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Breast Cancer and Botanical Medicine

By Steven Gomberg, LAc, CCN, RH (AHG), and Brandon Horn, PhD, JD, Lac

The authors are licensed acupuncturists and board certified oriental medicine practitioners for the Eastern Center for Complementary Medicine, Los Angeles; they both report no financial relationships relevant to this field of study.

THE FOLLOWING ARTICLE HAS TWO OBJECTIVES: TO PROvide clinically relevant information on the use of herbs in the treatment of breast cancer and to provide a context for their use. What follows is a distillation of some of the more effective botanicals, as well as some suggestions about how to use them in the setting of breast cancer.

Background

Breast cancer is one of the leading causes of cancer-related death in women.[1] The overall risk for women developing breast cancer is 1 in 8, with the highest risk occurring in women over the age of 60.[2] Breast cancer accounts for almost a third of all new cancers that are diagnosed in the United States, as well as 16% of all cancer-related mortalities in the United States.[3] Worldwide, 1 million cases of breast cancer are diagnosed annually. The five-year survival rates are almost 100% for stage I disease, but only 20% for stage IV.[4]

Risk Factors

Although there are general predisposing risk factors such as race, family history, and age, there are many individualized risk factors as well. As a broad overview, we will categorize cancer risk factors as: genetic/familial risks and environmental/ lifestyle risks.[5]

Genetic/Familial

Genetic factors seem to play a more significant role in the development of breast cancer in premenopausal women.[6] Mutations in the BRCA 1 and 2 tumor suppressor genes are among the most common genetic risk factors for developing cancer, with an overall lifetime risk of 60%-80%.[7] BRCA mutations are more prevalent among certain patient populations, such as women of Ashkenazic Jewish descent. Curiously, increased consumption of coffee may reduce breast cancer risk in these women.[8] Another genetic factor appears to be mutations in tumor suppressor genes, such as p53.[8]

Use of specific medications, or a history of certain illnesses, may also contribute to risk for breast cancer. For example, prior or current use of hormone replacement therapy,[9] obesity, certain forms of infertility, and fibrocystic breast disease are also known risk factors.

Environment/Lifestyle

Note: For an in-depth review of the various environmental/lifestyle exposures with citations, the reader is referred to: State of the Evidence 2008: The Connection between Breast Cancer and the Environment.[10]

Environmental exposures (eg, xenosteroids, organochlorines[11] and other chemicals, radiation,[12] etc.), lifestyle (eg, smoking, alcohol, etc.), and diet (eg, xenosteroidal compounds, growth hormones,[13] carcinogenic byproducts of manufacturing or cooking, food additives, etc.) may also be contributing factors. Clearly, there is substantial overlap. For example, recent studies have shown that high consumption of dietary fat does not pose a risk in and of itself.[14] However, certain high fat diets can lead to obesity, which is a risk factor for breast cancer.[15] Dietary fats can also contain high concentrations of fat soluble contaminants (eg, xenosteroids) which may contribute to cancer pathogenesis. High fat-to-complex carbohydrate ratio diets have also been associated in some studies with dense breast tissue, another known risk factor.[16]

The Strategic Use of Herbs in Breast Cancer

Many useful and novel compounds, with a wide range of effects, have been identified within the Chinese Herbal Pharmacopeia. Some are directly tumoricidal, while others inhibit aromatase, upregulate p53, induce apoptosis, inhibit cell-cell adhesion pathways, and so forth.

The choice of herbal research targets in breast cancer therapy is often derived from observance of traditional uses. Practitioners of Classical Chinese Medicine (CM) choose herbs based upon a complex synthesis of diagnostic parameters combined with an intricate theoretical model. Essentially, CM views tumors as a physiological response of the body to sequester a pathogen and attempt to keep it from spreading or harming other tissue. Metastasis, therefore, is seen as the loss of the body's ability to contain, eliminate, or repair the pathology.

Accordingly, three main factors are strategically addressed: 1) the underlying pathology (ie, aberrant cells); 2) the etiological factors involved in that pathology (ie, factors that create the microenvironment facilitating tumor development (these can include toxins, microorganisms, emotions/stressors, etc.); and 3) the body's ability to control the pathogen, prevent metastasis, and maintain homeostasis (i.e., immune system, digestive system, etc.).

Addressing the Underlying Pathology

Note to readers: please see accompanying chart for references to clinical statements.

The first factor involves directly addressing the aberrant cells in the tumor and their mechanisms of promoting abnormal cell growth (eg, estrogen receptors in an ER + tumor). In this respect, certain herbs may act synergistically with chemotherapy, radiation, and estrogen antagonists. Due to the novel actions of many herbs, it is also possible to utilize herbs where conventional therapies are not indicated, or as an option in cases where it is unclear whether conventional therapies will be more helpful or harmful.

Herbs used in this arena have various targets. Some seem to directly suppress tumor growth, induce apoptosis, or induce DNA repair mechanisms, where others seem to inhibit angiogenesis, cell adhesion pathways, metastasis, or block estrogen receptors. Several of the more useful herbs in this category include: *Curcumae longae* (eg, cell adhesion pathway inhibition), *Salvia miltiorrhiza* (eg, inhibits both estrogen receptor positive and negative tumors), *Boswellia serrata* (eg, metastasis inhibition), *Ganoderma lucidum* (eg, decreases estrogen receptor signaling and downregulates ER alpha expression), *Tanacetum parthenium* (eg, induces apoptosis), *Scutellaria baicalensis* (eg, inhibits multi-drug resistance and promotes DNA repair), and *Scutellaria barbata* (eg, selectively cytotoxic to breast cancer cells leaving normal mammary tissue unharmed).

Etiological Factors

Possibly the most important factor in tumor development is its microenvironment.[17] Indeed, recent research has shown the possibility of addressing even aggressive tumors by adjusting the microenvironment. As one Northwestern University researcher commented, "our observations highlight the potential utility of isolating the factors within the hESC [human embryonic stem cell] microenvironment responsible for influencing tumor cell fate and reversing the cancerous properties of metastatic tumor cells, such as melanoma."[18] The accumulating data on microenvironments implies that cancer therapies merely targeting the tumor itself, while leaving the original terrain intact, could possibly be less effective and leave the patient susceptible to recurrences.

Most potential etiologic factors can be roughly categorized as environmental toxins (ie, non-biological agents), infectious agents (biological), or internal issues such as digestive or emotional stressors.[19-21] While environmental toxins, dietary factors and, to some degree, chronic emotional stress are somewhat established etiological factors in conventional literature, infectious agents are a relative newcomer. Interestingly, there is a growing body of evidence implicating infectious agents, particularly viruses, in some breast cancers.[22] According to CM theory, one etiology of tumorigenesis is direct or indirect alterations in DNA by infectious agents. While the association is still unclear from a conventional standpoint, plausible mechanisms exist for both direct alterations of DNA (eg, viral) as well as collateral DNA damage caused by immunological defenses (eg, Reactive Oxygen Species, or ROS).

Further complicating matters, the etiology of many cases of breast cancer appears to be multi-factorial. For example, having a BRCA gene mutation does not, in and of itself, always result in breast cancer. Treating identifiable etiological factors is, therefore, extremely important.

Where information on exposure to particular types of carcinogenic compounds is available, herbs may be helpful in counteracting their effects. However, in many cases the exposures are unknown. Therefore, it is generally useful to take a more indirect approach that involves improving the body's detoxification capacity and downregulating hormone receptors, where appropriate. Research is demonstrating that herbs may be useful in this regard. For example, *Scutellaria barbata* (SBAR) increases the expression of the gene for glutathione S-transferase (GST) by 2.5-3.0-fold.[23] As GST increases phase II metabolism of xenobiotics, SBAR may prove helpful in a broader xenobiotic/mutagen prevention strategy. At the same time, it inhibits intratumoral aromatase expression in certain cancer cells, and so may help in other ways to prevent the promotion of tumor development.[24]

For protecting against radiation-induced damage, *Curcumae longae* may be very useful.[25] The herb paradoxically protects normal cells from radiation while sensitizing cancer cells to radiation. In addition, it may be prudent to prophylactically administer this, or other radioprotective substances, to women undergoing any kind of imaging involving ionizing radiation, such as mammography. We recommend 500 mg tid of a 5:1 concentrated aqueous extract (AE) for a course of 21 days, beginning seven days before the imaging is scheduled.

Addressing infectious agents is a complicated discussion from an herbal standpoint. In CM, there is an intricate theoretical basis for the identification and eradication of infections. If an infectious etiology is suspected, [redacted] using herbs that combine anti-tumor and anti-microbial properties can be considered. *Andrographis* and

Scutellaria baicalensis are examples of herbs that are both strongly anti-tumor and strongly anti-microbial.

In addressing digestive and immune function, adaptogenic herbs are often employed. These herbs tend to have an overall positive effect on resistance to external stressors. Some of the more popular and effective adaptogens include Astragalus, *Poria cocos*, and Eleutherococcus. Astragalus, for example, has general anti-tumor properties and has also been shown to have beneficial effects on the gut. It was shown to both prevent and treat colitis[26] and help restore intestinal microfloral balance.[27] *Poria cocos* also has digestive and immunological benefits with the additional function of being a mild diuretic. It also has anti-tumor properties.

Emotional factors are generally involved in breast cancer, most often as the result of the diagnosis. Therefore, addressing one's psychological state is very important. Several herbs are very helpful in this regard and, in addition to having anxiolytic properties, they also have other actions that help fight various breast tumors. Examples of some of the important herbs in this category are *Passiflora incarnata* and Chrysanthemum. Both contain chrysin, an anxiolytic flavonoid that has been shown both to inhibit aromatase[28]and metastasis.[29]

Maintaining Integrity of the Body

Many therapies for cancer are fairly aggressive and can damage healthy tissue. Adaptogens are utilized to help maintain the integrity of normal cells during the assaults on the tumor tissue. Adaptogens are herbs that have a regulatory effect on the body to help it "adapt" to various stressors. Given their function, questions have been raised about an adaptogen's ability to protect a tumor as well. While a plausible concern with some adaptogens, others have significant anti-tumor activity. *Eleutherococcus senticosa* (ES), for example, can be used concurrently with chemotherapy to mitigate side effects such as nausea, dizziness, and loss of appetite in patients undergoing treatment with cyclophosphamide.[30] Eleutherococcus also helps to restore immunologic function in patients undergoing myelosuppressive chemotherapeutic regimes.[31] In addition to strengthening the patient, ES also inhibits metastatic potential and has anti-tumor[32] and anti-viral[33] activity. Other useful adaptogens in oncology include Astragalus and Ganoderma.[34]

Administration of Herbs

In CM, herbs are commonly administered in formulas of 5-20 herbs. The framework of an herbal formula should be determined by the patient's condition. For example, a strong person with an aggressive tumor may have 70% of the formula attacking the tumor, 20% dealing with the etiology, and 10% providing adaptogens. A patient that is debilitated, perhaps from multiple chemotherapy rounds, may require 70% adaptogens, 20% anti-tumor and, 10% of the formula addressing etiology. This is where clinical judgment comes in. Of course many herbs overlap categories, so these percentages serve only a rough guide.

Next are issues with herb quality. As noted multiple times in the peer-reviewed literature, and especially so for Chinese patent medicines, it is of paramount importance that herbs be tested for heavy metals and other environmental toxins. The form of extraction is also important. In many cases, oral administration of aqueous extracts are used; however, some functions of herbs can only be accessed with other extraction methods (eg, ethanol) or other routes of administration. When considering adjuvant administration of herbs in the treatment of cancer, it is prudent to use herbs that have been standardized to specific active constituents. Identifying and recommending companies that adhere to GMPs (Good Manufacturing Practices) is of great benefit to patients.

In choosing the appropriate herbs to administer, whereas clinicians use laboratory tests and tissue pathology, where others combine these tests with traditional CM diagnostic methods such as tongue and pulse diagnosis. Generally in cancer therapy, dosages of administered herbs can be quite high. Therefore, it is prudent to concurrently monitor liver and kidney function. While the tolerance of herbal formulas is generally quite good, there have been rare instances of contamination by accidental administration of an inappropriate species that have resulted in serious complications. In most cases, these risks can be avoided through prudent monitoring, and should not be a deterrent to using herbs. In fact, many of the herbs used in therapy are both nephro- and hepato-protective and may allow for much higher tolerance of aggressive therapies such as chemotherapy. Ganoderma, for example, is both nephroprotective[35,36] and hepatoprotective.[37]

Conclusion

Breast cancer is a disease exhibiting a variety of different etiological and pathological mechanisms. The current paradigm, in which the main focus of treatment is the tumor itself, may not be the most effective approach. Recent data suggest that the tumor microenvironment may be of equal, if not greater, importance.

Chinese Medicine historically emphasizes both treatment of the tumor itself and the microenvironment. As such, CM treatments may be a very useful adjunct in the treatment and prevention of breast and other cancers. Biomedical research into the actions of herbs traditionally used in the context of breast cancer has revealed a number of novel and seemingly effective compounds. This research has also confirmed a number of mechanisms for their purported efficacy (eg, inhibiting angiogenesis, upregulating

Herb Name	Categories	Specific Effects	Dosage	Cx
Astragalus membranaceus	I, E	Enhances NK cell activity, increases interferon production, anti-viral properties.[1] Paradoxically enhances effect and reduces toxicity of certain chemotherapeutic regimes,[2] improves gut mucosa.[3]	Aqueous Extract (AE): 9-30 grams per day. Ethanol Extract (EE): 1:1 20 mL per day	
• *Poria cocos*	P, I, E	Induces apoptosis of MCF-7 breast cancer cells in vitro. Increases digestive capacity, anti-proliferative, induces cell differentiation[4]	AE: 10-15 g/day	
Eleutherococcus senticosa	I, E	Mitigates side effects and increases tolerance of chemotherapy,[5] increases interferon, anti-viral, anti-tumor activity[6,7]	AE: 9-27 g/day 10:1 dried extract standardized to 150-300 mg/day of eleutherosides B and E	One report on interference with blood digoxin levels, likely due to a contaminant in the herb.[31]
• *Ganoderma lucidum*	P, I, E	Significantly inhibits proliferation of breast cancer cells (MCF-7 and MDA-MB-231) without cytotoxic effects on normal breast tissue. Immune support and modulation, anti-angiogenic,[8] decreases estrogen receptor and nuclear factor kappa beta (NF-kB) signaling in certain breast cancer cell lines, downregulates expression of ER alpha,[9] synergistic with Herceptin (trastuzumab) in suppression of Her2/neu oncogene.[10]	AE: 3-15 g/day	Experimental data suggest water extracts may potentially aggregate blood in vitro, leading to cautions about interactions with anti-coagulants
• *Curcuma longae* (curcumin)	P, E	Significantly reduces tumor volume in MDA-MB-231 breast cancer cells. Reduces mutant p53 RNA, K67, increases apoptosis, reduces proliferation,[11] inhibits angiogenesis through inhibition of VEGF, b-FGF,[12] sensitizes cancer cells to gamma radiation,[13a] impairs cell-cell adhesion pathways,[13b] and has an effect on many other biological targets in carcinogenesis	AE: 9-12 g/day standardized to 400-600 mg curcumin — up to 1800 mg/day	Curcumin may, under some circumstances decrease the efficacy of Doxyrubicin, but it is unlikely.[31] Traditionally contraindicated in pregnancy.[32]
• *Scutellaria baicalensis*	P, E	Strongly inhibits breast cancer cell growth (MCF-7). Inhibition of multi-drug resistance,[14] anti-microbial activity,[15] anti-oxidant activities related to DNA repair,[16] hepatoprotective[17]	AE: 3-10 g/day	
• *Salvia miltiorrhiza*	P, E	Inhibits both ER+ and ER- breast tumors. Neo-tanshinlactone (component of SM) showed inhibition against two ER+ breast cancer cell lines and was 10-fold more potent and 20-fold more selective compared to tamoxifen. Also potently inhibited ER-, Her2 everexpressed cell line.[18] Synergistic with SBAI for even stronger inhibitory effects on breast tumors.	AE: 5-10 g/day	May potentiate anti-coagulant or anti-platelet drugs. May falsely elevate serum digoxin levels.[32]
Boswellia serrata	P	Anti-inflammatory AKBA (Acetyl-11-keto-beta-boswellic acid) inhibits 5-lipoxygenase pathway (5-LOX),[19] inhibits angiogenesis, VEGF, EGF.[20] Case report of BoS reversing breast cancer brain metastasis.	AE: 3-10 grams; 30% AKBA 600 mg	Traditionally contraindicated in pregnancy, may cause GI distress.[32]
• *Tanacetum parthenium*	P	Anti-inflammatory. Parthenolide induces apoptosis,[21] inhibits proliferation of several different cancer cell lines including MCF-7 breast cancer cells,[22] increases the cytotoxicity of paclitaxel[23]	EE: 1:5 25% (0.2% parthenolide) 5 mL/day	Exhibits platelet inhibiting properties, which may interact with other drugs
• *Scutellaria barbata*	P, E	Inhibits intracellular aromatase production. Broad spectrum anti-cancer agent that is selectively cytotoxic to breast cancer cells (leaving normal mammary tissue unharmed), likely through ROS induced DNA damage leading to necrotic cell death.[24] Currently in phase II clinical trials at the Ohio State University Medical Center (OSUMC).	AE: 10-30 g/day	
• *Andrographis paniculata*	P, E	In vitro and in vivo anti-tumor activity in breast cancer models. Anti-microbial,[25] immune enhancement through NK cell modulation, and increases immune-dependent cytotoxicity.[26] Andrographolide directly cytotoxic to cancer cell lines.[27] Antioxidant, anti-inflammatory,[28] inhibits Bcl-2 expression and increases apoptosis,[29] anti-angiogenic[30]	AE: 6-15 g/day	Traditionally used with caution during pregnancy.[32]

p53, selectively inducing apoptosis of tumors, inhibiting tumor and peripheral expression of aromatase, increasing anti-tumor immune activity, reducing side effects of conventional therapies, etc.). While large scale human trials are just beginning, and although the majority of data regard animal or lab research, given the wealth of historical information on the safety and efficacy of various herbs (some of them having been used for thousands of years), an herbal regimen could be considered as an additional and potentially effective tool in the treatment of breast cancer.

By utilizing herbs that have both historical data and modern research demonstrating potential mechanisms for efficacy, it is possible to maximize the chances of favorable outcomes while minimizing discomfort associated with conventional therapies. Where herb formulas are combined with conventional therapies, it is prudent to monitor the patient closely during the initial stages of administration for both efficacy (improvements in tumor markers or size) and safety (kidney and liver function). As with pharmaceuticals, herbs contain powerful chemical compounds. Therefore, even where biomedical research supports the use of a single herb or component, combinations with other herbs or pharmaceuticals can produce new chemical compounds that differ from the original chemicals, potentially impacting both safety and efficacy.

However, just as the lack of definitive data on the combined effects of most pharmaceuticals does not prevent their prescription, a lack of data on the combined effects of herbs and drugs should not necessarily be a hindrance to their use. The same prudent monitoring that allows for widespread use of untested pharmaceutical combinations can enable us to successfully apply the combined use of herbs and pharmaceuticals. With proper monitoring, herbs can be a substantial asset both in the treatment and prevention of breast cancer. Of course, further research is mandated, but for those in need now, select agents could be employed with confidence. Patient, CM practitioner, and oncologist should be involved in all such decision-making. ❖

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CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

17. Into which of the following herbal medicine categories would the traditional use of *Rhodiola* fit the BEST?

a. Vulnerary
b. Bitter
c. Antihypercholesterolemic
d. Antidepressant
e. Adaptogen

18. Extracts of *Rhodiola rosea* used in clinical trials are most often standardized to a percentage of the following compounds?

a. Rosavins
b. Epicatechins
c. Salidroside
d. a and c

19. Which of the following herbs is in phase II clinical trials for its selective cytotoxicity against breast cancer?

a. *Scutellaria barbata*
b. *Scutellaria baicalensis*
c. *Andrographis paniculata*

Answers: 17. (e); 18. (d); 19. (a)