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REVIEW ARTICLE

Chinese nutritional herbs as potential alternatives for therapy-resistant breast cancer stem cells

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ABSTRACT

Background: Expression status of hormone and growth factor receptors dictates treatment options for targeted chemo-endocrine therapy in breast cancer. Chemo-endocrine therapy is associated with systemic toxicity, therapy resistance and emergence of therapy-resistant cancer stem cells. These limitations emphasize identification of testable alternatives. Natural products including dietary phytochemicals and Chinese nutritional herbs exhibit low systemic toxicity, long-term human consumption and preclinical efficacy, and may function as testable therapeutic alternatives.

Objective: The main objective of this mini-review is to discuss published evidence on cellular models for clinical breast cancer subtypes, mechanistic leads for growth inhibition by nutritional herbs and applicability of drug-resistant cancer stem cell models to investigate stem cell targeting efficacy of nutritional herbs. Collectively, published evidence supports the concept that Chinese nutritional herbs may function as testable therapeutic alternatives for breast cancer.

Conclusion: The published evidence provides proof of concept that investigations on drug-resistant breast cancer stem cell models may provide mechanistic leads for effective nutritional herbs as novel therapeutic alternatives for breast cancer.

Future Prospects: Discussed evidence provides a conceptual basis for future investigations on patient-derived tumor explants and organoids. Experimental approaches using clinical tumor samples are likely to reduce extrapolation of the data for clinical relevance and translatability.

Keywords: Growth inhibition, Chinese nutritional herbs, breast cancer subtypes, cancer stem cell models.

Introduction

Progression of breast cancer to advanced stage metastatic disease represent a major cause of mortality in women. The American Cancer Society has estimated an incidence of 321,910 newly diagnosed breast cancers and 42,140 cancer related deaths for women in 2027[1]. Breast cancer remains a multi-factorial disease influenced by lifetime dietary practices where dietary phytochemical and nutritional herbs have documented preclinical and clinical mechanistic leads[2, 3]. .However, stronger epidemiological and clinical evidence remains to be established.

Conventional chemo therapy continues to represent mainstream treatment options for breast cancer. Traditionally, these options use combinatorial approach with cytotoxic DNA synthesis inhibitors that mechanistically distinct efficacy for DNA synthesis inhibition. The major limitations for this approach include systemic toxicity, off target effects and therapeutic resistance, leading to compromised patient compliance and continued disease progression[4].

In recent years, molecular pathway selective targeted therapy is being widely used. The selection of treatment option for targeted therapy is based on the expression status of hormone and growth factor receptors specific for individual breast cancer subtypes[4].

Despite a widespread use of conventional chemotherapy and targeted therapeutic approaches the presence of pharmacological agents represents one of the major limitation. Pharmacological chemotherapeutics is commonly associated with systemic toxicity, therapy resistance and emergence of therapy resistant cancer stem cell population. Collectively, these aspects define major limitations impacting disease progression and patient compliance[5]. Collectively these limitations emphasize investigations to identify effective therapeutic alternatives.

Natural products including botanicals, dietary phytochemicals and Chinese nutritional herbs used in may represent testable therapeutic alternatives to conventional chemo-endocrine therapy and small molecule based targeted therapy. Published evidence on natural products including dietary phytochemicals and widely used in nutritional herbs from traditional Chinese medicine (TCM) have provided reasonable evidence as testable alternatives for breast cancer[5]. Natural products have documented low systemic toxicity, long-term human consumption and preclinical efficacy in breast cancer models[5-8]. Collectively, these aspects provide a conceptual basis for a systematic discussion and review of published evidence.

The present mini-review discusses published evidence relevant to i) cellular models representing select clinical breast cancer subtypes, ii) chemo-endocrine therapy based treatment options for breast cancer subtypes and iii) development and applicability of drug-resistant breast cancer stem cell models as experimental approaches for stem cell targeted efficacy of Chinese nutritional herbs.

EXPERIMENTAL MODELS FOR BREAST CANCER SUBTYPES:

Human breast carcinoma-derived cellular models provide valuable experimental approaches to investigate growth inhibitory efficacy of natural products on breast cancer subtypes. The expression status of hormone and growth factor receptor determines the selection of appropriate chemo-endocrine therapy. Additionally, functional receptors provide quantifiable molecular markers to identify mechanistic leads for growth inhibitory efficacy of nutritional herbs. The cellular models for Luminal A, post-menopausal and triple negative breast cancer subtypes are summarized in Table 1.

Table 1: Experimental Models

Cell Line	Molecular Characteristic ER PR HER-2 AROM	Breast Cancer Subtype
MCF-7	+ + - -	Luminal A
MCF-7^{AROM}	+ + - +	Post-menopausal breast cancer
MDA-MB-231	- - - -	Triple negative breast cancer

ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; AROM, aromatase.

TREATMENT OPTIONS FOR BREAST CANCER SUBTYPES:

Existing chemo-endocrine therapy and molecularly targeted therapy for estrogen receptor (ER) positive Luminal A breast cancer subtype include pharmacological therapeutics that either modulate or degrade ER. The post-menopausal breast cancer frequently expresses the aromatase enzyme that is responsible for biosynthesis of estradiol. The triple negative breast cancer subtype that lacks the expression of hormone and growth factor receptor respond only to cytotoxic chemotherapy with DNA damaging anthracyclines, taxols and platins[4]. Commonly used therapeutic options for Luminal A, Aromatase positive and triple negative breast cancer subtypes are summarized in Table 2.

Table 2: Therapeutic Options for breast cancer subtypes

Breast Cancer Subtype	Treatment
Luminal A	SERM, SERD, CDK4/6 inhibitors
Aromatase positive breast cancer	Aromatase inhibitors
Triple negative breast cancer	DOX, PCT, CPL, CAP, PARP inhibitors

SERM, selective estrogen receptor modulator; SERD, selective estrogen receptor degrader; CDK, cyclin dependent kinase; DOX, doxorubicin; paclitaxel; CPL, carboplatin; CAP, capecitabine; PARP, poly(ADP-ribose) polymerase. Summarized from[1, 4].

The pharmacological agents used in chemo-endocrine therapy of breast cancer subtypes are associated with systemic toxicity and therapy resistance. This limitation emphasizes investigations to identify therapeutic alternatives Natural products such as Chinese nutritional herbs have exhibited growth inhibitory efficacy in cellular models for breast cancer subtypes via multiple mechanistic pathways relevant to growth inhibition via cell proliferation, cellular apoptosis and regulatory cell signaling pathways[7,8].

GROWTH INHIBITORY EFFICACY OF NUTRITIONAL HERBS IN CELLULAR MODELS FOR BREAST CANCER:

Herbal formulations represent major treatment options for breast cancer in traditional Chinese medicine (TCM). Nutritional herbs exhibit low systemic toxicity, human consumption and preclinical efficacy. In TCM aqueous decoction prepared from herbal formulations are used for treatment. To simulate the clinical administration, non-fractionated aqueous extracts from nutritional herbs are prepared. These extracts are used in the experiments designed to examine their growth inhibitory efficacy and to identify their mechanism of action. Nutritional herbs contain polyphenols, flavonoids and terpenoids function as potential bioactive agents and have documented anti-cancer activity in preclinical models. Published evidence has documented anti-proliferative and pro-apoptotic effects via distinct molecular mechanisms that involve growth regulatory cell signaling pathways and cancer cell survival

pathways. The mechanism of action of nutritional herbs depends on molecular characteristics of individual breast cancer subtype. Thus, in breast cancer cells that exhibit functional estrogen receptor the nutritional herbs target hormone receptor signaling, estrogen responsive gene expression and cellular metabolism of estradiol to generate anti-proliferative metabolites[9, 10]. In breast cancer cells that lack the expression of hormone/growth factor receptor, nutritional herbs affect RB signaling via cyclin D1-CDK4/6-pRB-E2F1 or Cyclin E-CDK2-pRB-E2F1 axes specific forproliferation[9-18]. The pro-apoptotic effects of nutritional herbs are universally operational via the intrinsic mitochondrial pathways such as BCL-2/BAX signaling and expression of Caspase 3/7[5-8].

Published evidence is systematically reviewed from select cellular models Such as estrogen receptor positive MCF-7 and MCF-7^{AROM,} and estrogen receptor negative MDA-MB-231 breast cancer subtypes.

MCF-7 MODEL:

The nutritional herb Cornus officinalis (CO) represents a major component of nutritional formulations used in traditional Chinese medicine for breast cancer, and anthocyanins represent a major bioactive agent responsible for biological efficacy of CO. Non-fractionated aqueous extract prepared from the fruit of CO was used for the treatment of MCF-7 cells The estrogen receptor (ER) positive MCF-7 cells exhibit growth stimulation in response to physiological levels of estradiol (E2). CO treatment at its maximum cytostatic concentration resulted in inhibition of E2-stimulated growth. Cellular metabolism of E2 generates E2 metabolites with distinct growth modulating effects. For example, 2-hydroxyestrone (2-OHE1) exhibits anti-proliferative effects while, 16α-hydroxyestrone (16α-OHE1) promotes cellular growth of MCF-7 cells in vitro and in vivo[13]. Mechanistically, CO treatment at its maximum cytostatic concentration increased the formation of 2-hydroxyestrone (2-OHE1), resulting in an increase in the 2-OHE1: 16α-OHE1 ratio[14]. .

MCF-7 ^{AROM} MODEL:

In post-menopausal breast cancer peripheral estrogen synthesis via aromatase activity is commonly observed. Aromatase is essential for estrogen biosynthesis via conversion of testosterone to estradiol (E2), and of androstenedione to estrone (E1). Treatment with pharmacological aromatase inhibitors represents a therapeutic option for aromatase positive post-menopausal breast cancer[4]. MCF-7 cells expressing aromatase represent a cellular model for post-menopausal breast cancer. Growth inhibitory efficacy and mechanism of action of a natural product is examined in the MCF-7 ^{AROM} model. [ADD: potential significance of aromatase mediated formation of E1 and, and modulation of cellular metabolism of E2}.

Tabebuia avellanedae (TA) is a tree native to the Amazon rainforest. A non-fractionated aqueous extract prepared from the inner bark of this tree has been used to examine its growth inhibitory efficacy on the MCF-7 model. The anti-proliferative and pro-apoptotic effects of TA are associated with differential expression of proliferation and apoptosis specific genes and genes responsible for E2 metabolism[9]. The anti-proliferative and pro-apoptotic effects of TA are also notable in MDA-MB-231 model for triple negative breast cancer subtype. In this model the growth inhibitory efficacy of TA is associated with inhibition of G1-S phase transition and downregulation of the RB signaling pathway via inhibition of phosphorylated RB. The pro-apoptotic effect of TA is associated with increase pro-apoptotic caspase 3/7 activity[15]. The growth inhibitory evidence of TA on the MCF-7 and MDA-MB-231 models provided a rationale for a study on the MCF-7^{AROM} model. TA also known as Taheebo NFD Marugoto (TNM) is reported to contain naphthofurandione (NFD) as a major bioactive agent. Treatment of MCF-7^{AROM} cells with maximum cytostatic concentration of 10 µg TNM (NFD: 2ng) resulted in S phase arrest, inhibition of anchorage independent growth and inhibition of aromatase activity. The pro-apoptotic effects were associated with increase in pro-apoptotic BAX and increased activity of pro-apoptotic caspase 3/7. In

addition, TNM treatment resulted in inhibited expression of several estrogen responsive genes including ESR-1, AROM, PR, pS2, GRB2 and cyclin D1[10].

The evidence for anti-aromatase activity of TNM in the MCF-7 ^{AROM} model prompted a comparative study to examine the extent of aromatase inhibition by TNM and pharmacological aromatase inhibitors letrozole, and exemestane. Based on its NFD content, TNM exhibited about 35.6 fold greater potency relative to letrozole and about 148 fold greater potency relative to exemestsane. These data provide strong evidence of superior anti-aromatase activity of naturally-occurring less toxic TNM compared to the commonly used clinical aromatase inhibitors[10].

MDA-MB-231 MODEL:

In the MDA-MB-231 model for triple negative breast cancer subtype the growth inhibitory efficacy of several mechanistically distinct nutritional herbs have been examined. The growth inhibitory effects of CO (major bioactive agent anthocyanins) involves cell cycle arrest via inhibition of G1 to S phase transition, inhibition of cyclin D1 and of phosphorylated RB. The pro-apoptotic effects are associated with increased cell population in the sub G0 (apoptotic) phase of the cell cycle, increased expression of pro-apoptotic BAX and increased caspase 3/7 activity[16]. Non-fractionated aqueous extract prepared from the seeds of Psoralia corylifolia (PC, major bioactive agent terpene) is used for treatment of the cells. The inhibitory effects are associated with G1 arrest and Inhibition of RB signaling via the cyclin D1-CDK4/6-pRB axis. The pro-apoptotic effects are associated with increased caspase 3/7 activity[17]. The effects of Dipsacus asperoides (DA, Major bioactive agent terpene) are associated with G2/M arrest and inhibition of RB, RAS, PI3K, AKT signaling[18]. The effects of Drynaria fortunei (DF root extract, major bioactive agent flavone) and of Viola yedoensis (VY, leaf extract, major bioactive agent terpene) involved S-phase arrest and inhibition of RB signaling via the cyclin E-CDK2-E2F1-pRB axis[11, 12].

The molecular mechanisms responsible for the growth inhibitory effects of Chinese nutritional herbs on the models for breast cancer subtype specific models are summarized in Table 3.The biomarker assays for transcriptomic, proteomic and metabolic quantitative end points have been stringently optimized and published. Appropriate references for the assays are provided in Table 3 as reference numbers in the Mechanism of Action column.

Table 3: Molecular mechanism for efficacy of nutritional herbs

Cellular Model	Breast cancer subtype	Nutritional herb	Mechanism of action
MCF-7	Luminal A	CO	E2 metabolism [14]
MCF-7^{AROM}	Post-menopausal breast cancer	TA/TNM	Aromatase inhibition, E2 response gene inhibition[10]
MDA-MB-231	Triple negative breast cancer	CO PC DA DF VY	Cyclin D1, pRB, BAX, caspase 3/7[16] G1, cyclin D1- CDK4/6-pRB[17] G2, RB, RAS, PI3K, AKT[18] S-phase, cyclin E-S-phase, CDK-2-pRB-E2F1[11] S-phase, cyclin E-CDK2-pRB-E2F1[12]

CO, Cornus officinalis; TA/TNM, Tabebuia Avellaneda/Taheebo NFD Marugoto; PC, *Psoralia corylifolia*; DA, *Dipsacus asperoides*; DF, *Drynaria fortunei*; VY*; Viola yedoensis*; E2, estradiol; pRB, phosphorylated retinoblastoma; BAX, BCL-2 associated protein X; CDK, cyclin dependent kinase; RB, retinoblastoma; RAS, oncogene; PI3K, phopho-insitol-3 kinase; AKT, protein kinase B; E2F1, E2F family transcription factor.

DRUG-RESISTANT STEM CELL MODELS:

Clinical and phenotypic therapy resistance to targeted therapy in breast cancer necessitates development of reliable cancer stem experimental approaches to investigate stem cell targeted efficacy of testable therapeutic alternatives. Stem cell models for MCF-7 and MDA-MB-231cells have been developed and characterized[19, 20]. Long-term treatment of MCF-7 cells with the selective estrogen receptor modulator tamoxifen (TAM) and of MDA-MB-231 cells with the DNA damaging chemotherapeutic agent doxorubicin (DOX) selected drug resistant phenotypes. The resistant cells were expanded under selective pressure of TAM and DOX, respectively. MCF-7/TAM-R and MDA-MB-231/DOX-R phenotypes were examined for the expression of biological and molecular stem cell specific markers. Tumor spheroids (TS), cell surface protein CD44, and transcription factors NANOG and OCT-4 represented quantifiable stem cell makers. Relative to Sensitive phenotypes the drug resistant phenotypes exhibited increased expression in the stem cell specific markers. Collectively, these data validate the two models to examine stem cell targeted efficacy of nutritional herbs and constituent bioactive agents. The expression status of stem cell markers in MCF-7/TAM-R, MDA-MB-231/DOX-R models is summarized in Table 4.

Table 4: Drug-resistant stem cell models

Phenotype	Stem Cell Marker			
	TS	CD44	NANOG	OCT-4
MCF-7/TAM-S	2.1	2.7	2.2	2.0
TAM-R	12.8	14.7	12.9	13.3
Relative to TAM-S	**5.1X**	**4.4X**	**4.9X**	**5.6X**
MDA-MB-231/DOX-S	2.5	2.1	2.7	2.9
DOX-R	24.8	16.8	24.9	18.8
Relative to DOX-S	**8.9X**	**7.0X**	**8.2X**	**5.5X**

TS, tumor spheroid; CD44, cluster of differentiation44; NANOG, DNA-binding nuclear transcription factor; OCT-4, octamer –binding protein-4; TAM-S, tamoxifen sensitive; TAM-R, tamoxifen resistant; DOX-S, doxorubicin sensitive; DOX-R, doxorubicin resistant. Data summarized from [5, 19 and 20].

Evidence for experimental modulation of stem cell markers represents an important aspect to validate stem cell models. Treatment with the endogenous metabolite of vitamin A all-trans retinoic acid and with the rosemary terpenoid carnasol resulted in substantial decrease in the expression of TS, CD44, NANOG and OCT-4 in a LAP-R model for HER-2-enriched breast cancer[5].

Conclusion

The present mini-review has discussed published evidence on cellular models for select breast cancer subtypes, growth inhibitory efficacy of mechanistically distinct nutritional herbs and applicability of drug-resistant stem cell models as innovative experimental approaches to identify stem cell targeting efficacy. Collectively, the subject matter of the review in general, and systematic discussion of clinically relevant published evidence in particular, has provided strong conceptual and technical background and scientifically robust rationale for select research directions.

In attempts to reduce required extrapolation of preclinical data generated from carcinoma-derived cell lines, development of models from patient-derived clinical breast tumor explants and organoids[28, 29] may represent valuable experimental approach to test whether nutritional herbs function as testable alternatives for therapy-resistant breast cancer. Overall, such an extension of research may provide clinical relevance and translatability of the data. Select research directions are discussed as future prospects.

Future Prospects

ER-β SIGNALING:

Estrogen receptor signaling has an opposing impact on estrogen responsive breast cancer. Estrogen receptor-α (ER-α) is encoded by ESR1 gene and functions as a positive growth regulator, while, ER-β encoded by ESR2 gene functions as a negative growth regulator[21]. Inhibition of ER-β signaling is related to resistance of therapy where MAPK and GCPR pathways play an essential role[22]. It is notable that naturally-occurring phytoestrogens present in nutritional herbs influence ER-β target gene expression via binding to estrogen response elements[23, 24]. In ER negative breast cancer growth inhibition by ER-β agonist TAM in combination with DNA damaging agent DOX is influenced via the ER-β-p53-p73 axis[25]. Constitutive bioactive agents from phytoestrogens, functioning as ER-β agonists, may represent testable drug candidates on relevant patient-derived models.

In addition to ER-β signaling, published evidence for modulation of estrogen metabolism and generation of growth modulatory metabolites[13, 14] may also be significant in the MCF-7^{AROM} model. The aromatase enzyme is essential for conversion of androstenedione to E1 and the latter functions as a precursor to generate the anti-proliferative metabolite. 2-OHE1. Thus, in the MCF-7^{AROM} model potential mechanisms of growth modulation by phtyo-estrogens via cellular metabolism of estradiol may represent an additional direction.

TGF-β SIGNALING:

Transforming growth factor-β (TGF-β) is a dual functional cytokine involved in tumor suppression of early stage disease and tumor progression of late stage disease. The negative growth regulation by TGF-β1-TGF-β2 -SMAD-3 pathway and crosstalk with ER signaling pathway impacts tumor response to anti-estrogenic agents. The growth modulatory function of TGF-β has been documented in ER positive and ER negative breast cancer models [26]. These aspects suggest that TGF-β signaling may represent a therapeutic target for the effect of phytoestrogens.

BIOACTIVE AGENTS AS POTENTIAL DRUG CANDIDATES:

Naturally-occurring bioactive agents present in Chinese nutritional herbs include polyphenols, flavones and terpenes[7, 8]. These molecules may represent potential drug candidates for therapy-resistant breast cancer subtypes. Network pharmacology of bioactive agents involves identification of mechanistic pathways and molecular targets. Genomic, proteomic and protein-protein interaction based functional assays on relevant models for breast cancer subtypes will identify and prioritize promising agents for testing in patient derived tumor models. This preclinical evidence suggests that botanicals may function as testable therapeutic alternatives either alone or in conjunction with conventional/targeted therapeutic approaches. These botanicals and constitutive bioactive agents are considered as potential drugs. Thus, these agents need to be submitted to functional transcriptomic and proteomic assays to select promising candidates. Subsequently, the selected agents should undergo human safety and efficacy studies prior to rigorous clinical trials as alternatives for secondary prevention and/or potential drug candidates[27].

Conflicts of interest statement:

The author declares that there are no conflicts of interest.

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