



## INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES (Int. J. of Pharm. Life Sci.)

### Herbal Medicinal Plant in the Treatment of Breast Cancer- An Overview

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#### Abstract

Plant sources of anti-cancer agents are herbal medicinal plant, the derivatives of which have been shown to be useable for the treatment or prevention of Cancer in humans. Many medicinal plants have been tested for anticancer activity such as antofine, acutiaporberine, etc. The compounds which have been isolated from these medicinal herbs include a variety of alkaloids, Coumarins, Polyphenol, Quinone, Dandelion, Vinca rosea, triterpenoids and Polysaccharides. Some of the formulas used in clinical tests have been combined with chemotherapy. They have been demonstrated to ameliorate or prevent adverse effect as a result of the use of synthetic drugs. Research on herbal medicinal plant for the treatment of breast cancer has not only been shown to an effect breast cancer but to also provide important methods for the study of breast cancer therapy. Herbal remedies are assumed to cause less complication and are less likely to cause dependency. The foremost reasons of herbal medicine popularity among breast cancer patients include improving quality of life, supporting conventional cancer treatment, preventing recurrence and eventually to prolong survival. This report review of herbal medicinal plant in the treatment of breast cancer will provide more valuable information in the breast cancer research.

Key-Words: Breast cancer, Herbal, Medicinal plants, Synthetic drugs

#### Introduction

Cancer that forms in tissues of the breast. The most common type of breast cancer is ductal carcinoma, which begins in the lining of the milk ducts (thin tubes that carry milk from the lobules of the breast to the nipple). Another type of breast cancer is lobular carcinoma, which begins in the lobules (milk glands) of the breast. Invasive breast cancer is breast cancer that has spread from where it began in the breast ducts or lobules to surrounding normal tissue. Breast cancer occurs in both men and women, although male breast cancer is rare.

Breast cancer is the most commonly occurring cancer in women, comprising almost one third of all malignancies in females. It is second only to lung cancer as a cause of cancer mortality, and it is the leading cause of death for American women between the ages of 40 and 55[1].

The lifetime risk of a woman developing invasive breast cancer is 12.6 % 2 one out of 8 females in the United States will develop breast cancer at some point in her life [2]. The death rate for breast cancer has been slowly declining over the past decade, and the incidence has remained level since 1988 after increasing steadily for nearly 50 years [3]. Twenty-five percent to 30% of women with invasive breast cancer will die of their disease [1]. But this statistic, as grim as it is, also means that 70% to 75% of women with invasive breast cancer will die of something other than their breast cancer. Hence, a diagnosis of breast cancer, even invasive breast cancer, is not necessarily the "sentence of death" that many women (and their insurance companies) imagine. Mortality rates are highest in the very young (less than age 35) and in the very old (greater than age 75) [4] It appears that the very young have more aggressive disease, and that the very old may not be treated aggressively or may have comorbid disease that increases breast cancer fatality [5]. Although 60% to 80% of recurrences occur in the first 3 years, the chance of recurrence exists for up to 20 years [6, 7].

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Many herbs have been used for a long time for demanded health benefits [8–10]. The medicinal herb is a plant (or a plant part) used for therapeutic properties. It is a widely recognized fact that many pharmacologically active drugs are derived from natural resources such as medicinal plants [11, 12]. Therefore, it is reasonable to search for novel drug molecules in herbs. Actually, herb-derived compounds have provided attractive possibilities for treatment strategies. Herbal medicine products are also provided as dietary supplements that people take to improve their health. For example, St. John's wort has been used in the treatment of anxiety, stomach upset, insomnia, and so on. Historically, herbs have enjoyed a rich tradition of use both for their flavor enhancement and for their medicinal properties. While herbs present interesting possibilities for health promotion, more information is required about the physiological and pharmacological responses to and the molecular targets for specific herbs. This paper focuses on antitumorigenic properties and anticancer contributions of herbs. Epidemiological evidences also point to herbs as dietary constituents with multiple anticancer characteristics [13]. It would be important to define appropriate strategies to achieve benefits from medicinal herbs. Studies show that some herbs can inhibit some ant apoptotic genes and activate some apoptotic genes [14, 15]. Systematic characterization of active components in medicinal herbs and their mechanisms of action is important for providing the rationale for their efficacy. Therefore, biotechnological work has to be done in order to provide evidence for the efficacy and to bring herbs and derived compounds to clinical use. In this paper, the relationship between medicinal herbs and some tumor suppressor molecules has been reviewed with a focus on gene expression and posttranslational modifications.

#### **Breast cancer**

Breast cancer is when cancer develops from breast tissue. Signs of breast cancer may include a lump in the breast, a change in breast shape, dimpling of the skin, fluid coming from the nipple, or a red scaly patch of skin. In those with distant spread of the disease, there may be bone pain, swollen lymph nodes, shortness of breath, or yellow skin.

Risk factors for developing breast cancer include obesity, lack of physical exercise, drinking alcohol, hormone replacement therapy during menopause, ionizing radiation, early age at first menstruation, and having children late or not at all. About 5–10% of cases are due to genes inherited from a person's parents, including BRCA1 and BRCA2 among others. Breast cancer most commonly develops in cells from the

lining of milk ducts and the lobules that supply the ducts with milk. Cancers developing from the ducts are known as ductal carcinomas, while those developing from lobules are known as lobular carcinoma. In addition, there are more than 18 other sub-types of breast cancer. Some cancers develop from pre-invasive lesions such as ductal carcinomas in situ. The diagnosis of breast cancer is confirmed by taking a biopsy of the concerning lump. Once the diagnosis is made, further tests are done to determine if the cancer has spread beyond the breast and which treatments it may respond to.

The balance of benefits versus harms of breast cancer screening is controversial. A 2013 Cochrane review stated that it is unclear if mammographic screening does more good or harm. A 2009 review for the US Preventive Services Task Force found evidence of benefit in those 40 to 70 years of age, and the organization recommends screening every two years in women 50 to 74 years old. The medications tamoxifen or raloxifene may be used in an effort to prevent breast cancer in those who are at high risk of developing it. Surgical removal of both breasts is another useful preventative measure in some high risk women. In those who have been diagnosed with cancer, a number of treatments may be used, including surgery, radiation therapy, chemotherapy, and targeted therapy. Types of surgery vary from breast conserving surgery to mastectomy. Breast reconstruction may take place at the time of surgery or at a later date. In those in whom the cancer has spread to other parts of the body, treatments are mostly aimed at improving quality of life and comfort.

Outcomes for breast cancer vary depending on the cancer type, extent of disease, and person's age. Survival rates in the developed world are high, with between 80% and 90% of those in England and the United States alive for at least 5 years. In developing countries survival rates are poorer. Worldwide, breast cancer is the leading type of cancer in women, accounting for 25% of all cases. In 2012 it resulted in 1.68 million cases and 522,000 deaths. It is more common in developed countries and is more than 100 times more common in women than in men.

#### **Types of Breast Cancer**

Breast cancer can begin in different areas of the breast — the ducts, the lobules, or in some cases, the tissue in between. In this section, you can learn about the different types of breast cancer, including non-invasive, invasive, recurrent, and metastatic breast cancers.

**Ductal Carcinoma In Situ**

Ductal carcinoma in situ (DCIS) is a non-invasive cancer where abnormal cells have been found in the lining of the breast milk duct. The atypical cells have not spread outside of the ducts into the surrounding breast tissue. Ductal carcinoma in situ is very early cancer that is highly treatable, but if it's left untreated or undetected, it can spread into the surrounding breast tissue.

**Breast cancer during pregnancy**

It is possible to be diagnosed with breast cancer during pregnancy, although it is rare and the breast cancer is not caused by the pregnancy. Women who are diagnosed with breast cancer during pregnancy have tremendous additional strain due to concern for the safety of the unborn child. It can be a traumatic and extremely difficult situation, but there is still hope for both mother and child, thanks to the many treatment options available.

If you are pregnant and have been diagnosed, be sure to communicate carefully with your obstetric care team as well as your oncology team, and it never hurts to verify that they have open communication with each other. Your medical team will take extra care in designing the treatment plan that best controls the breast cancer while protecting your unborn child.

**Invasive ductal carcinoma**

The abnormal cancer cells that began forming in the milk ducts have spread beyond the ducts into other parts of the breast tissue. Invasive cancer cells can also spread to other parts of the body. It is also sometimes called infiltrative ductal carcinoma.

- IDC is the most common type of breast cancer, making up nearly 70- 80% of all breast cancer diagnoses.
- IDC is also the type of breast cancer that can most commonly affects men.

**Triple Negative Breast Cancer**

A diagnosis of triple negative breast cancer means that the three most common types of receptors known to fuel most breast cancer growth—estrogen, progesterone, and the HER-2/neu gene— are not present in the cancer tumor. This means that the breast cancer cells have tested negative for hormone epidermal growth factor receptor 2 (HER-2), estrogen receptors (ER), and progesterone receptors (PR). Since the tumor cells lack the necessary receptors, common treatments like hormone therapy and drugs that target estrogen, progesterone, and HER-2 are ineffective. Using chemotherapy to treat triple negative breast cancer is still an effective option. In fact, triple negative breast cancer may respond even better to chemotherapy in the earlier stages than many other forms of cancer.

**Inflammatory breast cancer**

Inflammatory breast cancer (IBC) is a rare, but aggressive form of locally advanced breast cancer. It is called inflammatory breast cancer because its main symptoms are swelling (inflammation) and redness of the breast. About one to five percent of breast cancers are IBC. IBC tumors are often estrogen receptor-negative and HER2/neu-positive. Because these breast cancers are aggressive, most women with IBC have positive lymph nodes and 25 to 30 percent have metastasis when they are diagnosed. IBC also tends to have a higher proliferation rate than other breast cancers. The median age of diagnosis of IBC is slightly younger than the age of diagnosis of other breast cancers (57 versus 61). African-American women may be somewhat more likely than white women to be diagnosed with IBC.

**Metastatic Breast Cancer**

Metastatic breast cancer is also classified as stage-4 breast cancer. The cancer has spread to other parts of the body. This usually includes the lungs, liver, bones or brain. The spread of cancer usually happens through one or more of the following steps:

- Cancer cells invade nearby healthy cells. When the healthy cell is taken over, it too can replicate more abnormal cells.
- Cancer cells penetrate into the circulatory or lymph system. Cancer cells travel through the walls of nearby lymph vessels or blood vessels.
- Migration through circulation. Cancer cells are carried by the lymph system and the bloodstream to other parts of the body.
- Cancer cells lodge in capillaries. Cancer cells stop moving as they are lodged in capillaries at a distant location and divide and migrate into the surrounding tissue.
- New small tumors grow. Cancer cells form small tumors at the new location (called micrometastases.)

**Other types**

Although by far, the most common breast cancer type is ductal carcinoma in situ (DCIS), there are other types that are less commonly seen.

**Medullary Carcinoma**

Medullary carcinoma accounts for 3-5% of all breast cancer types. The tumor usually shows up on a mammogram, but does not always feel like a lump. At times, it feels like a spongy change of breast tissue.

**Tubular Carcinoma**

Making up about 2% of all breast cancer diagnosis, tubular carcinoma cells have a distinctive tubular structure when viewed under a microscope. It is usually

found through a mammogram and is a collection of cells that can feel like a spongy area of breast tissue rather than a lump. Typically this type of breast cancer is found in women aged 50 and above and usually responds well to hormone therapy.

#### **Mucinous Carcinoma (Colloid)**

Mucinous carcinoma represents approximately 1% to 2% of all breast cancers. The main differentiating features are mucus production and cells that are poorly defined. It also has a favorable prognosis in most cases.

#### **Paget Disease of the Breast or Nipple**

This condition (also known as mammary Paget disease) is a rare type of cancer affecting the skin of the nipple and often the areola, which is the darker circle of skin around the nipple. Most people with Paget disease evident on the nipple also have one or more tumors inside the same breast; generally either ductal carcinoma in situ or invasive breast cancer (1–3). Paget disease is frequently misdiagnosed at first because the first noticeable symptoms can easily be confused with more common skin conditions affecting the nipple. Like all breast cancers, the prognosis for Paget disease depends on a variety of factors, including the presence or absence of invasive cancer and whether or not it has spread to nearby lymph nodes.

#### **Symptoms of Breast Cancer**

The first sign of breast cancer often is a breast lump or an abnormal mammogram. Breast cancer stages range from early, curable breast cancer to metastatic breast cancer, with a variety of breast cancer treatments. Male breast cancer is not uncommon and must be taken seriously. In its early stages, breast cancer usually has no symptoms. As a tumor develops, you may note the following signs:

- A lump in the breast or underarm that persists after your menstrual cycle. This is often the first apparent symptom of breast cancer. Lumps associated with breast cancer are usually painless, although some may cause a prickly sensation. Lumps are usually visible on a mammogram long before they can be seen or felt.
- Swelling in the armpit.
- Pain or tenderness in the breast. Although lumps are usually painless, pain or tenderness can be a sign of breast cancer.
- A noticeable flattening or indentation on the breast, which may indicate a tumor that cannot be seen or felt.
- Any change in the size, contour, texture, or temperature of the breast. A reddish, pitted surface like the skin of an orange could be a sign of advanced breast cancer.

- A change in the nipple, such as a nipple retraction, dimpling, itching, a burning sensation, or ulceration. A scaly rash of the nipple is symptomatic of Paget's disease, which may be associated with an underlying breast cancer.
- Unusual discharge from the nipple that may be clear, bloody, or another color. It's usually caused by benign conditions but could be due to cancer in some cases.
- A marble-like area under the skin.
- An area that is distinctly different from any other area on either breast.

#### **Effect of Breast Cancer**

Chemotherapy and radiation for breast cancer destroy constantly dividing breast cancer cells. But these treatments can also affect healthy cells. Medications and other self-help methods can help ease many of these side effects:

#### **Loss of Appetite**

Loss of appetite is a common side effect of breast cancer treatment. Try these tips to ensure you are eating a healthy diet during treatment:

- Eat several small meals during the day, instead of three large meals.
- Try an "instant breakfast" mix or other nutritional shakes between meals.
- Eat the largest meal when you are most hungry, which varies from person to person.
- Drink beverages either a half hour before or after meals so they do not interfere with your appetite.
- Consider moderate exercise to increase your appetite.

#### **Nausea and Vomiting**

Some -- but not all -- cancer patients experience nausea. You can take medicines called *antiemetics* before chemotherapy to reduce nausea. Keep track of when you have nausea. Nausea can occur right after treatment or several days later.

- Eat small meals frequently and avoid fatty, greasy foods and citrus.
- Try foods at room temperature instead of very hot or cold.
- When nauseated, try bland foods like crackers, gelatin, ice chips, rice, plain mashed potatoes, or applesauce.

Contact your doctor if you have severe nausea or frequent vomiting. If you vomit, wait an hour before eating or drinking anything. Then, begin with ice chips and gradually add foods. Chamomile, ginger root tea, or ginger ale can sometimes help settle your stomach.



### **Weakness and Fatigue**

Weakness and fatigue can have many causes, including the treatment itself, worry or depression, not eating, pain, inactivity, and low blood counts.

- Make sure you get enough rest. Sleep at least eight hours a night and try to lie down during the day to rest if you are still tired. Avoid caffeine late in the day as it interferes with sleep.
- Exercise. Short walks can actually increase appetite and energy. Exercise can help you rest better, even if you are feeling fatigued.
- Be choosy about activities. Get help from family and friends with errands and other chores.
- If you feel pain, let your oncologist know. There is no need to suffer in silence.
- Eat a diet high in iron.
- If fatigue is caused by low red blood cell counts (anemia), you may be given a growth factor called erythropoietin or darbepoetin, which stimulates bone marrow to make red blood cells. It can be given by injection, which sometimes can be continued at home. Patients receiving this are carefully monitored for rashes, allergic reactions, and blood pressure.

### **Mouth Soreness**

Sometimes, a sore mouth or throat can be related to breast cancer treatment. Check with your doctor or dentist to rule out other causes of mouth pain.

- Ask your doctor about drugs to reduce mouth soreness.
- Choose soft foods that will not irritate your mouth, such as scrambled eggs, macaroni and cheese, pureed cooked vegetables, and bananas.
- Cut foods into small pieces.
- Avoid citrus, spicy, or salty foods and rough foods.

### **Long-term side effects of treatment**

Some breast cancer treatments can cause ongoing side effects, such as menopausal symptoms, fatigue or pain. Find out more about long-term side effects of breast cancer treatment and where to find help if you need it. Some treatments can also affect a woman's ability to get pregnant. If you're concerned about this, see our information on pregnancy and fertility.

### **Changes to your body**

Breast cancer and its treatments can cause changes to your body and how you feel about your body. This may be because of physical changes after surgery, hair loss from chemotherapy or weight gain, for example. We

also have information for women who wear prosthesis, including tips on finding suitable bras, clothing and swimwear.

### **Diet and physical activity**

In our section on diet and breast cancer, you can find out about the benefits of healthy eating, how some treatments may affect your appetite or what you eat, and how healthy eating could benefit you after treatment, for example if you want to lose weight. Physical activity can have many benefits for people who've had breast cancer, from relieving some side effects of treatment to helping you regain shoulder and arm movement after surgery.

### **Coping emotionally**

How you feel when you're diagnosed with breast cancer, having treatment and beyond is individual to you, and you may experience many different emotions over time.

### **Sex and intimacy**

Breast cancer can affect intimacy and sex in a number of ways. Some treatments have physical effects that can affect sex and desire. You may be anxious about your first sexual experience following your diagnosis, or about how breast cancer may affect an intimate relationship.

### **Herbal Medicine in Cancer Prevention**

Herbal medicine has been used since early times to treat malignancies in Asian countries [16]. The association between dietary patterns and the risk of developing breast cancer has also been shown in an Italian cohort, suggesting that a diet rich in raw vegetables and olive oil protects against breast cancer [17]. Furthermore, individuals consuming more raw vegetables, herbs, and spices have been associated with lower cancer risk [17]. Natural products are of importance in devising new drugs and providing unique ideas in cancer therapy. Actually, some herbs or spices have been approved to have a character of anticancer [18]. For example, the consumption of curcumin, a component of curry turmeric powder, has been reported to be a factor linked to a lower incidence of colon cancer [19]. Cells resistant to certain apoptotic inducers and/or radiation become susceptible to apoptosis when treated with curcumin. In addition, curcumin can also act as a chemopreventive agent in several cancers by suppressing colonic aberrant crypt foci formation and DNA adduct formation [20]. Furthermore, many cytotoxic chemotherapeutic agents such as etoposide are originally purified from herbs [20]. Two mechanisms have been proposed to be responsible for the anticancer action of the herbs and spices. One is via direct cytotoxic effects and the other is indirect through immunologicalmodulatory action.

The occurrence of cancer cells may be caused by the abnormal proliferation of cell or the inhibition of cellular apoptosis pathway. Many kinds of genes are involved in the cell proliferation and/or apoptotic regulation of cancer cells. The proliferation and the apoptosis of tumor cells are also affected by many factors and pathways such as drugs, radioactive ray, and medicinal herbs, via the modulation of some oncogenes or tumor-suppressor genes. One of the potential anticarcinogenic mechanisms of herbs is via an immunological modulation. It is supposed that anticancer action of medicinal herbs may be attributed to its power to exercise immune potentiation, which may have various therapeutic applications in prophylaxis of opportunistic infections and malignant diseases. In recent years, an active ingredient responsible for the immunomodulation of some herbs has been found to be a form of complex polysaccharides [21]. As several plants have potential medical and biological efficacy used by patients with oncological neoplasia, further studies are necessary to evaluate those efficacies, where the efficacy is based on the molecular mechanisms. Some medicinal herb plants which are very useful for cancer treatments.

#### **Astragalus (Huang Qi)**

A Chinese herb; an immune system booster, known to stimulate body's natural production of interferon. It also helps the immune system identify rogue cells. Work with the herb in both cancer and AIDS cases has been encouraging. The MD Anderson Cancer Centre in Texas conducted research showing that taking Astragalus when having Radiotherapy doubled survival times.

#### **Berberis Family (e.g. *Podophyllum peltatum*):**

Slow active purgative. Research has shown these herbs to have a strong action against cancer and they have been used with many cancers, especially ovarian cancer.

#### **Blood Root (*Sanguinaria canadensis*):**

Research shows consistent anti-neoplastic activity. It is effective against cancer tumours, and can shrink them; and has proven useful with sarcomas.

**Butchers Broom (*Ruscus aculeatus*):** The active ingredients of this herb have been found to be the ruscogenins which have tumour-shrinking and anti-oestrogenic abilities. Thus its use in the treatment of breast cancer.

#### **Cat's Claw (*Uncaria tomentosa*):**

An adaptogen and powerful immuno-stimulant, it enhances the white cells clean up process (phagocytosis). It is an excellent companion to astragalus, curcumin and echinacea. Research indicates it can reduce tumour size, particularly with skin

cancers. It also helps reduce the side-effects of chemo and radiotherapy.

**Chaparral (*Larrea mexicana*):** Cancer Watch covered a major research study from the US which heaped praise on this herb. It appears to boost the immune system, stop metastases and reduce tumour size. Seems especially interesting with breast cancer. It is also an anti-oxidant and anti-microbial, with low toxicity.

#### **Curcumin (Turmeric):**

This spice (*Curcuma longa* or Turmeric root) has been shown to have significant anti-microbial and anti-inflammatory activity. That alone seems enough for certain hospitals in America to consider using it in the treatment of polyps and colon cancer. However new research shows that it can both shrink cancer tumours and inhibit blood supply growth to tumours. It is a powerful antioxidant with liver protective benefits, and outperformed several anti-inflammatory drugs without side-effects in research.

#### **Dang Shen Root (*Codonopsis pilosula*):**

Increases both the white blood cell and red blood cell levels, so can be extremely helpful to patients having chemotherapy and radiotherapy, or to patients whose cancer diminishes levels of either.

#### **Echinacea:**

Another known immune system booster, it gained a populist reputation in treating colds. There is research on its helpfulness with brain tumours apart from its abilities to increase the levels of certain immune white cells in the body.

#### **Feverfew:**

This herb caused a storm when research from Rochester University in New York showed it to be more effective than the drug cytarabine in killing leukaemia cells. The US Food and Drug Agency put the active ingredient, parthenolide, on to its fast track programme. Nothing has yet been heard. But then, the FDA has never approved a herb for use as a cancer treatment.

#### **Goldenseal:**

One cause of stomach cancer can be the bacterium *Helicobacter pylori*. This burrows into the mucous lining of the stomach to hide from gastric acids, and then causes irritation, acid reflux, ulcers and even cancer. Goldenseal is generally anti-microbial and is used in the Caribbean and South East Asia against parasites. Goldenseal, helped by the mineral Bismuth, will kill *Helicobacter pylori*. Vets seem to know this, even if doctors don't.

#### **Milk Thistle:**

Known for years to be helpful to the liver, this herb has now been shown to be capable of protecting the liver during chemotherapy. Research in America showed

that leukaemia patients who took milk thistle had reduced liver toxicity and chemo side-effects. There is a little evidence that it has its own anti-cancer activity too.

#### **Red Clover:**

Research from a number of centres including the Royal Marsden has shown its potential as a part of a treatment programme against oestrogen-driven cancers, from breast to prostate. One active ingredient in the so-called Herb of Hippocrates is the anti-oestrogen Genistein.

#### **Skullcap (*Scutellaria barbata*):**

Research has shown action against many cancer types, for example against cancers of the lung, stomach and intestines.

#### **Sutherlandia (Cancer Bush):**

Peer reviewed research studies indicate that this herb is anti-inflammatory, anti-viral and anti-fungal. It boosts the immune system and inhibits Tumour Necrosis Factor, known to drive wasting in cancer patients.

#### **Thorowax or Hares Ear (*Bulpleurum scorzoneraefolium*):**

Research has shown its ability to enhance the production of natural interferon and it seems especially useful in bone cancer.

#### **Wheatgrass:**

One of the top private hospitals in South East Asia extols the benefits of freshly juiced wheatgrass. One shot gives you the chlorophyll of some 12 or more kilograms of broccoli. It acts as a blood purifier, and liver and kidney cleansing agent. After two weeks of daily use, blood and tissue oxygen levels improve, as does circulation. And oxygen is the enemy of the cancer cell, as Otto Warburg told the world.

#### **Wormwood:**

Another Chinese Herb, this has outperformed certain anti-malaria drugs and is now used by the aid agencies. It is strongly anti-microbial and anti-yeast and can be used as an effective part of an anti-candida diet. Also certain cancer treatments cause excesses of yeasts to form (for example, in Leukaemia treatment) threatening the patients health further. Excess yeasts are even felt by some cancer experts to be one of the causes of cancer. However, in recent research Wormwood has been shown to have direct anti-cancer properties.

#### **Conclusion**

Although breast cancer is a major cause of morbidity and mortality in women, and thus is of understandable concern to life underwriters, basic understanding of the disease often allows for aggressive underwriting in some cases. Women with DCIS and LCIS who have been correctly managed should still be eligible for optimistic ratings, whereas underwriting women with

cumulative risk factors described in this treatise, as well as unfavorable pathology and especially the presence of axillary metastases, calls for ever increasing caution. Of particular note to underwriting departments is the newer reports of the discriminating power of measurements of cyclin E and analysis of the levels of expression of thousands of genes simultaneously with the use of DNA microarray technology in identifying women with stage I and II breast cancers with both much better, and those with much worse, prognoses than is now available with knowledge of estrogen-receptor status and the presence or absence of lymph node metastases. In the section Risk Factors for Development of Breast Cancer, we have reviewed the data available at the time of this writing on the controversial role of hormone replacement therapy (HRT) in post-menopausal women. Although some controversial points remain, there does appear to be mounting evidence that HRT that includes both estrogen and progestin does entail risks that need to be considered in underwriting decisions. Perhaps the most significant finding in our review was that 70% to 75% of women with invasive breast cancer actually die of something other than their breast malignancy. Although there are certainly red flags that should raise serious concern in underwriting these women, there are many "breast cancer survivors" who are just that: they apparently have survived their disease. But only a firm understanding of all of the issues described in this review will allow for the selection of these insurable cases.

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**How to cite this article**

Islam N. et al. (2014). Herbal Medicinal Plant in the Treatment of Breast Cancer-An Overview. *Int. J. Pharm. Life Sci.*, 5(11):3958-3964.

Source of Support: Nil; Conflict of Interest: None declared

**Received: 19.10.14; Revised: 30.10.14; Accepted: 10.11.14**