

Running Head: ENDOCRINE MODULATING BOTANICALS: SAFETY AND
IMPACT OF CHINESE HERBAL MEDICINE (CHM) ON HORMONE
SENSITIVE BREAST CANCER - A SCOPING REVIEW

Endocrine Modulating Botanicals: Safety and Impact of Chinese Herbal Medicine
on Hormone Sensitive Breast Cancer - A Scoping Review

RQ 0145 Practice-Based Learning and Improvement

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Cover Sheet

Purpose, Intent of QIP

The intent of this project is to clarify what is known about the safety of endocrine modulating botanicals and their effect on patients being treated for, or at risk for, hormone-sensitive breast cancer as well as any herb-drug interaction that may exist between hormone therapy drugs and commonly proscribed Chinese Herbal Medicine (CHM.)

Needs Analysis, Gaps, Reason for QIP

Breast cancer is the most prevalent cancer worldwide. Many oncology patients seek adjunctive therapies to mitigate the side effects of common biomedical cancer treatments and to improve their quality of life. Chinese Medicine may address physical pain and emotional distress associated with a cancer diagnosis while moderating treatment side effects and improving the immune system. Patients and practitioners may be afraid of, or unsure of, herb-drug interactions between targeted therapy, like Tamoxifen, and CHM. The endocrine modulating properties of many Chinese herbs and Classical Chinese Herbal Formulas may not be fully considered or understood by practitioners who prescribe them in their clinical practice. Estrogen and progesterone may promote tumor proliferation in Hormone Receptor Positive (HR+) Breast Cancer, which is the predominant subtype. It is imperative that practitioners of CHM understand the risks associated with hormone modulating botanicals and potential herb-drug interactions before prescribing them in clinical practice.

Target Audience/Group

This Project is primarily geared towards practitioners of Chinese Medicine and other healthcare providers working within an Integrative Medicine framework to provide adjunctive therapy to cancer patients.

Description of Intervention, Solution, End Product to Fill Needs/Gaps

A Scoping Review was performed as a preliminary assessment of the available research on the safety of endocrine modulating botanicals for patients undergoing treatment for, or at risk for, hormone-sensitive breast cancer. The safety of Chinese Herbal Medicine and the potential effect on tumor proliferation was evaluated based on literature available through The National Center for Biotechnology Information (NCBI). Some botanicals which directly affect breast cancer cell proliferation, or which affect breast cancer gene expression, individually or when combined, were identified. Chinese Herbal Medicines which may work synergistically with, or counteract the effects of, hormone therapy or targeted therapy were identified along with confounding factors and gaps in current research.

Method(s) of Sharing End Product with Targeted Audience

This Scoping Review will be submitted for publication in a Journal such as *Meridians: The Journal of Acupuncture and Oriental Medicine (MJAOM)* or as an article for *Acupuncture Today* and may be further expanded into a more comprehensive Systematic Review.

Summary, Conclusions

While some preliminary data is available, further study is needed to conclusively determine the safety and effects of commonly prescribed CHM on gene expression and tumor proliferation in hormone-sensitive breast cancer. Practitioners must use their professional judgement, training and knowledge of herb-drug interactions when prescribing herbal medicine to cancer patients, tailoring formulas to the individual needs of each patient. Potential risks and interactions as well as expected benefits of treatment must be clearly communicated to allow patient and practitioner to collaborate on treatment decisions.

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Abstract

Background

Breast cancer is the most prevalent cancer and a leading cause of death worldwide. Many oncology patients seek adjunctive therapies to mitigate the side effects of common biomedical cancer treatments and to improve their quality of life. Estrogenic and progestogenic botanicals may promote tumor growth in Hormone Receptor Positive (HR+) breast cancer, which is the predominant subtype. The intent of this paper is to clarify what is known about the safety of use of endocrine modulating botanicals by patients being treated for hormone-sensitive breast cancer as well as to identify any herb-drug interactions that may exist between hormone therapy drugs like Tamoxifen and commonly proscribed Chinese Herbal Medicine (CHM.)

Methods

A non-systematic scoping review was performed as a preliminary assessment of the available research on the safety of commonly prescribed Chinese Herbal Medicines and their effect on tumor proliferation in patients with HR+ breast cancer. Research on herb-drug interaction between commonly prescribed Chinese formulas and the targeted therapy Tamoxifen was included. Several literature searches were performed using The National Center for Biotechnology Information (NCBI) resources, primarily via the PubMed and PMC databases. Search terms included “Chinese herbal medicine estrogen receptor positive breast cancer,” “Chinese herbal medicine estrogen sensitive breast cancer” and “Chinese herbs breast cancer.” Due to time and resource limitations, articles were reviewed based on title relevance to the objective. The initial search yielded over 3000 articles, so results were narrowed to include only articles published within the past five years.

Discussion

Oncology patients often seek adjunctive therapies to mitigate the side effects of common biomedical cancer treatments and to improve their quality of life. Chinese Medicine may address physical pain and emotional distress associated with malignancies while moderating treatment side effects and improving the immune system. Patients and practitioners may be afraid of, or unsure of, herb-drug interactions between targeted therapy and CHM and need to be well informed of the benefits and risks. Many commonly prescribed botanicals directly affect breast cancer cell proliferation or gene expression. It is well known that properties of individual herbs may be augmented when herbs are prepared in combination as Chinese Herbal Formulas. Individual constituents or herbal extracts may not retain the same properties as their whole. Although active herbal constituents may be antineoplastic, they may behave differently when used in combination such as the formula Si Wu Tang, which some research indicates should be avoided in cases of HR+ BC. CHM may work synergistically with, or counteract the effects of, hormone therapy or targeted therapy. Research has demonstrated positive synergistic relationships between common Chinese herbs and formulas and the pharmaceuticals Tamoxifen and Paclitaxel. Antineoplastic properties of many endocrine modulating botanicals appear to outweigh the risks of tumor proliferation, but research is not conclusive. Existing research focuses primarily on gene expression as it relates to common cancer cell lines. Most practitioners of CHM in the United States are not well versed in genetics making it difficult to apply study results to clinical practice. There are many confounding factors and gaps in current research. Ethical concerns limit human studies, and there are significant limitations to in vitro and animal model studies.

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Conclusion

The endocrine modulating properties of many Chinese herbs and Classical Chinese Herbal Formulas may not be fully considered or understood by practitioners who prescribe them in their clinical practice. Although hormone modulating botanicals may have a proliferative effect on breast cancer cell lines in vitro, this does not necessarily correspond to tumor growth in animal models. Further research is necessary to determine how hormone receptor modulation and altered genetic expression is specifically relevant for clinicians who prescribe CHM. It is imperative that practitioners of CHM understand the risks associated with hormone modulating botanicals and potential herb-drug interactions before prescribing them in clinical practice. Additional high-quality studies are needed to conclusively determine safety of CHM for HR+ breast cancer patients and to identify which CHF combinations are most likely to have antineoplastic or tumor proliferative effects.

Key Words

Chinese herbal medicines; breast cancer; hormone-receptor positive breast cancer, hormone sensitive breast cancer, hormone modulating botanical, Tamoxifen.

Introduction

Breast cancer is the most prevalent cancer and a leading cause of death worldwide.¹⁻³ Patients being treated for hormone-sensitive breast cancer frequently seek adjunctive therapies to mitigate the side effects of common biomedical cancer treatments and to improve their quality of life.⁴⁻⁸ Estrogenic and progestogenic botanicals may promote tumor growth in Hormone Receptor Positive (HR+) breast cancer, which is the predominant subtype.^{9,10} The intent of this paper is to clarify what is known about the safety of very commonly prescribed endocrine modulating botanicals, as single herbs and Chinese Herbal Formula combinations. Chinese Medicine may address physical pain and emotional distress associated with malignancies while moderating treatment side effects and improving the immune system.^{8,11,12} Patients and practitioners may be afraid of, or unsure of, herb-drug interactions between targeted therapy and CHM and need to be well informed of the benefits and risks. It is necessary to clarify if commonly prescribed botanicals which directly affect breast cancer cell proliferation or gene expression can be used safely in clinical practice with this patient population.^{3,9} It is also necessary to identify any herb-drug interactions, or synergistic relationship that may exist between hormone therapy drugs like Tamoxifen and commonly proscribed Chinese Herbal Medicine (CHM.)

Method

A non-systematic scoping review was performed as a preliminary assessment of the available research on the safety of commonly prescribed Chinese Herbal Medicines and their effect on tumor proliferation in patients with HR+ breast cancer. Research on herb-drug interaction between commonly prescribed Chinese formulas and the targeted therapy Tamoxifen was included. Several literature searches were performed using The National Center for Biotechnology Information (NCBI) resources, primarily via the PubMed and PMC databases. Search terms included “Chinese herbal medicine estrogen receptor positive breast cancer,” “Chinese herbal medicine estrogen sensitive breast cancer,” “Chinese herbs breast cancer” and “phytoestrogen hormone modulation breast cancer.” Due to time and resource limitations, articles were reviewed based on title relevance to the objective. The initial search yielded over 3000 articles, so results were narrowed to include only articles published within the past five years. While the role phytoestrogens may play in clinical treatment of breast cancer is of great interest to the author, this topic was determined to be far too broad to include in this review and it was determined that this topic should

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be investigated separately. The first few pages of search results were assessed, based on relevance, and articles which made specific reference to Classical Chinese Formulas or herbal ingredients contained in very commonly prescribed formulas were flagged for further review with approximately 50 articles reviewed over a period of 12 months.

Results

It is well known that properties of individual herbs may be augmented when herbs are prepared in combination as Chinese Herbal Formulas. Individual constituents or herbal extracts may not retain the same properties as their whole. Although active herbal constituents may be antineoplastic, they may behave differently when used in combination such as the formula Si Wu Tang (SWT,) which research indicates should be avoided in cases of HR+ BC. “[SWT] not only is able to upregulate the HER2 and ER α expression in MCF-7 cells but also stimulates the cell proliferation in BT474 (ER+, HER-2 high), MDAMB231 (ER-, HER-2 low), and SKBR3 (ER-, HER-2 high) mammary duct cell lines” making it a poor choice for all types of breast cancer. CHM may work synergistically with, or counteract the effects of, hormone therapy or targeted therapy. This 2013 study, performed in vitro and in vivo using a mouse model, concluded that SWT reversed the antiproliferative effects of Tamoxifen on tumor density and volume while simultaneously enhancing expression of estrogen receptor α and N-cadherin. SWT also “reversed Trastuzumab-induced antiproliferative activity in HER2+ cell lines (SK-BR-3 and BT-474)” meaning that SWT not only increased tumorigenesis, but counteracted the effects of targeted therapies.^{9,13,14} A 2014 follow-up study examined 22 commonly prescribed Chinese single herbs and 6 formulas in vitro, studying their effects on ERBB2 and ESR1 gene expression in the MCF-7 cell line. Herbal concentrations that resulted in less than 80% cytotoxicity were used. Thirteen of the individual herbal extracts and five formulas were found to promote either ERBB2 or ESR1 activity. Chuan xiong (*Ligusticum*) demonstrated a significant effect on ERBB2 gene expression and stimulated MCF-7 proliferation when exposed to estrogen. Three additional formulas were found to promote HER2 or ER α protein expression, including Si Wu Tang (SWT,) Kuan Shin Yin (KSY) and Suan Zao Ren Tang.³ While it may be useful to understand how these botanicals effect gene expression, this study does not give us conclusive information about how these substances behave in vivo when dosage induces cytotoxicity.

Research has also identified positive synergistic relationships between common Chinese herbs and formulas and the pharmaceuticals Tamoxifen and Paclitaxel. Jia Wei Xiao Yao San (JWXYS) is a classical Chinese formula, prescribed for centuries, which is the formula most often prescribed in combination with the targeted therapy Tamoxifen. Although some of the individual botanical ingredients in JWXYS may upregulate *ERBB2* and *ESR1* gene expression, JWXYS does not upregulate these genes. This is likely due to chemical interactions between the herbal components of JWXYS.¹⁴ JWXYS taken in combination with Tamoxifen was associated with reduced risk of subsequent endometrial cancer.¹⁵ Additionally, there is evidence that when combined with chemotherapy drugs, JWXYS has the potential to reduce chemo-resistance and improve effectiveness.¹⁶

In vitro studies of Dang gui (*Angelica sinensis*) have confirmed estrogen modulating properties and indicated it may increase tumor proliferation in ER+ breast cancer cell lines. While dang gui was found to increase breast cancer cell growth in vitro, in vivo animal studies did not demonstrate an increase in tumor growth.¹⁷ Dose dependent antiproliferative effects on ER+ cell lines have also been demonstrated for Huang Qi.¹⁸

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Discussion

Oncology patients often seek adjunctive therapies to mitigate the side effects of common biomedical cancer treatments and to improve their quality of life. Chinese Medicine may address physical pain and emotional distress associated with malignancies while moderating treatment side effects and improving the immune system. Patients and practitioners may be afraid of, or unsure of, herb-drug interactions between targeted therapy and CHM and need to be well informed of the benefits and risks.

Antineoplastic properties of many endocrine modulating botanicals appear to outweigh the risks of tumor proliferation, but research is not conclusive. Existing research focuses primarily on gene expression as it relates to common cancer cell lines. Most practitioners of CHM in the United States are not well versed in genetics making it difficult to apply study results to clinical practice. There are many confounding factors and gaps in current research. Ethical concerns limit human studies, and there are significant limitations to in vitro and animal model studies as well as challenges associated with extrapolating wet lab and rodent studies to human clinical practice.

It is well known that Chinese Herbal Formulas take on different properties when decocted than their individual constituents and herbal extracts may not display the same properties as their whole. Although active herbal constituents may be antineoplastic, they may behave differently when used in combination. Chuan xiong/ Ligusticum was identified as a substance which increased the proliferation of several common breast cancer cell lines. The commonly prescribed formula Si Wu Tang (SWT) which contains chuan xiong was also shown to increase tumor growth in an animal model. The formula Suan Zao Ren Tang contains chuan xiong, but it was found to be anti-proliferative. Si Wu Tang is prescribed frequently for symptoms of blood deficiency or anemia, which is a common pattern experienced post-chemotherapy, however prescription of SWT should be avoided for this population due to the potential to stimulate tumor proliferation in all breast cancer cell types and the likelihood that it will counteract targeted therapies such as Tamoxifen and Trastuzumab.

CHM may work synergistically with, or counteract the effects of, hormone therapy or targeted therapy. Jia Wei Xiao Yao San (JWXYS,) known as “Free and Easy Wanderer” is one of the most frequently prescribed classical formulas to alleviate side-effects of breast cancer treatment. Research has demonstrated positive synergistic relationships between JWXYS and Tamoxifen and between JWXYS and Paclitaxel. Dang gui, which is an estrogen modulating botanical, appears to have antineoplastic properties which outweigh the risks of tumor proliferation, but research is not conclusive.

Hormone therapy is proscribed frequently for long term use in patients with hormone sensitive cancers. Breast cancer patients look to practitioners of Chinese Medicine to mitigate side the effects of these drugs and other biomedical cancer treatments but may also seek treatment for pain, or psycho-emotional disorders. Many Chinese Medicine practitioners will see patients taking hormone therapy in their practice and should be aware of the herb-drug interactions between some commonly proscribed medications, like Tamoxifen, and Chinese Herbs. The hormone modulating properties of these Chinese herbs and Classical Chinese Herbal Formulas should be better understood by practitioners to provide the best possible care. Further, many patients are aware that exogenous hormones can have a deleterious effect on their health but are unsure of the risk hormone modulating herbs may present to them if they have a genetic predisposition to hormone sensitive cancers. This QIP seeks to answer these questions.

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The endocrine modulating properties of many Chinese herbs and Classical Chinese Herbal Formulas may not be fully considered or understood by practitioners who prescribe them in their clinical practice. It is imperative that practitioners of CHM understand the risks associated with hormone modulating botanicals and potential herb-drug interactions before prescribing them in clinical practice. Additional high-quality studies are needed to conclusively determine safety of CHM for HR+ breast cancer patients.

Conflicts of Interest

The author has no financial or scientific conflicts of interest related to the research described in this paper.

References

1. Tsai Y-T, Lai J-N, Wu C-T. The use of Chinese herbal products and its influence on tamoxifen induced endometrial cancer risk among female breast cancer patients: a population-based study. *J Ethnopharmacol*. 2014;155(2):1256-1262. doi:10.1016/j.jep.2014.07.008
2. Li Y, Li S, Meng X, Gan RY, Zhang JJ, Li H Bin. Dietary natural products for prevention and treatment of breast cancer. *Nutrients*. 2017;9(7). doi:10.3390/nu9070728
3. Chiu J-H, Chang C-J, Wu J-C, et al. Screening to Identify Commonly Used Chinese Herbs That Affect ERBB2 and ESR1 Gene Expression Using the Human Breast Cancer MCF-7 Cell Line. *Evid Based Complement Alternat Med*. 2014;2014:965486. doi:10.1155/2014/965486
4. Liao Y-H, Lin C-C, Lai H-C, Chiang J-H, Lin J-G, Li T-C. Adjunctive traditional Chinese medicine therapy improves survival of liver cancer patients. *Liver Int*. 2015;35(12):2595-2602. doi:10.1111/liv.12847
5. Hou ML, Lu CM, Tsai TH. Effects of Jia-Wei-Xiao-Yao-San on the peripheral and lymphatic pharmacokinetics of paclitaxel in rats. *Evidence-based Complement Altern Med*. 2016;2016. doi:10.1155/2016/5614747
6. Ye L, Jia Y, Ji KE, et al. Traditional Chinese medicine in the prevention and treatment of cancer and cancer metastasis. *Oncol Lett*. 2015;10(3):1240-1250. doi:10.3892/ol.2015.3459
7. Zhu X, Moylan EJ, Xu Y, Yang Y, Porter DP, Fahey P. Chinese medicine for immunological functions in women with breast cancer or a history of breast cancer. *Cochrane Database Syst Rev*. 2018;2018(10). doi:10.1002/14651858.CD013144
8. Greenlee H, DuPont-Reyes MJ, Balneaves LG, et al. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. *CA Cancer J Clin*. 2017;67(3):194-232. doi:10.3322/caac.21397
9. Chen JL, Wang JY, Tsai YF, et al. In vivo and in vitro demonstration of herb-drug interference in human breast cancer cells treated with tamoxifen and trastuzumab. *Menopause*. 2013;20(6):646-654. doi:10.1097/gme.0b013e31827b2240
10. Chiu J-H, Chang C-J, Wu J-C, et al. Screening to Identify Commonly Used Chinese Herbs That Affect ERBB2 and ESR1 Gene Expression Using the Human Breast Cancer MCF-7 Cell Line. *Evidence-Based Complement Altern Med*. 2014;2014:1-11. doi:10.1155/2014/965486

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11. Moore F (AOMA GS of IM. *Extraovarian Primary Peritoneal Carcinoma: Summary of Findings: TCM Etiology, Pathology, Assessment, Diagnoses, Syndrome Differentiation, Treatment and Outcomes*. Austin, TX; 2018.
12. Lyman GH, Greenlee H, Bohlke K, et al. Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline. *J Clin Oncol*. June 2018;JCO2018792721. doi:10.1200/JCO.2018.79.2721
13. Yue GG-L, Wong L-S, Leung H-W, et al. Evaluation of the safety profiles of estrogenic Chinese herbal medicines in breast cancer. *Phytomedicine*. 2019;56:103-117. doi:10.1016/j.phymed.2018.10.003
14. Chiu JH, Chang CJ, Wu JC, et al. Screening to identify commonly used chinese herbs that affect ERBB2 and ESR1 gene expression using the human breast cancer MCF-7 cell line. *Evidence-based Complement Altern Med*. 2014;2014. doi:10.1155/2014/965486
15. Tsai YT, Lai JN, Lo PC, Chen CN, Lin JG. Prescription of Chinese herbal products is associated with a decreased risk of invasive breast cancer. *Med (United States)*. 2017;96(35). doi:10.1097/MD.00000000000007918
16. Yang K, Zeng L, Ge J. Exploring the Pharmacological Mechanism of Danzhi Xiaoyao Powder on ER-Positive Breast Cancer by a Network Pharmacology Approach. *Evidence-based Complement Altern Med*. 2018;2018. doi:10.1155/2018/5059743
17. Is Danggui Safe to be Taken by Breast Cancer Patients?-A Skepticism Finally Answered by Comprehensive Preclinical Evidence. - PubMed - NCBI. <https://www.ncbi.nlm.nih.gov/pubmed/31293425>. Accessed October 28, 2019.
18. Extract from Astragalus membranaceus inhibit breast cancer cells proliferation via PI3K/AKT/mTOR signaling pathway. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5845298/>. Accessed December 18, 2019.