvant in breast cancer patients.

More evidence is required to confirm these early findings before the question of black cohosh's safety and efficacy in this population can be conclusively answered. Given the lack of adequate safe therapies particularly hormone replacement therapy and the unlikely impact of black cohosh on breast cancer risk or recurrence, the use of black cohosh for hot flashes by the women surviving breast cancer may be warranted in some cases provided that there are no allergic contraindication.

Further studies and experiments, including the advance techniques like flow cytometer and fluorescence microscopy, would be valuable to further understand the mechanisms by flax seed oil induce cell death in breast cancer cells and to explore its clinical relevance in the breast cancer therapy.

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