

Botanical Remedies for the Management of Breast Cancer: A Comprehensive Analysis of the Clinical Evidence Available

Abstract

Breast cancer is a primary reason for mortality in females, necessitating the creation of innovative and efficient anticancer substances. Recently, about 80% of females identified with breast cancer have turned to specific alternative or supplementary therapies as a viable option for treating their cancer. Botanical extracts have demonstrated potential as anticancer agents with reduced toxicity, excellent safety, and fewer recurring resistance instances than hormonal-targeting anticancer substances. Natural substances commonly act as chemotherapeutic enhancers, antimetastasis, and relieving the toxic and adverse effects caused by anticancer agents. Besides, numerous botanicals enhanced the living standard of individuals with breast cancer. This research focused on clinical experiments and meta-analyses pertaining to the utilization of herbs in the management of breast cancer. This review summarized the majority of the documented clinical investigations concerning the application of ten herbs in the area of breast cancer, including black cohosh, ginseng, ashwagandha, garlic, turmeric, green tea, black seed, flaxseed, guarana, and peppermint. After examining the available research, it seems that the most established medicinal applications of herbal medicine in breast cancer patients involve easing the nausea and vomiting caused by chemotherapy, mitigating the hot flashes caused by hormonal therapy, reducing skin inflammation caused by radiotherapy, alleviating gastrointestinal disorders, and treating mucositis.

Keywords: *Breast cancer, Botanical, Anticancer, Hormonal therapy, Clinical trials*

Introduction

Breast carcinoma is deemed to be the most frequently detected form of neoplasm among the female population across the world. It constituted 24.5% of total occurrences of cancer and 15.5% of fatalities globally.^[1] Breast cancer is the primary reason for cancer-related mortality in women aged 20 to 59.^[2] In 2018, it was the most frequently identified form of cancer and the second most significant cause of mortality after leukemia in Saudi Arabia (SA).^[3] Breast carcinoma poses a significant challenge to the public health sector in SA. From 2001 to 2017, there was a significant elevation of 55% in the frequency of breast cancer cases, making it responsible for 30.9% of all cancer cases diagnosed among Saudi women.^[4]

There is no enduring remedy for any form of cancer. However, screening, radiation therapy, surgical interventions, chemotherapy, hormonal treatments, and immunotherapies have contributed to the reduction of mortality rates caused by breast cancer (**Figure 1**).^[5] All of treatment having

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some adverse reactions, some of these effects are minor and temporary, others can be severe and pose a threat to the patient's life.^[6] The most frequent side effects linked with cytotoxic chemotherapy comprise tiredness, nausea, vomiting, temporary hair loss, diarrhea, a drop in blood cell number, rash, alteration in body mass, neuralgia, breathing issues, mouth sores, and pharyngitis.^[5]

Radiation therapy is a potent remedy for breast cancer. Approximately half of the cases with malignant breast tumors undergo radiation therapy, and the majority of them seem to endure it well. Nonetheless, individuals can suffer severe side effects brought on by this treatment. The primary adverse reactions of radiation therapy consist of swelling and density in the breast, tiredness, skin irritation, and changes to the targeted region that resemble sunburns. These variations in the breast tissue and dermis usually subside within six to twelve months, and, on occasion, the breast may shrink and harden following radiation therapy. The sebaceous glands and hair follicles are highly vulnerable to small

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doses of radiation, leading to the immediate adverse outcomes of alopecia and skin dehydration.^[7]

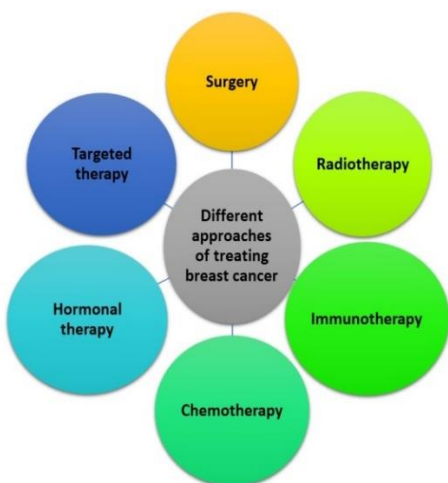


Figure 1. Different approaches in breast cancer treatment

Botanical extracts have exhibited encouraging outcomes as antineoplastic and anti-carcinogenic agents. It has been reported that these anti-cancer herbal agents exhibit increased efficacy, reduced toxicity, and lower incidence of multidrug resistance, which is a common occurrence with many other anti-cancer drugs.^[8] These applications arise from their capacity to function as antioxidants and anti-inflammatory agents, along with their ability to modify the immune system and trigger anti-proliferative and anti-apoptotic responses in cancerous cells. The botanical essence employed in combatting cancer can serve as both a preventative and curative measure, and can be utilized over extended periods without risk. The bioactive substances found in botanical extracts, including flavonoids, alkaloids, terpenoids, and coumarins, possess potent anti-inflammatory and antioxidant characteristics also the ability to stimulate lymphocyte activity, which is necessary immunomodulatory properties that can help to combat or counteract cancerous cells.^[9] Natural substances exhibit diverse anticancer properties, primarily comprising antioxidant, anti-inflammatory, antimutagenic, and apoptosis-promoting effects, which can potentially impede the progression of cancer during its initial phase.^[10] Metastasis may be to blame for the majority of cancer-related deaths. Nevertheless, numerous natural polyphenols can reduce the migration and formation of new blood vessels (antiangiogenic) and anti-metastasis in a diverse range of cancer cells (**Figure 2**).^[11] Natural substances commonly act as chemotherapeutic enhancers by operating via three mechanisms: Boosting the anticancer efficacy directly by increasing the responsiveness of cancer cells to conventional anticancer drugs, minimizing anticancer resistance by reducing their efflux and elevating their concentration inside the cancer cells, also relieving the adverse and toxic effects induced by anticancer agents (**Figure 3**).^[12]

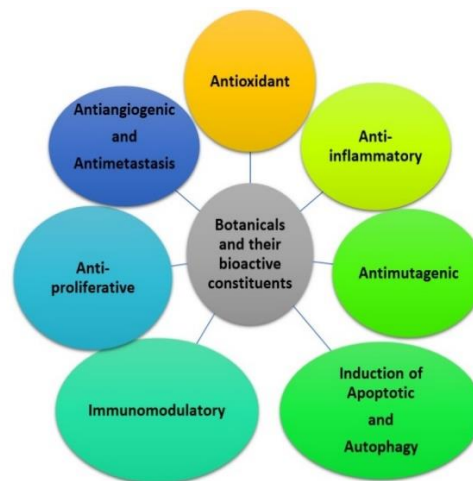


Figure 2. Characteristics of botanical compounds that contribute to their cancer-fighting properties

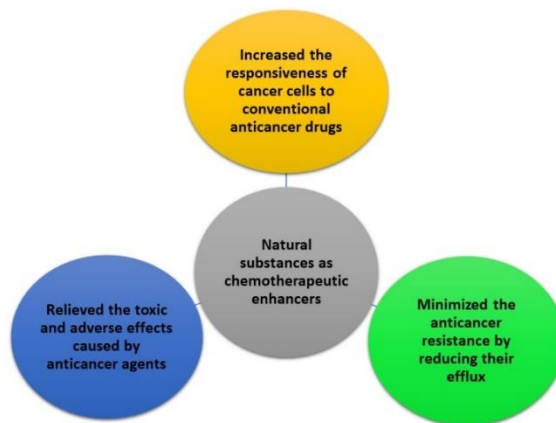


Figure 3. Mechanisms by which natural substances acted as chemotherapeutic enhancers

Approximately 80% of females with breast cancer resort to some kind of alternative or complementary medicine as a treatment option for their cancer. Some researchers have presented proof of the effectiveness of botanicals as natural substances in the creation of anti-cancer medications.^[13] Newly review articles provide extensive details on certain specific botanical sources such as *Nigella sativa*, *Annona muricata*, *Alpina galaga*, *Ficus carica*, *Murraya koenigii*, *Rosmarinus officinalis*, and *Urtica dioica*. These articles discuss the significance of these plants in the controlling of breast cancer.^[14, 15]

This review centered on the clinical studies that documented the activity of natural herbs and their bioactive constituents as therapeutic agents (single and adjuvant) (treatment and prevention) and as a safeguard against chemotherapy-induced side effects during breast cancer remedy.

Black cohosh

Black cohosh, *Actaea racemosa*, is a buttercup-family perennial plant endemic to North America. This plant is often sold as a natural supplement to relieve menopausal symptoms.^[16] It is antiestrogenic, antiproliferative, and

antioxidant.^[17] Black cohosh root contains tannins and alkaloids, triterpene glycosides, and phenolic acids. Black cohosh's main active ingredients include triterpene glycosides like cimracemoside, 23-epi-26-deoxyactein, and actein and phenylpropanoids such isoferulic acid. Caffeic acid, piscidic acid, and fukiic acid are among polyphenolic chemicals investigated in black cohosh.^[18] Research also found formononetin in black cohosh.^[19]

Clinical trials using black cohosh to prevent hormonal therapy-associated menopausal symptoms in breast cancer cases

Hormone therapy in individuals who have survived breast cancer can result in significant menopausal symptoms that might hinder treatment adherence.^[20] The utilization of black cohosh extract appears to be a sensible therapeutic choice for breast cancer cases undergoing tamoxifen therapy with primarily psycho-vegetative symptoms. An observational trial was conducted on 50 women with breast cancer who were undergoing tamoxifen therapy. All the women had previously undergone surgery, while the majority of them had also received radiation treatment and nearly half had undergone chemotherapy. Each woman was administered black cohosh isopropanolic extract (2.5 mg, 1-4 tablets) for 6 months. The decline in the overall menopausal assessment score while being treated with black cohosh was statistically different. The symptoms of hot flashes, perspiration, insomnia, and anxiety exhibited an improvement, whereas the complaints related to urogenital and musculoskeletal areas remained unaltered.^[21]

An open uncontrolled investigation was conducted on 23 Asian women who had gynecological cancers, with two cases of breast cancer included. The results indicated a marked decrease in the Kupperman Menopause Index, along with hot flashes, perspiration, and feelings of depression after undergoing black cohosh treatment (one tablet twice per day for three months). No effect was observed concerning gonadotropin and estradiol levels.^[22]

In a randomized double-blind controlled proposal, 85 breast cancer females, who were primarily administered tamoxifen, were given isopropanolic black cohosh extract (n = 59 with tamoxifen (1 tablet twice per day or n+43 with placebo) for 2 months. The study revealed a similar decline (27%) in hot flashes severity in all groups. However, patients who received isopropanolic black cohosh extract showed a significant decline in sweating relative to the placebo group. Throughout the treatment course, the gonadotropin levels did no significant alterations.^[23]

A total of 136 individuals who had survived breast cancer following therapy either with adjuvant chemotherapy, segmental or complete mastectomy, or radiation therapy were distributed to two groups. Group one (n=46) took only the usual-care treatment of tamoxifen 20 mg orally per day. The second group (n=90) received the same dose of tamoxifen along with black cohosh as an intervention. Tamoxifen treatment lasted for five years following international standards for adjuvant therapies, while black cohosh treatment

lasted for 12 months only. The results showed a satisfactory decrease in the frequency and intensity of hot flashes was achieved by administering tamoxifen and black cohosh in combination for 12 months. Roughly 50% of the subjects in the black cohosh cohort experienced relief from hot flashes.^[24]

Clinical trials using black cohosh to increase disease-free survival in breast cancer cases

In retrospective cohort observational study in pharmacoepidemiology analyzed 18,861 women who survived breast cancer, out of which 1102 received remedy with black cohosh isopropanolic extract. The search revealed that the use of black cohosh isopropanolic extract did not lead to extended disease-free survival. The untreated group had a recurrence rate of 14% within two years of diagnosis, while the group treated with an isopropanolic extract of black cohosh got this rate after 6.5 years.^[25]

Clinical trials using black cohosh to decrease breast cancer risk

In a German study that compared control and cases, the correlation between the long-term consequences of herbal products that contain phytoestrogens in addition to black cohosh on the probability of breast cancer in 10,121 postmenopausal females (6,657 controls and 3,464 cases) was examined. The utility of herbal products was found to be in reverse correlated to invasive breast cancer in a manner that was dependent on the dosage. The risk of invasive ductal tumors and combined lobular/mixed/tubular tumors was also similarly declined by the use of any herbal products, but not for carcinomas in situ.^[26]

The outcomes of a study based on population, which involved 949 breast cancer cases and 1524 controls and used black cohosh, indicated a notable protective effect against breast cancer. This correlation was consistent between women who acknowledged using either remifemin (a herbal medication obtained from black cohosh) or black cohosh.^[27]

Ginseng

Ginseng, an Araliaceae plant, has several powerful chemicals, including ginsenosides or panaxosides. Panax ginsenosides are antioxidant, vasodilatory, anti-inflammatory, anti-allergic, antidiabetic, and anticancer.^[28]

Clinical trials using ginseng to decrease fatigue, increase quality of life and survival in breast cancer patients

The researchers assessed the correlations between the utilization of ginseng as an adjunctive treatment and the longevity and quality of life in a group of 1,455 individuals diagnosed with breast cancer. Roughly 27% of individuals involved in the study had been consuming ginseng consistently prior to being diagnosed with cancer. In comparison to those who had never utilized ginseng, individuals who consumed it regularly had a notably lowered chance of experiencing mortality. The usage of ginseng after being diagnosed with breast cancer showed a positive correlation with scores of

quality of life.^[29]

Chinese patients who had undergone surgery and had been diagnosed with cancer, and were currently receiving chemotherapy or radiotherapy, were included in a study that was placebo-controlled, double-blind, and randomized. The patients were grouped into a placebo and an intervention group (given Shen-Mai-San, which is a combination of processed *Ginseng radix*, *Schizandrae fructus*, and *Liriope spicata*), and observed for 4 weeks. The results indicated that Shen-Mai-San was efficacious in treating cancer-associated exhaustion and exhibited anti-fatigue properties.^[30]

Ashwagandha

Withania somnifera (Also known as ashwagandha, dunal, or Indian Winter cherry) is a frequently used medicinal plant found extensively across Asia.^[31] It belongs to the Solanaceae plant family, which consists of flowering plants.^[32]

Clinical trials using ashwagandha to decrease chemotherapy-induced fatigue and ameliorate quality of life among breast cancer patients

The potential of ashwagandha to mitigate cancer-associated fatigue and enhance the quality of life is noteworthy. In an open-label, nonrandomized, prospective comparative trial, 100 breast cancer patients at all stages (77% of whom were in stages II and III) were administered either a combination of oral ashwagandha and chemotherapy or chemotherapy alone. Throughout the chemotherapy course, patients in the study group received 2 g of ashwagandha root extract every 8 hours. The control group felt significantly higher fatigue scores than the study group. Additionally, 7 out of 18 symptoms on the quality of life-C30 symptom scales were significantly changed between the intervention and control groups.^[32]

Garlic

Garlic (*Allium sativum*), belonging to Fam. Amaryllidaceae is commonly used in traditional medicine.^[33] The primary constituents accountable for its sharp taste and fragrant essence are the organosulfur compounds such as diallyl disulfide and allicin. They are the primary antioxidant compounds. Aged garlic extract has been proven to boost the immune system and prevent cancer and heart ailments.^[34] Historically, garlic and its active constituents have various biological actions such as free radical scavenging, blood sugar regulating, kidney safeguarding, cholesterol-lowering, bacteria-fighting, fungus-fighting, and blood pressure-lowering effects.^[33] Garlic is commonly used in traditional medicine as treatment and prophylaxis of various forms of malignancy including those affecting the blood, breasts, prostate, ovaries, and gastrointestinal tract.^[35] The dietary recommendations for breast cancer advocate for elevated consumption of garlic, as an element of nutritional intervention, to enhance the general wellness of individuals with breast cancer.^[36]

Clinical trials using garlic to decrease the risk of breast cancer

A meta-analysis, including a total of 17 studies, was recently published to investigate the link between the risk of breast cancer and consuming allium vegetables, garlic, and onion. The findings revealed that a considerable consumption of allium vegetables might offer protection against the occurrence of breast cancer.^[37]

A case-control study was conducted to evaluate the association between consuming onion and garlic and the susceptibility to breast cancer. The study identified 314 primary breast cancer cases among females aged 30-79 from hospital and clinic records. The control group consisted of 346 women with no cancer history other than nonmelanoma skin cancer. The study indicated a negative correlation between breast cancer and high or moderate intake of garlic. The authors propose that a high intake of garlic may safeguard against breast cancer among Puerto Ricans.^[38]

Furthermore, a study conducted in Iran, involving 285 female participants (who had recently been diagnosed with breast cancer of grade II, III or clinical stage II, III) established a negative association between the intake of Allium vegetables, specifically garlic and leek, and the likelihood of developing breast cancer.^[39]

A meta-analysis of case-control studies was conducted to explore the occurrence of various cancer types with the use of garlic. The study on breast cancer included 3,122 controls (median age: 56 y) and 2900 cases (median age: 55 y). Findings supported the function of garlic in lowering the incidence of breast cancer.^[40]

In a case-control analysis of 345 individuals diagnosed with primary breast carcinoma, to assess the diet impact on breast cancer risk. The dietary history survey included a 6-day food diary, a self-administered food frequency questionnaire, and an energy expenditure record. The findings revealed that the breast cancer risk decreased with an elevate in the consumption of garlic.^[41]

Turmeric (curcumin)

Turmeric, *Curcuma longa* (Zingiberaceae family), rhizome and rootstock contain curcumin, the primary component responsible for its medicinal properties.^[42] Curcumin possesses a multiple array of pharmacological actions, such as antioxidant, antimicrobial, anti-inflammatory, and antineoplastic characteristics.^[43] Due to its phenolic components, curcumin is recognized to have anti-cancerous properties. Curcumin acts as a regulator for various targets during various phases of cancer advancement, including growth, spread, blood vessel formation, and programmed cell death.^[44]

Clinical trials using turmeric alongside chemotherapy for breast cancer management

A clinical study (phase II) included 150 patients was carried out to investigate the risks and benefits of curcumin intravenous infusion and paclitaxel combination in metastatic and advanced breast tumor cases. In this study, participants

received paclitaxel with a 300 mg solution of curcumin or paclitaxel only once a week for 12 weeks, followed by 12 weeks of monitoring. The outcomes revealed that the paclitaxel - curcumin mixture had a greater result on breast tumor participants' objective response rate and physical performance than paclitaxel alone. Moreover, at the end of the intervention and after the monitoring period, the tiers of carcinoembryonic antigen in the participants' blood significantly decreased. The patient's self-evaluation of overall performance status also indicated better survival in the curcumin and paclitaxel patients than in the paclitaxel-only patients. In addition, the evaluation of adverse reactions revealed that the administration of curcumin had no significant risk concerns and did not reduce the quality of life but effectively reduced fatigue.^[45]

The outcomes of the research confirmed that the amalgamation of curcumin and docetaxel is feasible, secure, and well-tolerated in 14 patients suffering from metastatic and advanced breast cancer. In this research, individuals who had progressed or spread breast cancer were registered. The suggested amount of curcumin to be taken is 6000 mg per day for 7 days, repeated every 3 weeks, along with a regular dosage of docetaxel. The experimented blend of blood toxicity did not exhibit any augmented frequency. The amalgamation of curcumin and docetaxel notably decreased vascular endothelial growth factor levels following three rounds of therapy.^[46]

Clinical trials using turmeric to decrease radiotherapy-induced side effects among breast cancer patients

Radiation-induced skin dermatitis is an overall adverse outcome encountered by individuals undergoing radiotherapy for cancer cure. About 95% of those patients developed radiation dermatitis, with 10% experiencing a severe condition.^[47] Based on the research, curcumin utilization in conjunction with radiation therapy resulted in enhanced treatment results. Some of the benefits observed included the prevention of skin-related symptoms, the alleviation of pain and discomfort experienced by patients, the improvement of their quality of life, and the decrease of interruptions or undesired pauses during the radiation therapy process.^[48]

A randomized, triple-blinded, and placebo-controlled methodology study demonstrated that nano-curcumin has the potential to alleviate skin toxicity resulting from radiotherapy in breast cancer cases. The trial involved a sum of 42 breast cancer cases, who were divided into 2 groups: one receiving placebo and radiotherapy, and the other receiving radiotherapy and nano-curcumin (80 mg/day). The study revealed that the patients who were given the nano-curcumin supplement experienced significantly less severe radiotherapy-induced skin toxicity by the seventh week relative to the placebo group. Additionally, cases in the nano-curcumin group reported significantly less pain than the second group.^[49]

In a clinical trial involving 191 breast cancer patients, conducted across multiple locations and employing randomization, blinding, and placebo control, it was observed

that the application of curcumin topically, in a preventive manner, may have the potential to mitigate radiotherapy-induced skin toxicity and alleviate pain among those with greater breast separation, who face an elevated risk of severe skin toxicity.^[50]

A randomized study was conducted to compare the effectiveness of Vicco turmeric Ayurvedic cream and Johnson baby oil against radiotherapy-induced skin reactions in breast cancer cases. The cream was used daily from the beginning of radiation therapy for five weeks in females undergoing radiation therapy. The study results demonstrated that Vicco turmeric Ayurvedic cream significantly postponed and alleviated radiotherapy-induced skin reactions. Additionally, there was a simultaneous reduction in the average severity during the therapy weeks.^[51]

Clinical research was conducted to evaluate the efficacy of curcumin in diminishing the radiation dermatitis severity in 30 breast cancer females. Cases were assigned randomly to obtain either 2000 mg of curcumin or placebo orally 3 times daily during their entire radiation therapy course. Curcumin decreased radiation dermatitis severity in contrast to the placebo.^[52]

Clinical trials using turmeric to decrease hormonal therapy-induced side effects and ameliorate quality of life among breast cancer cases

A clinical study was conducted with 45 postmenopausal breast cancer patients having high C-reactive protein levels who were primarily treated with hormonal therapy. The study was multicenter, prospective, single-arm, and open-label in design. The study objective was to assess whether a mixture of curcumin, omega-3 fatty acids, and olive-derived polyphenol hydroxytyrosol could decline musculoskeletal symptoms and C-reactive protein levels. The therapy led to a decline in C-reactive protein levels, which persisted even after the 30-day treatment for an additional month. Those with the highest initial C-reactive protein levels showed the most significant decline with the treatment. Also, pain scores were reduced during the treatment, and no noteworthy negative effects were detected. The mixture lessened irritation, as demonstrated by a decrease in C-reactive protein, and mitigated suffering in individuals experiencing musculoskeletal manifestations brought about by hormonal therapy.^[53]

Green tea

The botanical term for green tea (GT) is *Camellia sinensis*. Typically, dry leaves of GT comprise approximately 30% (w/w) of catechins. The primary catechins consist of epigallocatechin, epigallocatechin-3-gallate, (-)-epicatechin-3-gallate, and (-)-epicatechin, encompassing over 60% of the complete catechins. Epigallocatechin gallate shields cells from DNA harm due to reactive oxygen species. The immune system is not only stimulated by GT catechins, but they also prevent the spread of tumor cells. The consumption of GT and its primary catechins can decrease the risk of cancer in various body parts. In addition, GT can assist in mitigating the detrimental impact of radiation.^[54]

Clinical trials using green tea to decline breast cancer risk

In the research, based on information from 45,744 women from the United States and Puerto Rico, consuming ≥ 5 servings of GT per week could pertain to a decrease in the likelihood of developing breast cancer.^[55]

Research conducted on 1551 breast cancer patients in Guangzhou revealed that the women who consumed GT regularly had a superior progression-free survival rate. The positive correlation was more pronounced in women with average total cholesterol levels. Furthermore, the prognosis improved with elevated drinking of GT (7 times or more per week).^[56]

A different investigation was carried out in Shanghai, China, to evaluate whether consistent intake of GT was linked to breast cancer risk among 3454 newly diagnosed cases and 3474 controls in a case-control design. In comparison to those who did not drink GT, habitual consumption of GT was linked to a minor reduction in the risk of breast cancer. In premenopausal women, a decrease in risk was detected for the duration of GT consumption, and a proportional relationship was also noted between the quantity of GT consumed/month and the risk reduction.^[57]

In case-control research of individuals (female, n=1099) diagnosed with primary breast cancer and controls (n=1009 matched for age) in China, persistent intake of dry GT leaves safeguards to protect breast cancer. This protective effect depends on the amount of GT consumed, regular consumption, number of cups consumed, and fresh batches prepared daily.^[58]

Additionally, a study carried out on 472 women with breast cancer (stage I, II, and III) demonstrated an evident connection between a rise in drinking GT and a lower incidence of axillary lymph node metastases in premenopausal women with stage I and II. In postmenopausal females, elevated drinking GT was linked to heightened expression of estrogen receptor and progesterone receptors. Moreover, the study revealed that increased intake of GT was related to decreased recurrence of breast cancer (stage I and II).^[59]

A systematic examination and updated meta-analysis of published case-control research was conducted to determine the correlation between drinking GT and the likelihood of developing breast cancer. Fourteen studies met the criteria for meta-analysis, with 14,058 breast cancer patients and 15,043 controls. The research revealed that individuals who regularly consume GT have a decreased likelihood of developing breast cancer in the future.^[60] Another meta-analysis comprising 163,810 women with breast cancer across 5 case-control studies and 8 cohort studies revealed a significant inverse correlation between breast cancer risk and the intake of GT.^[61] A meta-analysis study of five databases on breast cancer hazard and reappearance, involving 5,617 women with breast cancer presented an opposite correlation between escalated GT intake (more than 3 cups per day) and the likelihood of breast cancer reappearance.^[62] Likewise, in a meta-study of 3 case-

control investigations, it was found that there is a 30% decline in the risk of breast cancer for individuals who regularly consume GT.^[63] The findings of an earlier meta-analysis suggest that drinking GT lowers the breast cancer risk. Based on four studies, the collective outcomes revealed that breast cancer risk was lower for individuals who had the highest consumption of GT relative to individuals who had non/lowest intake.^[64]

In a prospective cohort research carried out in China, urinary levels of tea polyphenols (specifically epicatechin, epigallocatechin, and 40-methyl-epigallocatechin) and their metabolites, as well as flavonols like quercetin and kaempferol, were analyzed using mass spectrometry in breast cancer (cases n=353) and in matched controls (n=701). A vast majority of the participants had a habit of drinking at least 1 cup of GT. A negative correlation between the concentration of epicatechin in urine and developing breast cancer.^[65]

In a survey that included 3,315 Chinese individuals diagnosed with breast cancer, it was detected that individuals who habitually consumed GT (especially women who had undergone menopause) showed a significant decrease (19.5%) in mammographic density (MD) percentage in comparison to women did not consume GT.^[66] A subsequent placebo-controlled, double-blind, randomized clinical research investigation was done on 1,075 postmenopausal females who were in good health. During one year, these females were provided with four pills of decaffeinated GT every day, including 1315 mg catechins, with 843 mg of epigallocatechin-3-gallate. The findings indicated a notable reduction (4.40%) in the percentage adjustment of MD contrary to elevation (1.02%) observed in premenopausal females.^[67]

The presence of polymorphism in the gene for catechol-O-methyltransferase led to a reduction of 40% in enzymatic activity, which could alter the relation between GT intake and breast cancer risk.^[68] An investigation involving 589 new breast cancer females and 563 controls, all of whom were Asian-American females, found that drinking GT was significantly linked to a decrease in breast cancer risk among those with a low-activity catechol-O-methyltransferase allele in comparison to controls. Conversely, no link was found between GT intake and breast cancer risk among those with a high-activity catechol-O-methyltransferase allele compared to non-drinkers. According to these findings, those who have a low-activity catechol-O-methyltransferase allele may not be as efficient at getting rid of GT catechins and may get the most from them.^[69]

Clinical trials using green tea to decrease the risk of breast cancer recurrence

Being obese following breast cancer treatment can enhance the likelihood of a woman experiencing recurring illness and/or developing cardiovascular disease at an early age. The impact of consuming decaf GT regularly on weight, physical structure, and modifications in energy consumption, basal metabolic rate, insulin, glucose, lipids, and homeostasis model assessment insulin resistance was assessed among overweight

women who had survived breast cancer. Fifty-four women were chosen at random and assigned to consume either decaf GT (960 mL) or a placebo daily for 6 months. Consumption of decaf GT for half a year was linked with a minor decrease in body mass and better regulation of high-density cholesterol and glucose homeostasis.^[70]

Clinical trials using green tea alongside radiotherapy for the management of breast cancer

Recent clinical research carried out on individuals with breast cancer receiving radiation revealed that an oral administration of 400 mg capsules of epigallocatechin-3-gallate three times per day could enhance the impact of radiotherapy. This suggests that epigallocatechin-3-gallate found in tea could serve as a therapeutic adjunct for human metastatic breast malignancy.^[71]

Clinical trials using green tea to decrease radiotherapy side effects among breast cancer cases

Local application of epigallocatechin-3-gallate might be a viable option for managing radiation dermatitis. A clinical trial was conducted in phase 2, which was double-blind and placebo-controlled, and consisted of 180 Chinese breast cancer females undergoing postoperative radiotherapy. Females were chosen randomly (2:1) to receive either a solution of epigallocatechin-3-gallate (660 µmol/L) or a placebo that was sprayed over the entire radiation area from the first day of the radiotherapy to two weeks post-radiation. The epigallocatechin-3-gallate group showed a significant reduction in the occurrence and intensity of grade 2 or worse radiotherapy-induced skin toxicity relative to the placebo group.^[72]

In addition, a single-arm experiment was carried out to examine the theory that topical epigallocatechin-3-gallate is efficacious in treating radiotherapy-induced skin reactions in breast cancer females receiving radiation. The work comprised 49 women who underwent mastectomy and then underwent adjuvant radiation. Epigallocatechin-3-gallate was locally applied once daily, beginning when grade I dermatitis manifested and stopped 2 weeks post-radiation. The highest dermatitis recorded during the epigallocatechin-3-gallate therapy was: Grade 1 dermatitis (35 women); Grade 2 dermatitis (14 women); and no patients had Grade 3 or 4 dermatitis. Epigallocatechin-3-gallate also decreased burning sensation, pain, tenderness, itching, and pulling.^[47]

An earlier study included breast cancer females (n=24) who underwent radiotherapy on the chest wall following mastectomy; the epigallocatechin-3-gallate solution was topically applied to the radiotherapy area from the beginning grade 1 radiotherapy dermatitis until 2 weeks after the completion of radiotherapy. While eight patients experienced grade 2 radiation dermatitis during or after radiotherapy, all returned to grade 1 after receiving epigallocatechin-3-gallate therapy. According to patient-reported manifestations scores, there was a significant decrease in pain, burning, itching, and tenderness two weeks after the end of radiation.^[73]

Black seed

Black seed, scientifically recognized as *Nigella sativa*, is a healing plant and a yearly blooming herb belonging to Fam. Ranunculaceae. It has a significant religious and historical significance. In the Muslim community, black seed is regarded as an exceptional type of medicinal treatment. This is because a Prophetic hadith states that black seed can cure all ailments except for death. Additionally, it is advised to incorporate black seed into one's regular health regimen according to Prophetic Medicine.^[74] As the primary element of the essential oil found in the black seed, thymoquinone is responsible for the seeds' therapeutic applications, showcasing features such as immunomodulatory, anti-inflammatory, antidiabetic, antimicrobial, anticancer, and hepato-protective properties, as well as antioxidant abilities.^[75] The traditional medicinal use of the black seed includes treatment for a variety of illnesses, including bronchitis, asthma, inflammation, headache, rheumatism, dorsalgia, dermatitis, amenorrhea, anorexia, palsy, cognitive impairment, and high blood pressure.^[76]

Clinical trials using black seed to decrease radiotherapy adverse effects among breast cancer patients

During clinical randomized, placebo-controlled, double-blind research, 62 females with breast cancer undertaking radiotherapy were given black seed 5% gel to apply twice daily during radiation therapy. The result was a significant decrease in the severity of radiation dermatitis (grades 2 and 3), a delay in the occurrence of moist desquamation, and a decrease in the mean score of the worst pain.^[77]

Flaxseed

Flaxseed (FS) (*Linum usitatissimum*), frequently referred to as linseed, belongs to the family of Linaceae and is primarily grown in Europe, Asia, and the Mediterranean area. FS is among the earliest cultivated plants and is composed of two varieties, yellow (also known as golden) and brown, which possess similar amounts of short-chain omega-3 fatty acids and nutritional properties. FS contains around lignans 800 times more than any other plants. These are phytoestrogens that are phenolic compounds, non-nutritional, bioactive, and mainly consisting of secoisolariciresinol diglucoside (95% of the lignin content).^[78] The potential advantages for health associated with FS are primarily linked to its lignan content, which possesses both antioxidant and estrogenic properties.^[79] Several medical research have indicated that FS may have a significant part in reducing the likelihood of breast cancer, particularly in females who have undergone menopause.^[80]

Clinical trials using flaxseed and its lignans to decrease the risk of breast cancer

Several observational investigations proposed that the intake of FS can diminish the probability of developing breast malignancy. In the study comprising 2999 occurrences of breast malignancy and 3370 instances of healthy control, the consumption of FS was linked to a significant reduction of breast malignancy risk.^[81] Recently diagnosed postmenopausal females with breast cancer participated in a

clinical study that followed a double-blind, randomized, and placebo-controlled approach, were chosen (19 patients were given a 25 g muffin containing FS while 13 patients were given a placebo muffin). The consumption of FS decreased tumor growth, concurrent with the suppression of HER2 expression (a protein that may accelerate the growth and metastasis of tumor) and a decrease in the Ki-67 labeling index (a marker for cancer cell proliferation).^[82]

Several systematic analyses have evaluated the effectiveness of FS or its lignans in diminishing the chances of developing breast cancer. According to Fower *et al.*'s study of 10 investigations, FS might be linked to a lower breast cancer risk. FS displays antiproliferative properties in the breast tissue of females who are susceptible to breast cancer and could deliver protection against initial breast cancer. Furthermore, the probability of mortality among individuals living with breast cancer may be decreased.^[83] A different meta-analysis comprising 21 research studies, consisting of 11 studies on prospective cohorts and 10 studies on case-controls, indicated a connection between increased consumption of lignin and the declining possibility of breast cancer in menopausal females.^[84] Likewise, in three distinct meta-analyses, elevated quantities of enterolignan or lignan consumption considerably diminish the likelihood of developing breast cancer.^[85] In a case-control analysis, the greatest consumption of lignans was linked to markedly reduced mortality due to postmenopausal breast cancer; however, this connection was not observed in relation to mortality caused by premenopausal breast cancer. A different case-control investigation, which also employed the registry database of Ontario cancer, administered a food-frequency survey to determine whether consuming phytoestrogens during adolescence could act as a safeguard against breast cancer in later life. These research findings suggest that consuming more phytoestrogens, specifically lignans and isoflavones, during adolescence may lead to a decline chance of developing breast cancer.^[86] A study following a group of 58,049 French women who had gone through menopause discovered that those who consumed the most lignans (>1,395 µg/day) had a marked reduction in their chances of developing breast cancer. The data revealed that the beneficial impacts of lignans were limited to breast cancer that tested positive for estrogen and progesterone receptors. In a separate clinical experiment, scientists opted for approximately 45 premenopausal females who had a rice possibility of occurrence of breast cancer (due to either doubtful breast biopsies or previous breast cancer patients) and ingested them with 50 mg of secoisolariciresinol diglucoside lignan every day, which is equivalent to two tablespoons of FS powdered. The needle biopsies on the breast tissue were performed before and after the study, which lasted for one year. The study revealed that females who consumed FS lignans daily for one year had a reduction in precancerous breast alterations compared to their initial levels before the study. Also, a decline in Ki-67 concentrations was found in 80% of the subjects, implying a decline in cellular growth detected by this biomarker. Based on this clinical trial, lignan has the potential to decrease the risk of breast cancer.^[87]

Clinical trials using flaxseed and its lignans to prolong the life of breast cancer patients

An investigation used food records and serum lignan levels to measure the exposure to lignans and concluded that an increased exposure resulted in a significant decrease in mortality and a decline of in deaths caused by breast cancer. Lignans may likely increase the longevity of breast cancer patients.^[86] Women who have successfully battled breast cancer and possess elevated levels of lignans in their blood and dietary intake appear to have a substantially longer lifespan.^[88]

Guarana

The *Paullinia cupana*, commonly known as Guarana. Roasted seed extracts have been utilized in therapeutic drinks for their stimulating, aphrodisiac, and tonic properties since the pre-Columbian era.^[89] The invigorating characteristics of guarana are typically linked to the existence of caffeine, theophylline, and theobromine.^[90] The plant's stimulant features have also been ascribed to a significant quantity of saponins and tannins, with the latter potentially responsible for the confirmed antioxidant properties of guarana.^[91] In human subjects, a small, randomized, placebo-controlled trial revealed that a daily intake of 75mg of guarana exhibited beneficial impacts on memory and cognitive function.^[92]

Clinical trials using Guarana to decrease chemotherapy-induced fatigue and ameliorate quality of life among breast cancer patients

Guarana is a cost-effective, efficient, and safe substitute for the temporary controlling of exhaustion in females with breast cancer undergoing systemic chemotherapy. In a clinical trial that involved the crossover of breast cancer patients experiencing advanced fatigue after the first chemotherapy cycle, 32 patients were randomly assigned to obtain guarana (50 mg orally twice a day) while 43 patients were given a placebo for 21 days. The obtained data demonstrated that guarana significantly improved the global scores and symptoms of Chronic Illness Therapy-Fatigue, and Brief Fatigue Inventory in comparison to the placebo on days 21 and 49. No adverse consequences with grades 2, 3, or 4 were reported for guarana and it did not negatively impact the quality of sleep or develop anxiety or depression.^[93]

The findings of a systematic review included eight investigations comprising of breast cancer females (n=932) revealed that the utilization of guarana extract along with a nutrition plan that is abundant in whole foods, omega-3 fatty acids, fruits, and vegetables can be employed for the management of cancer-related fatigue among patients.^[94]

A clinical trial was conducted in Seoul, South Korea, between February 2016 and December 2016. The trial was double-blind and randomized, and it involved breast cancer patients who had experienced permanent chemotherapy-induced hair loss. The patients were randomized 3.5 years after chemotherapy, and a total of 35 females were included in the trial. The intervention group comprised 18 patients, while the placebo group had 17 patients. The participants were instructed to

apply a topical lotion that consisted of a special patented mixture of four plant-based components, including citrus, cocoa, guarana, and onion, or a placebo twice daily for six months. The study observed the tolerability, safety, and potential efficacy of the lotion compared to the placebo, particularly about hair density and self-reported improvement.^[95]

Peppermint

Peppermint (*Mentha piperita*) is a renowned plant in the culinary and medicinal sectors and is primarily utilized in the shape of oily preparations or indispensable essences. Menthol is the main component found in peppermint essential oil is referred to as, with roughly 70% of the oil consisting of free menthol and menthol esters.^[96] Peppermint essential oil is commonly used to alleviate symptoms such as spasms, cramps, headaches, migraines, indigestion, nausea, and flatulence, and it also exhibits antibacterial properties.^[97]

Clinical trials using peppermint alongside chemotherapy for the management of breast cancer

A recently conducted clinical research (enrolled 84 patients divided into experimental and control groups, with each group comprising 42 patients) has demonstrated that the utilization of peppermint (a mixture of peppermint extract 40 drops) in tap water (20 ccs) to be taken every eight hours) as a complementary medicinal approach can potentially ameliorate anorexia, vomiting, and nausea in breast cancer females undergoing chemotherapy.^[98]

In a different research, a spray containing neroli hydrolat and peppermint was pitted against a spray with plain water to determine the preferred option, in a randomized single-blind control crossover study. Out of the 44 participants, only 18 (41%) favored the hydrolat spray over the plain water spray, which did not meet the 80% threshold needed to recommend this spray as a standard solution for managing hot flashes. Nonetheless, a handful of users who selected it found it to be immensely beneficial. Both sprays seemed to alleviate the discomfort of hot flashes.^[99]

Conclusion

Breast cancer remains a serious concern for many women worldwide, and effective treatment options are critical in improving their quality of life. Based on the reviewed studies, it appears that there is insufficient substantial proof to endorse the utilization of botanical supplements as an adjunct therapy for breast cancer and its associated adverse effects. However, the most established therapeutic applications of plant-based medicine in breast cancer patients include the alleviation of chemotherapy-induced nausea and vomiting, hormonal therapy-induced hot flashes, radiotherapy-induced skin inflammation, gastrointestinal disorders, and mucositis. More research is required to fully identify the benefits of herbal medicine in breast cancer management, but these findings offer hope for enhancing the overall treatment experience and upgrading the quality of life for patients.

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Conflict of interest

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Ethics statement

None.

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