

A Review on the Pharmacological Properties of Medicinal Plants Effective in the Prevention and Treatment of Breast Cancer in the Past 20 Years

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Review Article

Received: 04-Mar-2020, Manuscript

No. RRDD-20-7942;

Editor assigned: 10-Mar-2020,

PreQC No. RRDD-20-7942 (PQ);

Reviewed: 24-Mar-2020, QC No.

RRDD-20-7942;

Revised: 25-Aug-2022;

QI No. RRDD-20-7942; Manuscript No.

RRDD-20-7942 (R);

Published: 22-Sep-2022, DOI:

10.4172/resrevdrugdeliv.6.4.001

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Keywords: Breast cancer; Medicinal plants; Prevention; Traditional medicine

ABSTRACT

Breast cancer is the most common cancer in women with high mortality. One million new breast cancer cases are diagnosed each year and about 400,000 of them die each year. New therapies in people with cancer have increased the life expectancy. However, the recurrence of the disease is frequently seen, leading patients and many physicians worldwide to turn their attention to the traditional medicine with particular interest in the use of herbal products to manage and reduce cancer. Studies have shown that taking herbal remedies along with current medications in the treatment of cancer can reduce the adverse effects of chemotherapy or radiotherapy, which can improve the quality of life. The purpose of this article is to review the studies on the efficacy of medicinal plants in the treatment of breast cancer with the aim of enhancing the quality and longevity of patients and facilitating the understanding of the usefulness of medicinal plants as adjuncts to the treatment of breast cancer. The present paper is a review study that collected data from articles published during the last two decades (2000-2019) in both Persian and English languages from SID, Medlib, google scholar, Pubmed and Science Direct databases. In this study, we examined the main sources of Iranian traditional medicine and other countries to see how much they are effective in the breast cancer treatment.

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Evidence and results of the studies indicated that Complementary and Alternative Medicine (CAM) in the treatment of breast cancer can control the disease and reduce the side effects of chemotherapy and other modern medicine therapies which plays an important role in enhancing the survival and quality of life of cancer patients. This article attempts to emphasize the evidence-based knowledge to enhance the use of medicinal plants in the prevention, control and treatment of breast cancer. However, there are still issues such as quality control of herbal remedies, standardization of methods in the use of CAM, and research into the use of natural resources.

INTRODUCTION

Breast cancer is the most common cancer in women with high mortality. One million new breast cancer cases are diagnosed each year and about 400,000 of them die yearly. Breast cancer occurs in the breast tissues and ducts (the tubes that carry milk to the nipple) and the lobules (the milk-producing glands). Although it is rare in men, it occurs in both gender. Breast cancer is the second leading cause of cancer deaths among American women after lung cancer.

Breast cancer is categorized into non-invasive and invasive. New therapies have prolonged life expectancy for patients. Chemotherapy is essential for the effective treatment of cancer. But this treatment results in more palliative therapy than cure. Recently, several recombinant biological agents such as interferons that are effective in treating cancer have been identified. Ideal anticancer drugs should be able to kill cancer cells without damaging normal body tissues. Anticancer drugs include several therapeutic groups such as alkylating agents (DNA alkylation in the cell nucleus is likely to be an important reaction leading to cell death), anti-estrogens, gonadotropin agonists, antiandrogens, chemotherapy antibiotics, herbal alkaloids (including taxanes, vinca alkaloids and podophilotoxins), antimetabolites, tyrosine kinase inhibitors, immunosuppressants, immune modulators and monoclonal antibodies [1].

However, the recurrence of the disease is frequently seen, leading patients and many physicians worldwide to turn their attention to the traditional medicine with particular interest in the use of herbal products to manage and reduce cancer. Surgery and chemotherapy are the main methods of treatment in various cancers. The use of herbs or herbal remedies for cancer treatment can be considered for a variety of reasons, such as lower side effects, greater accessibility and cheapness. For this reason, the World Health Organization (WHO) supports the use of traditional medicines subject to significant efficacy and non-toxicity. Currently, evidence suggests that Complementary and Alternative Medicine (CAM) can be considered as an acceptable method for the treatment and control of cancer. This approach has had an important role in extending the life expectancy and improving the quality of life of patients with breast cancer because of the better disease control and fewer side effects. Advanced countries such as the United States, Germany, France, Japan and China have been able to improve the quality of herbal remedies used in cancer treatment by conducting many drug studies. Today, we are in a much better position to identify medicinal plants with anticancer properties due to advanced knowledge of molecular science and techniques of isolating and identifying plant structures and compounds. The therapeutic effects of these herbs

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are mainly by producing more protective enzymes against cancer, stimulating repair mechanisms and having antioxidant properties, as well as enhancing the activity of the immune system.

LITERATURE REVIEW

Some herbs also help protect the body by boosting detoxification and inhibiting cancer progression *via* modulating the activity of certain hormones and enzymes. In addition, a number of medicinal herbs reduce the toxic effects of chemotherapy and radiation. Scientists around the world have focused on herbal remedies to boost the immune system against cancer. Thus, by understanding the synergistic interaction of different constituents of anticancer medicinal plants, various formulations of herbal remedies can eliminate cancer cells with minimal damage to the natural cells of the body [2].

The present study is a review study that collected data from articles published during the last two decades (2000-2019) in both Persian and English languages from SID, Medlib, google scholar, Pubmed and Science Direct databases. In this study, we examined the main sources of Iranian traditional medicine and other countries to see how much they are effective in the breast cancer treatment. In this study, a comprehensive search was conducted using the keywords of breast cancer, MCF-7, ethnopharmacology, alternative medicine. All articles were selected based on inclusion criteria (such as keywords in their title) using advanced search capability. And after initial review of different articles and removal of duplicate articles, all articles were studied [3].

DISCUSSION

Effective medicinal plants in the treatment of breast cancer

***Elettaria cardamomum* (L.) maton:** It is an important herbal medicine in traditional medicine, often used in the treatment of asthma, hypertension and indigestion. Essential oils of *Elettaria cardamomum* (L.) Maton are effective in reducing the side effects of chemotherapy. In addition, it contains minerals and nutrients needed by the body. One of the most effective properties of *Elettaria cardamomum* (L.) Maton in the treatment of diseases is its strong antioxidant, anti-inflammatory and detoxifying properties. Regular consumption of *Elettaria cardamomum* (L.) Maton components such as IC3 and DIM can prevent breast cancer. The mechanism of this plant in cancer prevention and treatment is mainly through DNA repair, cell cycle and hormonal regulation, differentiation and apoptosis.

***Syzygium cumini*:** It is one of the indigenous herbs of India that has been studied in a clinical trial for its anti-cancer properties on MCF-7 cell line. *In vitro* anti-cancer activity studies was confirmed in a dose-dependent manner. Phytochemical studies show that the anticancer properties of this plant may be due to the presence of flavonoids, alkaloids and steroids [4].

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Ammi maju: This plant belongs to the family *Apiaceae* that sprouts annually in autumn. It grows in humid and soft soil. Often cultivated in Europe and the Mediterranean region, West Asia and India. Ethanolic extract of this plant has lethal effects on MCF-7 cells which have been attributed to its phenolic compounds.

Artemisia absinthium: It has 200 to 400 different species. This species (*Artemisia absinthium*) is native to temperate regions of Asia, North Africa, and Large areas of America. Anti-cancer research has shown that it inhibits apoptosis and cell migration, prevents angiogenesis, and reduces the response of receptors in the cell nucleus to inhibit breast cancer progression [5].

Citrullus colocynthis: It belongs to the family *Cucurbitaciae*, commonly known as bitter apple. This plant grows extensively in India and Arab countries mainly Sudan. It is commonly used as a traditional medicine for the treatment of congestion, colic, constipation, fever, sciatica and scorpion sting. In addition, the leaves of this plant have antitumor, antibacterial and antifungal activity. It has many chemical constituents, including cucurbitacin glycosides, which have been proven to have anticancer properties. In addition, purified alkaloids from the plant have also been shown to have anti-cancer activity in the MCF-7 cell line in the laboratory. Numerous studies have shown that this is accomplished by inhibiting the cell cycle and inducing apoptosis in MCF-7 cell lines.

Myrtus communis: It is an evergreen shrub in southern Europe and northern Africa. Anticancer studies have shown that this plant has cytotoxic effects on cancer cell lines including breast cancer due to its phenolic compounds [6].

Rosa beggeriana schrenk: Rose is a plant that is very popular in Iranian traditional medicine. An *in vitro* trial on MCF-7 cells showed the anticancer properties of aqueous and ethanolic extracts of this plant. Metabolites of the phenols derived from this plant probably target a specific protein in a cellular pathway. Natural molecules found in medicinal plants such as *R. beggeriana* typically target several signaling pathways.

Trigonella foenum: *Trigonella foenum* induces apoptosis in MCF-7 cells and does so by altering the Fas receptor. It is a traditional herb used in the treatment of diseases such as diabetes, high cholesterol, wound healing and gastrointestinal problems. *In vitro* research has shown that the methanolic extract of this plant is able to inhibited MCF-7 cells growth [7].

Aerva javanica: It belongs to the family *Amaranthaceae*, which is widely distributed in many tropical regions of Africa, South and Southwest Asia. The root of this plant is deep and plays a revitalizing role in the desert. This herbal medicine is used in traditional medicine to treat diseases such as cancer. A case

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study shows that leaf extract of this plant has antiproliferative effect on MCF-7 cell line. In addition, *A. lanota* leaf extract can induce apoptosis in the breast cancer cell line.

Lagenaria siceraria: It belongs to the family *Cucurbitaceae* and cancer wounds can heal when it is applied topically. Alcoholic extract of this plant has shown anticancer properties on MCF-7 and SKHIP1 cell lines [8].

Astragalus membranaceus: AM is widely used in traditional Chinese medicine. It has some diuretic and skin-enhancing properties. It is also used in the treatment of various cancers. In practice, the herb is prescribed in combination with other herbs such as *Angelica*, *Poria* and *Ginseng*. AM contains several types of bioactive compounds, including flavonoids, polysaccharides and saponins. The plant induces its effects by enhancing NK cell activity, interferon production and antiviral effects and reducing chemotherapy toxicity. However, further studies are needed to see effects of AM in the treatment of breast cancer.

Poria cocos: It is used to treat breast cancer. It has anti-proliferation and anti-cell differentiation properties. It also increased cellular digestion capacity. The effects of this plant to induce apoptosis in MCF-7 cells have been proved [9].

Ganoderma lucidum: *Ganoderma* significantly inhibits the proliferation of breast cancer cells without damaging the normal breast tissue. In addition, it regulates alpha (ER) gene expression by regulating cell function, inhibiting angiogenesis, reducing estrogen receptors and NF- κ β signaling pathway in breast cancer cells.

Scutellaria barbata: This plant induces its anticancer effects by inhibiting intracellular aromatase production. Intracellular effects are most likely induced by RNA damage *via* ROS, which results in cell death and necrosis [10].

Saffron (*Crocus sativus*): A case study shows that aqueous-alcoholic extract of saffron induces apoptosis in MCF-7 cell line. Apoptosis in the control and prevention of cancer cells is very important. Caspase activity appears to be involved in many of the molecular and structural alterations in apoptosis. Apoptosis is a gene regulated phenomenon and is the mechanism of many drugs used in chemotherapy.

Artemisia aucheri: Research has shown that some parts of this plant are able to induce apoptosis in breast cancer cells. The capacity to induce apoptosis rather than induction of necrosis has been accepted as a mode of action for antitumor drug. Thus, studies in this field have expanded and demonstrated that apoptotic markers were well observed in MCF-7 cell lines affected by the extract [11].

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Glycyrrhiza glabra: Aqueous extract of this plant had inhibitory effects on the growth and proliferation of MCF-7 cells mediated by induction of apoptosis. And also because *Glycyrrhiza glabra* is cheap and natural, dietary inclusion of it can be effective in the treatment of breast cancer.

Camellia sinensis: Laboratory studies suggest that there is an inverse relationship between increased consumption of green tea and the risk of cancer. Green tea polyphenols contains active components (EGCG), which has beneficial effects on LDL levels and glucose-related markers in patients with breast cancer. In addition, consumption of green tea in breast cancer patients reduces body weight and improves serum HDL levels and glucose homeostasis. Research has shown that green tea polyphenols can be used as adjunctive therapy for the treatment of breast cancer along with chemotherapy [12].

Aloe vera: *Aloe vera* is a plant that has long been used in traditional medicine. From ancient times it has been used to treat skin problems and other disorders. The anti-cancer properties of *Aloe vera* have recently been approved. This plant exerts its anticancer effects in the treatment of breast cancer by inhibiting proliferation and angiogenesis and also inducing apoptosis in cancer cells. In addition, this plant can reduce the effects of radiotherapy. However, the anti-cancer effects of *Aloe vera* have not been fully recognized and cannot yet be definitively used as an anticancer drug approved by laboratory and clinical research.

Hymenocrater platystegius: The genus *Hymenocrater* comprises more than 21 species in the world. The antioxidant effects of this plant in breast cancer cells due to its high antioxidant effects. Phenolic content of this plant has radical scavenging activity, which dramatically reduces cancer cell viability. Extract of this plant decreases the growth of breast cancer cells which is dose dependent. Important constituents of the genus *Hymenocrater* include flavonoids, phenolic acids, and terpenoids. Pharmacological studies confirm the antimicrobial, anticoagulant, antioxidant, anti-cancer and anti-diabetic activity of the genus *Hymenocrater* [13].

Scrophularia Umbrosa dumort: It was shown in a laboratory trial, methanol extract and dichloromethane of *S. umbrosa* have cytotoxic effects on breast cancer and induce apoptosis in these cells, while the extract of this plant has no toxic effect on normal cells. Further studies are needed to determine the mechanism of action of the plant extract.

Red clover: Essential fatty acids of red clover were studied to evaluate the antitumor properties. Various studies have confirmed the anticancer effect of the oils of red clover and *B. scoparia*. These compounds cause morphological changes in breast cancer cells as well as induce apoptosis in this cell line, which is

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dose dependent. By interfering with the cell cycle Fruit oil present in *Scoparia* suppresses the G1 phase, which in turn reduces cancer cell viability [14].

Marrubium pesicum: This herb is used in Armenia, Azerbaijan, Turkey and Iran as an alternative to chemotherapy and anticancer drugs. The extract of this plant has shown anti-proliferative effects on MCF-7 cancer cell line. This feature can be attributed to the high content of phenolic and flavonoids found in this plant that can help by inducing apoptosis. In addition, studies have clearly shown that this plant has significant antioxidant activity that can improve disease by reducing the oxidative stress effects of cancer cells [15].

Other research on medicinal herbs used in the treatment of cancer has shown therapeutic effects that need further investigation. The efficacy of these herbs may be due to the reduction of blood complications caused by chemotherapy. However, it is not clear exactly how these compounds exert their effect on the hematological toxicity caused by chemotherapeutic drug. Some of these plants are mentioned below:

Astragalus membranaceus, Poria cocos, Atractylodes, Glehnia littoralis, macrocephala, Lycium chinense, Ligustrum lucidum, Paeonia lactiflora, Paeonia obovata, Citrus, reticulata, Ophiopogon japonicus, Millettia reticulata, Oldenlandia diffusa, Scutellaria barbata, Prunella vulgaris, Avicennia marina, Artemisia sieberi, Silybum, Nigella sativa, Artemisia absinthium, Urtica dioica, marianum, Crocus caspius, Kelussia odoratissima Mozaff and Scrophularia oxypepala.

For example, analysis of plant constituents shows that *Avicennia marina* contains compounds such as iridoid glycosides, terpenoids, naphthoquinone derivatives, triterpenes. Simon, Karun and Thymoquinone are the most important substances isolated from *Nigella sativa*. Flavonoids, steroids, terpenoids, saponins, tannins and volatile oils have been isolated from *Artemisia absinthium* [16].

Cancer treatment encompasses a range of methods, from non-specific treatments such as surgery, radiotherapy, hormone therapy and chemotherapy to specific and targeted therapies in the field of personalized medicine. Breast cancer is the most common cancer in women and the second leading cause of cancer death. About one million women are diagnosed with the cancer every year. Lack of an adequate diagnostic method is an obstacle in breast cancer. Early diagnosis, providing accurate prognosis and anticipation of response to treatment are essential to improve breast cancer. The current method used to identify breast tumors is mammography [17].

Conventional drugs for treating cancer have irreversible side effects, so achieving new drugs with the least side effects is an important goal in treating all types of cancer. Studies on concomitant use of medicinal plants with chemotherapy drugs have been largely limited by the limited number of patients,

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lack of control or placebo group in the study and not good evaluation of the side effects associated with chemotherapy made it difficult to recommend a suitable drug regimen of these compounds. Due to the necessity of using chemotherapy drugs in patients as well as the specific conditions of patients, it is difficult to design and conduct randomized, double-blind, placebo-controlled clinical trials. Therefore, the results obtained in previous studies are not very effective. However, limited studies with promising results have been conducted on the protective effect of herbal remedies on the prevention of radiotherapy-induced skin complications [18].

Most researchers have stated in their studies that herbal ingredients are effective in preventing and treating cancer as well as in reducing the adverse effects of chemotherapy. However, we need randomized placebo-controlled trials with a larger number of patients to demonstrate the efficacy of medicinal plants in combination with chemotherapy or radiotherapy.

Chemotherapy and radiotherapy are two effective ways to treat cancer and are widely used today to kill cancer cells and increase patient survival. Although these two methods are effective for many cancers, they have two major limitations. First, the low therapeutic efficacy for some cancers and second the side effects of radiotherapy and chemotherapy, so that patients treated with these two methods discontinue treatment due to severe side effects. In this regard, supplements that are prescribed to patients can reduce side effects without reducing the efficacy of chemotherapy and radiotherapy. Ionizing rays affect healthy cells by producing free radicals. On the other hand, herbal products have a protective effect against radiotherapy by trapping free radicals or increasing antioxidant enzymes inside the cell [19].

Studies have shown that the use of herbal remedies along with current medications in the treatment of cancer can reduce the adverse effects of chemotherapy or radiotherapy, which can improve the quality of life of patients. In this study, we aimed to gather resources of medicinal plants with the potential for prevention, control and treatment of breast cancer along with the mechanism of their effects.

Because of the increased negative effects of drugs used in chemotherapy, such as nausea, diarrhea, lethargy and headaches, they appear to have less efficacy in the treatment of cancer patients. Thus, with improved efficacy and increased quality control of herbal medicines, it seems that future use of these medicines will be inevitable.

Nowadays, new techniques to extract herbal compounds from plants have made it easier to use these natural resources in treatment. Research on alternative medicine as an adjunct to chemotherapy or radiation therapy has accelerated in the past few years. This breakthrough paves the way for understanding how alternative medicine works and how to reduce cancer rates. Evidence from *in vitro* and *in vivo* experiments regarding herbs and acupuncture indicates the positive effect of complementary

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medicine in reducing complications from chemotherapy and radiotherapy, strengthening the immune system, relieving pain and fatigue, reducing cytotoxicity and angiogenesis [20].

CONCLUSION

Today, more than half of all medicines are of plant origin. It is therefore quite clear that medicinal herbs in the near future will be significantly used in the treatment of cancer. In this article, we have tried to expand the use of herbs for the prevention, control and treatment of breast cancer, based on scientific evidence. However, issues such as quality control of herbal remedies, standardization of methods in the use of CAM, and research into the use of natural resources are to be improved. Finally, we recommend a Complementary Therapy Package that can include herbal remedies, acupuncture, homeopathy, prayer therapy as a classical alternative medicine package, which requires extensive research.

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