A REVIEW ON BREAST CANCER W.S.R. TO HERBAL DRUGS

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ABSTRACT:

Introduction

Breast cancer is a disease in which cells in the breast grow out of control. Breast cancer is one of the principal causes of death among women and there is a pressing need to develop novel and effective anti-cancer agents. Natural plant products have shown promising results in breast cancer. Their effectiveness is reported as decreased toxicity in usage, along with safety and less recurrent resistances compared with hormonal targeting anti-cancer agents.

Materials and Methods:

A literature search was conducted for all English-language literature published prior to September 2022. The search was conducted using electronic databases, including PubMed, Embase, Web of Science, and Cochrane Library. The search strategy included keywords such as breast cancer, herbs, anti-cancer biologically active components, clinical research, chemotherapy drugs amongst others.

Observation and Results: The literature provides documented evidence of the chemo-preventative and chemotherapeutic properties of Ginseng, garlic (Allium sativum), Black cohosh (Actaea racemose), Tumeric (Curcuma longa), Camellia sinenis (green tea), Echinacea, Arctium (burdock), Flaxseed (Linum usitatissimum) and Black Cumin (Nigella sativa).

Discussion and Conclusions:

The various herbs displayed effective as breast cancer properties and their outcomes However, more clinical trials and cohort human studies should be conducted to provide key evidence of their medical benefits.

Keywords: Anti-cancer, breast cancer; herbal drugs,; chemotherapy

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INTRODUCTION

Ayurvedic texts about cancer treatment During the 7th century BC, Atreya and Dhanwantari used herbal medicines for treating the early stages of cancer and surgery in advanced cases. In the 8th century AD, Vagbhata, a Buddhist physician composed two texts: Astanga Hrdaya and Astanga sangraha where new methods for cancer treatment were introduced. Other Ayurvedic texts of internal medicine, viz., Chakradatta composed by Chakrapani (10th century AD), the Sarangadhara Samhita by Sarangadhara (14th century AD), the Bhavaprakasha Samhita by Bhavamisra (15th century AD), the Satmya Darpan Samhita by Viswanath (16th century AD),

the Vaisajya Ratnabali by Binoda Lala Sen Gupta (18th Century AD), the Rasatarangini by Sadananda Sharma (19th century AD), etc. explain numerous remedies to treat internal and external neoplasms.

Cancer is becoming more common globally. Breast cancer is one of the most prevalent forms of cancer and one of the main causes of cancer mortality. While modern medicine has been used as the primary cure for this disease, traditional herbal medicine has been commonly used as a complementary and alternative strategy in some developed and developing countries.

To provide scientific justification for the use of herbal medicine, it is necessary to record and publish preclinical and clinical evidence-based research. Concerns with herbal medicine including the consistency and standardization of the herbal product (particularly the presence of bioactive compounds responsible for the effect), effectiveness, mode of action, safety, and herb-drug interaction if used as complementary and/or alternative medicine need to be further explored.

This article seeks to provide a forum for researchers to publish the most recent advances and clinical studies in the use of herbal medicines for breast cancer prevention and treatment, including ethnopharmacology, natural product chemistry, effectiveness, safety, dosage and toxicity, in vitro and in vivo preclinical trials, herb-drug relationship, clinical trials, and potential biochemical and molecular pathways. this special issue included fifteen articles which were carefully reviewed and accepted for publication and briefly described as follows. The plant extracts from different countries of the world, and their potential to treat and prevent breast cancer using in vitro and/or in vivo methods are described in this article.[1]

Traditional herbs used for the prevention of breast cancer around the world

Breast cancer is a condition that should be avoided. Estrogens play an important function in the proliferation of both normal and neoplastic breast epithelial cells. Estrogen receptor positive breast cancer accounts for almost 40%-70% of all breast cancers. As a result, one of the important ways for the detection and chemoprevention of breast cancer is to block the oestrogen receptor. Phytoestrogens, or estrogen-like compounds found in plants, were first proposed as cancer preventive agents. An epidemiological analysis found a low incidence of breast cancer in the soy-consuming community, substantiating this argument. Flavones, flavanones, lignans, coumestans, and stilbenes are the structural groups of phytoestrogen. Isoflavones are abundant in soybeans and soy products. Legumes and lignans, which can be present in beans, nuts, whole grains, berries, and vegetables, are two other phytoestrogen groups. The incidence of breast cancer in the United States has historically been 4-7 times higher than in Asian populations, where dietary isoflavone intake is comparatively as high as 20 mg/d to 80 mg/d. Furthermore, epidemiological findings showed an insignificant 30% decrease in breast cancer risk for women who consumed a higher percentage of dietary lignan. As a result, eating a phytoestrogen-rich diet is one of the many possible breast cancer-prevention lifestyles. Recent data suggests that phytoestrogen production prevents the function of essential steroidogenic enzymes involved in the production of estradiol from circulating androgens and oestrogen sulphate. As a result, this practise can play a key role in breast cancer prevention. Phytoestrogens have also been confirmed to stimulate the G-protein coupled receptor, GPR30 or GPER1, which has been identified as a novel oestrogen receptor and plays a key role in estrogen-dependent diseases including breast cancer (Qi et al. 2010). The function of phytoestrogens, on the other hand, is unknown and is dependent on a number of factors, including their composition, metabolism, and relative abundance compared to endogenous oestrogen. Phenolic acids, flavonoids, tannins, quinones, anthocyanins, and other naturally occurring phenolic compounds play an important role in cancer prevention and/or treatment. These phenolic compounds are found in medicinal herbs and dietary plants in abundance. By virtue of their wide variety of biological activities, some phenolic compounds contribute to the inhibition of carcinogenesis mechanisms and exhibit chemopreventive properties.[23]

Traditional herbs used for the treatment of breast cancer around the world

Plants have played an important role in human survival and development since they have supported fundamental human needs such as food, clothes, shelter, and medicine since the dawn of time. Plants are the foundation of

western medicine systems such as Ayurveda, Unani, and Chinese traditional medicine, which have fulfilled humanity's health needs for thousands of years. Herbal medicine is used by a considerable portion of the population of developing and underdeveloped countries to cure their primary health problems. Traditional herbal remedies have grown in popularity as a result of their low cost, abundance, and lack of side effects. In recent years, there has been a greater emphasis on plant science around the world in order to discover drug-like compounds from commonly used medicinal plants. Furthermore, some naturally occurring plant-based compounds such as curcumin, resveratrol, quercetin, and others have shown positive anti-cancer effects and are gaining popularity as a chemotherapeutic adjuvant. Furthermore, naturally occurring chemicals are less harmful to healthy cells and exhibit selective toxicity against dysfunctional or diseased cells in some circumstances. This may explain why a vast percentage of products on the market currently have structures that are structurally identical to those found in nature. Herbal compounds include a wide range of anticancer properties, including antioxidant, anti-inflammatory, antimutagenic, and apoptosis-inducing properties, which can aid deter cancer from developing in the first place (Shareef et al. 2016; Marchbanks et al. 2016; Lambert et al. 2003). By cell cycle arrest, induction of apoptosis, controlling carcinogen metabolism and oncogenic expression, inhibiting cell adhesion, proliferation, and migration, and blocking signalling pathways that are important for cancer progression, dietary consumption of adequate amounts of these herbal products can aid in the prevention and treatment of breast cancer. Between 1981 and 2014, 136 anticancer drugs were approved around the world, with herbal compounds or derivatives accounting for nearly 83 percent of them. Vincristine, vinblastine, paclitaxel, and docetaxel are among the anticancer medications currently being used to cure breast cancer. Despite herbal products' effectiveness in treating breast cancer and its complications, few herbal products make it to preclinical or clinical trials. As a result, further work would be required to effectively move these agents to an appropriate therapeutic environment in order to determine their herbal therapy ability.[4]

A few natural\herbal products used in treatment are listed below:[5678910]

Garlic: Garlic (Allium sativum) has been used to cure a variety of ailments for hundreds of years. It includes a hundred or so therapeutically beneficial secondary metabolites, such as alliin, alliinase, and allicin, to name a few. Garlic oil contains alliin, an amino acid that is converted to allicin after the rhizomes are crumpled. Allicin, which is responsible for odour and medicinal properties, is an originator of sulfur-containing compounds. Ajoene, a sulfur-binding compound used in garlic oil, is another sulfur-binding substance. While selenium acts as an antioxidant, ajoene slows the progression of cancer. Garlic also contains bioflavonoids such as cyanidin and quercetin, which have antioxidant effects. Garlic's anti-cancer properties are due to the high content of organic sulphides and polysulfides (Wheat and Currie 2008). The mechanism behind anti-tumor activity promoting lymphocytes and macrophages is that they destroy cancerous cells and disrupt the metabolism of tumour cells.

Echinacea:

Echinacea is a member of the Asteraceae family. It is an uninhabited aromatic plant that grows mostly in North America's Great Plains and eastern areas, as well as in Europe. Echinacea purpurea, Echinacea angustifolia, and Echinacea pallida are the three most widespread plants used in herbal remedies. However, E. purpurea is the most widely used species for study and care. Purple coneflower, Kansas snakeroot, and black Sampson are several common names associated with Echinacea. Researchers discovered that E. purpurea increases the number of natural killer cells in mice under study. In the future, E. purpurea may be used as an anti-cancer treatment. Echinacea contains flavonoids, which serve as immune stimulants. Flavonoids stimulate lymphocyte activity, which enhances macrophage phagocytosis and the action of natural killer cells, prompting interferon assembly, and it has also lessened the harmful effects of radiotherapy and chemotherapy, according to Winston et al. Flavonoids promote lymphocyte activity, which improves phagocytosis by macrophages and the action of natural killer cells, prompting interferon assembly, and it has also lessened the harmful effects of radiotherapy and chemotherapy, according to Winston. It also aids people in extending their life time as their disease progresses. Commercial preparations of

Echinacea juice have been shown to increase macrophage cytokine production (Wheat and Currie 2008). T-cell and B-cell 7 activation and proliferation have less direct results. Several Echinacea components are examined to see whether they play a part in the immune system's unique sound effects.

Carotenoids:

Green, herb with leaf, rose hips contain an active compound known as "carotenoids." Saffron, annatto, and paprika are examples of aromatic plants that are used as dyeing agents. Vegetable and fruit consumption has been related to less tumour growth in various ways. Dietary intake of carotenoids also lowers the risk of tumour development. The carotenoid compounds are powerful antioxidants with a wide range of therapeutic properties, including scavenging free radicals, shielding cells from oxidative damage, improving gap intersections, stimulating the immune system, and regulating enzyme function, all of which contribute to cancer development and promote the activity of the body's immune system.

Burdock:

Arctium lappa is the scientific term for burdock. Its root can be found in Europe and Asia and is used there. Burdock is used in a variety of herbal medicines for a variety of ailments. It has a gummy feel and a soft flavour. Burdock was once used to treat arthritis, tonsillitis, and measles, but it has now been discovered that it has antitumor properties (Sałaga et al. 2014). It contains active ingredients that influence oncogene shifts. Burdock has been used to cure breast cancer, ovarian cancer, bladder cancer, malignant melanoma, lymphoma, and pancreatic cancer cells. It reduces pressure, shrinks tumours, and extends the period of survival. During cancer, a large amount of nutrients is needed to survive the rapid proliferation and division of cells. Cancer cells, on the other hand, may survive under stressful environments such as low oxygen and low carbohydrates since they have a high capacity for stress. Arctigenin is an important ingredient used in burdock seeds. Arctigenin has been shown to be capable of removing tumour cells even though nutrients are scarce. Burdock root contains anti-oxidants of the flavonoid and polyphenol types, which may have an inhibitory effect on tumour development. The extract of root protects normal body cells from radioactive agents and reduces cell mutation. Tannin, a phenolic acid, is the most essential active ingredient found in burdock. It activates macrophages, prevents cancer from spreading, and maintains immune-modulatory properties (Ho et al. 2002).

Turmeric:

Curcuma longa is the scientific word for turmeric. Turmeric gives food a dark yellow flavour. Turmeric's active ingredient, curcumin, is found in the rhizome and rootstock. Curcumin's phenolic compounds are believed to have anticancer properties. Turmeric inhibits the spread of lung, breast, scalp, and stomach cancers. Curcumin, an antioxidant, affects the synthesis of eicosanoids including prostaglandin E-2 (PGE-2). In humans, it also has anti-inflammatory properties. Curcumin has been shown to have inhibitory effects on cancer development at all stages, including initiation, promotion, and proliferation. Turmeric inhibits the synthesis of nitrosamine, resulting in an improvement of the body's natural antioxidant activity (Barreto et al. 2000). Curcumin increases the amount of glutathione and other non-protein sulphahydryls in the body, and these sulphahydryls work directly on various enzymes.

Flax Seed:

Tiny brown and golden hard-coated seeds are produced by the flax plant. All of the active ingredients are present in these tiny seeds. Flax seeds are high in dietary fibre, omega-3 fatty acids, and lignans, both of which are beneficial to your health. The metabolism of lignans to enterodiol and enterolactone, which occurs in the digestive tract, results in estrogenic development in flax seeds. Flax seeds contain more active phytoestrogens than soy products, and eating flax seeds induces a significant difference in 2-hydoxyesterone reduction relative to soy protein. Ground flax seeds have been found to have potent anti-cancer efficacy by Lilian Thompson's study group at the University of Toronto (Sałaga et al. 2014). An experiment was carried out on mice in which cancer was first caused in the mice by administering carcinogens, and then anti-cancer activity of flax seed was detected in one population by combining lignin in the mice's diet. The tumour load was reduced as a result of this experiment. The malignancies were reduced by flax seeds and secoisolariciresinol diglycoside. This research group recently used human breast

cancer cells to cause tumours in mice. Although cancer spreads, mice were fed a bland diet for eight weeks after cancer cells were injected. One party was given 10% flax seeds, while the other was given a standard diet. Flax seeds reduced the rate of cancer growth by 45 percent. Flax seeds enhance the morphogenesis of mammary glands in rodents. Female mice fed a 10% flax seed diet had a higher number of terminal end buds and terminal ducts in their mammary glands, according to the researchers. Extra epithelial cell division is present. Females of both sexes have increased distinction. Females have demonstrated a low occurrence of breast tumours after being injected with carcinogens in the mammary glands. As a result, flax seeds in female offspring will improve mouse mammary tissue differentiation, prevent malignancies, and reduce tumour growth, rendering them less vulnerable to carcinogens (Gratus et al. 2009).

Green Tea:

Camellia sinensis is the scientific name for green tea. Polyphenolic compounds are thought to have anticancer properties. C. sinensis contains a small volume of Epigallocatechin Gallate (EGGG), a polyphenol. Green tea has been shown to have antitumor and antimutagenic properties, according to studies. EGGG protects cells from the DNA damage caused by oxygen reactive species. Green tea polyphenols inhibit cancer cell proliferation and promote tumour cell necrosis and apoptosis, according to animal studies. Tea catechins not only activate the immune system, but they also suppress tumour cell metastasis and angiogenesis. Green tea has been found to be effective against colon and stomach cancer in several trials. Tea and its main catechins lower the chance of tumours in a variety of body organs. Green tea can help to reduce the harmful effects of radiation. Tea's antioxidant function is responsible for all of the health benefits.

Ginseng:

Panax ginseng is the scientific name for ginseng. It is a long-lived plant that grows mostly in China, Korea, Japan, and Russia. The dried root of this plant is included. It may be used to treat a variety of ailments, including cancer. Ginseng's active ingredients have been shown to minimise or inhibit the production of tumour necrosis factor in mouse skin, hinder the proliferation and metastases of cancerous cells, promote cell differentiation, and increase interferon levels. Some types of cancerous cells can also be hampered by the ingredients in ginseng. In addition, a study conducted in Korea concluded that ginseng decreases the risk of cancer in humans (Ohnishi and Takeda 2015). In comparison to fresh sliced ginseng, juice, or tea, the most effective and active form of ginseng for cancer prevention is its extract and dried powder. Ginseng prevents tumour growth by interfering with DNA synthesis. The active compound of P. ginseng has many beneficial properties, including the reactivation of natural killer cells that have been damaged by chemotherapy and radiotherapy, the induction of macrophages, and the enhancement of antibody production.

Black cohosh:

Cimicifuga recemosa is the scientific word for black cohosh. It's a shrub that grows in North America's eastern forests. Black cohosh was most widely used for breast cancer patients during radiotherapy and chemotherapy. It has been used for decades by Native Americans to relieve menopausal symptoms, premenstrual discomfort, and dysmenorrhea. It also causes complications similar to abortion. Lydia Pinkham's Vegetable Compound was a well-known patent drug, and this herb was a key ingredient. It was also used in pharmacopoeia from the 19th century (Dass and Mathur 2009). In drug stores, you can find a wide variety of black cohosh preparations. Herbalists have shown that they are a healthy and successful treatment option for menopausal symptoms. Females who were advised by their doctors to avoid Hormonal Replacement Therapy (HRT) have done so. The herb's effects on menopausal symptoms have been shown in the majority of tests. While the active principles of black cohosh are unknown, it is thought to include triterpene glycosides, as well as a trace amount of resins and caffeic, isoferulic, and fukinolic acids. There are some ambiguities about black cohosh's estrogenic and anti-estrogenic function. Various scientific findings have shown conflicting reports, with some claiming that it increases or decreases cancer cell development in culture. When given in conjunction with other chemotherapeutic agents, black cohosh has synergistic effects for breast cancer patients, according to the literature.

Vitamin D:

Skin exposure to the sun produces vitamin D. In the summer, simple touch with palms, muscles,

and face produces a large quantity of vitamin D. Standing in the sun on the beach before the skin turns pink is equivalent to a 20,000 IU vitamin D2 oral dosage. To sustain an adequate level of vitamin, our bodies only need 1000 IU per day (Da-Yong and Ting-Ren 2019). In the lack of sunlight, oral vitamin D uptake is the best way to keep the levels up. 4000 IU can be taken conveniently in one day while still providing other benefits. The kidneys are in charge of keeping the active hormonal form of vitamin D in the blood. This active form of vitamin D has anti-cancer properties. Vital organs of the body performed their functions by converting the main circulating source of vitamin D, 25(OH) D, into the hormonal form, 1, 25(OH) 2D. Many of these organs have a local pathway for converting the circulating form into hormonal form, which is aided by exposure to sunlight.

Cytotoxic herbal cure

The selective toxicity of herbal treatments against cancer cells is one of their most intriguing characteristics. A variety of phytocompounds have been shown to have selective toxicity against breast cancer cells. One of them, artemisinin, was isolated from Artemisia annua L. and found to be selectively cytotoxic against breast cancer cells when a sufficient amount of iron (ferrous iron) was present in the cells. Artemisinin and its analogues can selectively kill cancer cells under high iron concentrations when cancer cells have a higher iron influx. Polyphenols from Artemisia annua L (Jaradat et al. 2016) were also found to inhibit the adhesion and Epithelial-Mesenchymal Transformation (EMT) of MDA-MB-231 cells, which are extremely metastatic breast cancer cells. Aside from that, polyphenol-rich extracts of Hibiscus sabdariffa and aqueous extract of Brucea javanica have also been shown to have selective cytotoxicity against MCF7 and HTB-126 breast cancer cell lines, respectively. However, further research is needed to isolate the specific cytotoxic components of these plants.

Combination therapy by herbal remedies and synthetic drugs[1112131415]

Combination treatment, which combines natural therapy with synthetic medications, could be the only option for women with advanced breast cancer who are unable to undergo surgery. A herbal drug's combination effect with conventional cancer drugs can increase one of the drugs' bioavailability, making the treatment more successful. Furthermore, combining natural therapies with chemotherapy reduces the dosage of conventional treatment, resulting in reduced toxicity and side effects. Several scholars have proposed that medicinal compounds be used as a treatment modality because they improve the anticancer efficacy of currently available medications (Ezhilarasan 2018).

Herbal supplements and nutraceuticals for treatment[1617181920212223]

Cancer has been found to be a condition that can be avoided by changing one's diet and nutrition. According to a recent study, diet is linked to about 35% of cancer cases. Several epidemiological and experimental trials have shown that a healthy consumption of fruits, vegetables, and herbal products is inversely related to the prevalence of breast cancer. A diet high in phytoestrogens, polyphenols, and other chemopreventive agents lowers the risk of breast cancer. Herbal dietary supplements are less poisonous and more readily metabolised. Furthermore, in post-chemotherapy patients, nutritional intake of these herbal therapies aids in the reduction of side effects. Hot flushes are one of the most common signs of adjuvant chemotherapeutic injury in post-treatment breast cancer patients (Cohen et al. 2002). Black cohosh, also known as Actaea racemosa, is a common treatment for hot flushes in breast cancer patients, with mixed but positive outcomes

In some cases, a new generation of ICT technique (i.e., network pharmacology and molecular docking) was used to determine the potential plant phytochemicals and their possible mechanism of action to treat and/or prevent the incidence of breast cancer. In addition to that, in vitro and in vivo studies were also being conducted to confirm the anticancer activity from the network pharmacology results.

In some cases, a partial phytochemical isolation and further characterization was performed. One clinical trial was conducted to determine the efficacy of herbal medicines to treat and/or prevent breast cancer in human patients. Of these, several works involve herbal preparations from single and/or polyherbal formulations from standardized herbal traditional Chinese medicine.

W. Chen et al. investigated the anticancer potential of herbal traditional Chinese medicine

Fuzheng Yiliu formula (FZYLF) against MDA-MB-231/Adr cell line with high invasive ability and multidrug-resistant breast cancer cells. Using in vitro (established cancer cells) and in vivo (MDAMB-231/Adr tumor xenografted in nude mice) approaches, they conclude that FZYLF can inhibit the invasion and metastasis as well as induce cytotoxicity in MDA-MB-231/ Adr human breast cancer cells. they propose the regulation of WAVE3 expression as the possible molecular mechanism of action of FZYLF as anticancer agent.

L. B. Moses et al. investigated the anticancer capacity of Eurycoma longifolia (Jack.) or locally known as "Tongkat Ali" leaf extracts and their probable anticancer mode of action in vitro against non-hormone-dependent MDA-MB231 and hormone-dependent MCF-7 breast cancer cell lines. the leaves of E. longifolia were converted into both unfermented and fermented products, which were then screened with their action against both cancer cell lines. Flow cytometry was used to investigate apoptotic cell quantification, cell cycle distribution, and the expression of caspases and apoptotic proteins. MDA-MB-231 cells had substantial activities of cytochrome c, caspase-3, Bax, and Bcl-2 apoptotic proteins, while MCF-7 cells had significant activities of caspase-8, cytochrome c, Bax, p53, and Bcl-2 apoptotic protein. this extract has the highest levels of phenolics such as gallic acid, chlorogenic acid, ECG, and EGCG, which can contribute to its potent anticancer action.

The secondary metabolites, antioxidant, and antiproliferative activity of Dioscorea bulbifera leaves collected from Endau Rompin, Johor, Malaysia, was explored by M. M. Mainasara et al. The results showed that the plant extracts displayed high antioxidant activity and induced cytotoxicity in both MCF-7 and MDA-MB-231 breast cancer cell lines. Apoptosis and cell cycle arrest have been shown to be part of the mechanism of action. These authors found that the plant contains at least of 39 metabolites that might synergistically contribute to the bioactivity.

C. Zhu et al. reported the anticancer potential of berberine (BBR), a kind of isoquinoline alkaloid that is extracted from Coptidis Rhizoma or Huanglian. BBR has been shown to display diverse health benefit properties such as antimicrobial, cardioprotective, and antidiabetic properties. They investigate the suppressive abilities of BBR on both MCF-7 and MDA-MB-231 breast cancer cells and confirm its underlying mechanisms with miR-214-3p. they found that BBR has the potential to suppress the proliferation of MCF-7 and MDA-MB-231 breast cancer cells by upregulating the expression of miR-214-3p and increasing its inhibition to stem cell transplant (SCT). As a conclusion, miR-214-3p/SCT axis is a potential therapeutic target in the mechanism of BBR to suppress breast cancer.

T. Tuy-on et al. investigated the anticancer potential of selected the traditional cancer remedies to induce cytotoxicity in breast, cervical, and ovarian cancer cells in vitro. the hierarchical cluster analysis (HCA) was used to classify the extracts by their cytotoxic characteristics. they design this method to predict the correlation between the plant's bioactive compounds and biological activities. the results showed that eleven plants normally used in the traditional medicine (TTM) were active against at least one of the cancer cell lines, while about 2/3 of all extracts were active against all tested cell lines. the remaining plant extracts might not be considered as active but may be needed as complementary medicine according to the TTM theory. they suggested further studies (i.e., in vivo work) to determine the exact efficacy of the herbal remedies.

Carvacrol is a phenol monoterpene and has been found as the dominant phytochemical in the essential oil of aromatic herb species in the family Lamiaceae such as oregano and thyme. this compound has been reported to display protective effects in chemically induced breast cancer models in vivo. O. Herrera-Calderon et al. proposed and evaluated the possible mechanism of action of carvacrol by using an in silico study on selected receptors involved in breast cancer progression by docking analysis, molecular dynamics, and drug-likeness studies. their findings suggest that mTOR signaling pathway could be a possible mechanism of action for its preventive properties on the breast cancer model.

Cynanchum paniculatum (Bge.) Kitag (CP) (also known as dog strangling vine, radix cynanchi paniculata, Shu Changching in Chinese) has been used in conjunction with other medicinal plants to treat cancer in TCM. S.-Y. Yang et al. investigated the anticancer potential of this plant extract against selected breast cancer cell lines with different mutation types (i.e., MDA-MB-231,

MCF-7, and ZR-75-1 and SK-Br-3). they found out that negative estrogen receptor and progesterone receptor cells are more sensitive to CP treatment in terms of direct cytotoxicity, which is not regulated by caspase-3, but highly correlated to MMP-2 regulation. they conclude that CP displayed effective anticancer potential against selected breast cancer cells through diverse mechanisms of action specifically targeting the inhibition of proliferation of triple negative MDA-MB-231.

Cinobufacin is a patent-protected traditional Chinese medicine that has been widely used for the treatment and prevention of breast cancer in China. the medicine is obtained from the skin of toad, Bufo gargarizans that contains diverse components such as toadoxin, dehydroxytoluotoxin, serotonin, and arginine complex. J. Xu et al. reviewed the efficacy and safety of cinobufacin combined with chemotherapy for advanced breast cancer treatment. they found out that the ORR (overall response rate), CBR (clinical benefit rate), and pain relief rate of cinobufacin combined with the chemotherapy group were statistically better than in the chemotherapy group. Cinobufacin combined with the chemotherapy group can also reduce the tumour markers in cancer patients with low negative side effects.

Aidi injection (ADI) is a mixture of selected traditional Chinese herb injections that is composed of the extracts from Panax ginseng C. A. Mey, Astragalus propinquus Schischkin, Acanthopanax senticosus (Rupr. Maxim.) Harms, and Mylabris phalerata Pallas and has been used widely to treat breast cancer in China. Y. Chai et al. conducted the systematic review and meta-analysis of ADI to treat advanced breast cancer. they believe that, based on the few available clinical trials, therapy with ADI in advanced breast cancer patients dramatically alters the overall reaction rate and disease control rate, as well as improves quality of life with few side effects. More randomised control experiments with greater sample sizes, though, should be carried out, as should elucidation of the detailed mechanisms of action (biochemical and molecular level).

Meanwhile, C. Wu et al. investigated and compared the efficacy and safety of a combination of ADI and chemotherapy versus chemotherapy alone in the treatment of breast cancer in a systematic review of clinical evidence. From the 20 studies available, they found out that the response rate (RR) and performance status (KPS) in the ADI + chemotherapy group were significantly higher than those of the chemotherapy alone group. they conclude that ADI could act synergistically to enhance the efficacy of chemotherapy drugs with reduced/no additional adverse side effects. they suggest the promotion of ADI as a potent adjunct anticancer drug especially in breast cancer treatment.

In China, compound Kushen injection (CKI) (made from Sophora flavescens and Smilax glabra) has been widely used to treat breast cancer. Its molecular mechanism, however, is unknown. As a result, S. Liu et al. used network pharmacology and molecular docking verification to explore alternative mechanisms of action. the findings revealed that 16 active CKI compounds were recognised, corresponding to 285 putative targets. they discovered that CKI is involved in numerous and complex mechanisms of action in the treatment of breast cancer, including several common cancer pathways, chemical carcinogenesis, oestrogen signalling pathway, TNF signalling pathway, and leukocyte transendothelial migration. Given that this study is primarily focused on data processing, additional biological studies are needed to validate the findings.

FDY003 is an herbal formulation that comprises three herbal preparations, namely, Lonicera japonica thunberg, Artemisia capillaris thunberg, and Cordyceps militaris, that have been shown to display potent antitumour effects in different types of cancer cells. As many herbal medicine preparations, the possible mechanism of action is still lacking. Using network pharmacology approaches, H.-S. Lee et al. investigated the mechanisms of FDY003 against breast cancer in the systemic level. they discovered that the herbal mixture modulated cellular processes such as cell proliferation, cell cycle mechanisms, and cell apoptosis, as well as many oncogenic pathways that play important roles in breast cancer pathology.

K. Xiao et al. reported the anticancer potential of Chaihu-Shugan-San, a traditional Chinese medicine that was formulated from seven different kinds of herbal preparations. According to the principles of traditional Chinese medicine, the clinical syndrome of breast cancer refers to

the "Liver-Qi" stagnation and Chaihu-Shugan-San is one of the popular treatments for "Liver-Qi" stagnation. In this study, they investigated the possible pathway of Chaihu-ShuganSan in the treatment of breast cancer by network pharmacology. Preliminary results showed that 157 bioactive compounds and 8074 potential drug targets were obtained. Network pharmacology analysis showed that the pathway responsible for the potent anticancer agent includes (but not limited to) mRNA and RNA catabolic processes, telomere organization, apoptosis, cell cycle progression, transcriptional dysregulation, endocrine resistance, and viral infection. they conclude that the treatment of ChaihuShugan-San on breast cancer involves multicomponent, multitarget, and multipathway interactions.

Shuganhuazheng formula (SGHZF) is an anticancer formulation that has been used widely in selected TCM and conventional hospitals in China for many years, especially to treat triple-negative breast cancer (TNBC). B. Wang et al. examined the medicinal effect and mechanism of SGHZF against TNBC using network pharmacology and further verified the efficacy in animal models. they found out that SGHZF has been shown to inhibit the proliferation of breast cancer growth in experimental animal models and the possible mechanism of action might involve the inhibition of Akt and HIF-1α expression.

One randomised clinical trial was conducted using moxibustion, a type of TCM that involves the burning of moxa, a cone or stick made of ground mugwort leaves, on particular points on the body with the intention to protect health and prevent disease. Previous studies showed that moxibustion may reduce the incidence of cancer and the side effect of chemotherapy. As a result, Y. Ji et al. explored the therapeutic effectiveness of moxibustion for breast cancer patients undergoing adjuvant chemotherapy who have chemotherapy-induced myelosuppression (CIM). they conclude that moxibustion is useful for treating CIM in breast cancer patients undergoing adjuvant chemotherapy, especially in patients undergoing high-dose, long-term, and mixed chemotherapy regimens. Furthermore, moxibustion can reduce the occurrence of SAE (in myelosuppression) and AE (such as nausea, vertigo, bone, joint, and muscle pain, and incision pain) and improve the compliance and safety of chemotherapy.

A wide range of contributions from a diverse research scope that includes isolation and semipurification of bioactive compounds, preclinical (in vitro and in vivo) studies, possible mechanisms of action using molecular and bioinformatics (network pharmacology and molecular docking) approaches, systematic reviews and meta-analysis of published clinical data, and clinical trials of herbal medicine showed the promising potential of herbal medicine as prevention and therapy in breast cancer.

CONCLUSIONS

Multi-factorial factors are involved for breast cancer; many factors act independently or may be in combination, especially in high-risk individuals. It is important to know the pathogenesis of this common disease which is associated with high mortality and morbidity especially if not detected early. So, the role of early screening in high-risk individuals as well as proper surveillance of treated case in order to detect recurrence at early stages has been advocated.

REFERENCES

[11] Anim J.T., John B., Prasad A., Saji T., Akhtar N., Ali V., Al-Saleh M. (2005). Relationship between the expression of various markers and prognostic factors in breast cancer. Acta histochemica 107: 87-93. https://doi.org/10.1016/j.acthis.2005.01.002

[2] Ozer H., Armitage J.O., Bennett C.L., Crawford J., Demetri G.D., Pizzo P.A. (2000). 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. J Clin Oncol 18: 3558-3585

[3] Damery S., Gratus C., Grieve R., Warmington S., Jones J., Routledge P., Greenfield S., Dowswell G., Sherriff J. and Wilson S. (2011). The use of herbal medicines by people with cancer: a cross-sectional survey. Br J Can 104: 927-933. https://doi.org/10.1038/bjc.2011.47

[4] Shareef M., Ashraf M. A., Sarfraz M. (2016). Natural cures for breast cancer treatment. Saudi Pharm J 24: 233-240. https://doi.org/10.1016/j.jsps.2016.04.018

[5] Marchbanks P.A., McDonald J.A., Wilson H.G., Folger S.G., Mandel M.G., Daling J.R., Weiss L.K. (2002). Oral contraceptives and the risk of breast cancer. New Eng J Med 346: 2025-2032. 10.1056/NEJMoa013202

[6] Lambert J.D., Yang C.S. (2003). Mechanisms of cancer prevention by tea constituents. J Nutr 133: 3262S-3267S. 10.1093/jn/133.10.3262S

[7] Freudenheim J.L., Marshall J.R., Vena J.E., Laughlin R., Brasure J.R., Swanson M.K., Graham S. (1996). Premenopausal breast cancer risk and intake of vegetables, fruits, and related nutrients. J Natl Cancer Inst 88: 340-348. 10.1093/jnci/88.6.340

[8] Donaldson M.S. (2004). Nutrition and cancer: a review of the evidence for an anti-cancer diet. Nutr J 3: 1-21. 10.1186/1475-2891-3-19

[9] Chen W.Y., Colditz G.A., Rosner B., Hankinson S.E., Hunter D.J., Manson J.E., Speizer F.E. (2002). Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. Annals Int Med 137: 798- 804. https://doi.org/10.7326/0003-4819-137-10-200211190-00008

[10] Barreto A.M., Schwartz G.G., Woodruff R., Cramer S.D. (2000). 25-Hydroxyvitamin D3, the prohormone of 1, 25-dihydroxyvitamin D3, inhibits the proliferation of primary prostatic epithelial cells. Can Epidemiol Biomarkers Preven 9: 265-270.

[11] Sałaga M., Zatorski H., Sobczak M., Chen C., Fichna J. (2014). Chinese herbal medicines in the treatment of IBD and colorectal cancer: a review. Curr Treat Options Oncol 15: 405-420. 10.1007/s11864-014- 0288-2

[12] Gratus C., Wilson S., Greenfield S.M., Damery S.L., Warmington S.A., Grieve R., Routledge P. (2009). The use of herbal medicines by people with cancer: a qualitative study. BMC Complementary Altern Med 9: 1-7. 10.1186/1472-6882-9-14

[13] Ohnishi S., Takeda H. (2015). Herbal medicines for the treatment of cancer chemotherapy-induced side effects. Front pharmacol 6: 14. 10.3389/fphar.2015.00014

[14] Dass S., Mathur M. (2009). Herbal drugs: ethnomedicine to modern medicine. K.G. Ramawat (Ed.). New York, USA. Springer pp: 7-32.

[15] Da-Yong L., Ting-Ren L. (2019). Herbal medicine in new era. Hos Pal Med Int Jnl 3: 125-130. 10.15406/hpmij.2019.03.00165

[16] Qi F., Li A., Inagaki Y., Gao J., Li J., Kokudo N., Tang W. (2010). Chinese herbal medicines as adjuvant treatment during chemo or radiotherapy for cancer. Biosci Trends 4: 297-307

[17] Ho J.W., Leung Y., Chan C. (2002). Herbal medicine in the treatment of cancer. Curr Med Chem Antican Agents 2: 209-214. 10.2174/1568011023354164

[18]Treasure J. (2005). Herbal medicine and cancer: an introductory overview. Semin Oncol Nurs 21: 177-183. 10.2174/1568011023354164

[19] Richardson M.A. (2001). Biopharmacologic and herbal therapies for cancer: research update from NCCAM. J Nutr 131: 3037S-3040S. 10.1093/jn/131.11.3037S

[20] Wheat J., Currie G. (2008). Herbal medicine for cancer patients: An evidence based review. J Altern Med 5: 1-20.

[21] Jaradat N.A., Shawahna R., Eid A.M., Al-Ramahi R., Asma M.K., Zaid A.N. (2016). Herbal remedies use by breast cancer patients in the West Bank of Palestine. J Ethnopharmacol 178: 1-8. 10.1016/j.jep.2015.11.050

[22] Ezhilarasan D. (2018). Herbal therapy for cancer. Understanding Cancer Therapies pp: 129-166.

[23] Cohen I., Tagliaferri M., Tripathy D. (2002). Traditional Chinese medicine in the treatment of breast cancer. Semin oncol 29: 563-574. 10.1053/sonc.2002.50005