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REVIEW ARTICLE

Hormone Metabolites and Herbal Bioactive Agents: Potential Drug Candidates for the Luminal A Breast Cancer subtype

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ABSTRACT

Abstract

Background: Hormone receptor positive, human epidermal growth factor receptor negative Luminal A breast cancer subtype responds to targeted endocrine therapy, signal transduction inhibitors and cyclin dependent kinase inhibitors. Estrogen and progesterone receptor mediated signal transduction involves receptor-DNA binding and transcriptional activation of downstream target genes. In addition to hormone receptor signaling, cellular metabolism of estradiol and progesterone exhibit distinct roles in cancer growth modulation. Targeted therapy is associated with systemic toxicity, therapy resistance and emergence of chemo-resistant cancer initiating stem cells. These limitations emphasize identification of testable drug candidates for therapy resistant breast cancer. Cellular metabolism of ovarian steroid hormones generates oxidative metabolites with distinct growth modulating effects. Anti-proliferative metabolites may represent potential drug candidates.

Objectives: The objectives of the present review are to provide i) Systematic discussion of published evidence relevant to the role of ovarian steroid hormone metabolism in growth modulatory effects on cancer progression, ii) Evidence for applicability of Luminal A breast cancer and drug-resistant cancer stem cell models to identify mechanistic leads for efficacy of anti-proliferative hormone metabolites, and iii) Future research directions for clinical translatability of patient derived preclinical data.

Conclusions: Contrasting growth modulatory effects ovarian steroid hormones, anti-proliferative effects of individual metabolites of ovarian steroid hormones, growth inhibitory efficacy of nutritional herbs via altered cellular metabolism of estradiol and development of drug-resistant cancer stem cell model represent salient features of this review. Collectively, present evidence validates experimental approaches to identify growth inhibitory hormone metabolites and bioactive agent from nutritional herbs as potential drug candidates for therapy-resistant breast cancer.

Future Research: This review provides a rationale for future investigations to evaluate stem cell targeted efficacy of anti-proliferative hormone metabolites and herbal bioactive agents. These directions may include functional significance of estrogen receptor-β, and telomerase expression. Furthermore, investigations using patient-derived tumor explant and tumor organoid models from therapy-resistant breast cancer may facilitate experimental approaches to expand preclinical evidence for its clinical relevance and translational potential.

Introduction

Progression of early stage breast cancer to therapy resistant metastatic disease represents a major cause of mortality. Expression status of hormone and growth factor receptors provides molecular classification of breast cancer sub types that include Luminal A, Luminal B, HER-2-enriched and triple-negative breast cancer subtypes[1]. Molecular classification dictates selection of appropriate treatment options. Thus, for the estrogen and progesterone receptor positive Luminal A breast cancer targeted endocrine therapy represents a mainstream treatment option and includes the use of estrogen receptor modulators, estrogen receptor degraders, anti-progestins and aromatase inhibitors Use of pharmacological agents is associated with systemic toxicity, spontaneous or acquired therapy resistance and emergence of chemo-resistant cancer initiating stem cells[2]. These limitations emphasize identification of potential drug candidates as testable therapeutic alternatives.

Ovarian steroid hormone receptors belong to a superfamily of ligand activated nuclear transcription factors that bind to cognate DNA response elements and activate the expression of downstream target genes. For estrogen receptor signaling estrogen responsive genes including Sp1, GRB2 and cyclin D1are critical for the signal transduction process[3]. Progesterone receptor signaling represents one of the major transduction pathway[4]. Additionally, paracrine effects relevant to progesterone action involve the NFkB pathway via receptor activator of nuclear factor kB (RANK) and its ligand RANK-L[5].

In addition to estradiol (E2) and progesterone (PRG)-mediated receptor signaling pathways, cellular metabolism of estradiol and progesterone generates metabolites that exhibit divergent growth modulatory effects on hormone responsive breast epithelial cells, as well as on breast cancer cells[6-9].

Resistance to endocrine therapy is responsible for drug-resistant cancer stem cells that facilitate metastatic progression of breast cancer[10, 11]. Thus, development of reliable cancer stem cell models identify experimental approaches for investigations on stem cell targeting efficacy of potential drug candidates.

The goal of the present review is to provide i) Systematic discussion of published evidence for divergent growth modulatory effects of ovarian steroid hormones estradiol and progesterone, ii) Applicability of cellular models and drug-resistant stem cell models for Luminal A breast cancer subtype to identify efficacious anti-proliferative hormone metabolites and herbal bioactive agents, and iii) Future research directions for clinical relevance and translatability of preclinical evidence.

Experimental Models

Relevant cellular models for cancer subtypes provide experimental approaches that identify mechanistic pathways and potential molecular targets directly on cancer phenotypes. The human breast carcinoma derived MCF-7 and T47D cells represent well-established cellular models for hormone receptor positive Luminal A breast cancer subtype. These celli lines express estrogen receptor-α, progesterone receptor and non-amplified human epidermal growth factor receptor-2 (HER-2). The MCF-7 model has been documented to exhibit hyper-proliferation via accelerated cell cycle progression, downregulated cellular apoptosis via decrease of cells in the sub G0 (apoptotic) phase of the cell cycle, and anchorage independent colony formation. Formation of non-adherent anchorage independent colonies represents an in vitro surrogate marker for the persistence of tumorigenic phenotype[12].

CELLULAR METABOLISM OF ESTRADIOL (E2) AND PROGESTERONE (PRG)

In addition to hormone receptor signal transduction pathways, cellular oxidative metabolism of ovarian steroid hormones plays an important role in generation of metabolites with divergent growth modulatory effects. For example, hydroxylation of E2 at C2 position generates 2-hydroxy estradiol (2-OH E2) and hydroxylation at C4 position generates 4-hydroxy estradiol (4-OHE2). The 2-hydroxylated metabolite has documented anti-proliferative effects, while the 4-hydroxylated metabolite promotes proliferation[6].

Estrone (E1) represents a common precursor for subsequent enzymatic conversions. Hydroxylation at C2 position generates 2-hydroxy estrone (2-OHE1), and at C16α position generates 16α-hydroxy estrone (16α-OHE1). 2-OHE1 functions as an anti-proliferative metabolite, while 16α-OHE1 facilitates proliferation[13]. MCF-7 cells treated with 16α-OHE1 exhibit increased cell proliferation, while treatment with 2-OHE1 exhibits decreased cell proliferation. Similar growth modulatory effects are observed in tumor formation from transplanted MCF-7 cells in vivo[14].

Functional significance of PRG receptor signal transduction and cellular metabolism of PRG is

context dependent. Thus, positive or negative growth regulation is evident depending on specific target cell type. Cellular metabolism of PRG generates 3α-dihydro metabolite 3α-P and 5α-dihydro metabolite 5α-P. The 3α-P metabolite has documented anti-proliferative effects, while the 5α-P metabolite promotes proliferation in human breast carcinoma derived MCF-7, T47D and MDA-MB-231 cell lines[9]. The growth modulatory effects of PRG metabolites are associated with the expression of cyclin dependent kinase inhibitors p18 and p27[15].

In cellular models for the Luminal A breast cancer subtypes positive growth regulation by E2 and negative growth regulation by PRG is documented[16]. In tissue explants from estrogen receptor (ER) positive tumors treatment with E2 increases, while that with PRG decreases cell proliferation[17-19]. Since E2 and PRG metabolites exhibit divergent growth modulatory effects, molecular/metabolic pathways responsible for E2 and PRG signaling may provide potential mechanistic leads. Opposing growth modulatory effects of the metabolites support the significance of data presentation as the ratio of anti-proliferative and proliferative metabolites. Experimental upregulation of this ratio may provide mechanistic leads for the efficacy novel therapeutic alternatives as drug candidates.

GROWTH MODULATION BY ESTRADIOL (E2) AND PROGESTERONE (PRG)

Positive or negative growth regulation by ovarian steroid hormones has been extensively documented in hormone receptor positive breast epithelial cells, as well as in breast cancer cells. Growth modulatory effects of E2 and PRG on MCF-7 cells are summarized in Table 1. Cells adapted to grow in culture medium supplemented with 0.7% serum (E2 and PRG < 0.01 nM) represented the control. Cells treated with physiologically achievable concentration of E2 exhibited increased cellular growth, while PRG treatment at equimolar concentration resulted in inhibition of cell growth as quantified by viable cell number.

Table 1: Modulation of Growth by Ovarian Steroid Hormones

Treatment	Concentration	Viable cell number ($x10^5$)	Modulation (Relative to serum)
Serum	0.7%	12.5±0.7	----
E2	20 nM	29.9±1.6	+1.4x
Serum	0.7%	12.9±0.7	----
PRG	20 nM	5.9±0.7	-54.3%

0.7% Serum: E2, PRG < 0.01 nM, E2, 17β-estradiol; PRG, progesterone.

EFFECT OF ESTRADIOL (E2) AND PROGESTERONE (PRG) ON CELL CYCLE PROGRESSION

Hyper-proliferative breast cancer cells are notable for accelerated cell cycle progression. Possible mechanistic leads for growth modulation by E2 and PRG were investigated on cell cycle progression in the MCF-7 model. In response to treatment with E2 the G1: S+G2/M ratio was decreased due to an increase in S+G2/M (proliferative) phase of the cell cycle, while in response to treatment with PRG the ratio was increased in favor of cells in the G1 (quiescent) phase of the cell cycle These data are summarized in Table 2.

Table 2: Effects of Ovarian Steroid Hormones on Cell Cycle progression

Treatment	Concentration	G1: S+G2/M Ratio	Modulation (Relative to serum)
Serum	0.7%	1.5±0.4	----
E2	20 nM	0.4±0.1	-73.3%
PRG	20 nM	3.7±0.4	+1.5x

0.7 % serum: E2, PRG < 0.01 nM, E2, 17β-estradiol; PRG, progesterone

EFFECT OF ESTRADIOL (E2) AND PROGESTERONE (PRG) ON CELLULAR APOPTOSIS

Cellular apoptosis is responsible for elimination of aberrantly proliferative cancer cells. To enhance survival cancer cell phenotype frequently exhibits downregulation of cellular apoptosis. The effects of E2 and PRG on cellular apoptosis are summarized in Table 3. The proliferative effect of E2 is associated with inhibition of apoptosis, while the anti-proliferative effect of PRG is associated with increased apoptotic cell population.

Table 3: Effects of Ovarian Steroid Hormones on Cellular Apoptosis

Treatment	Concentration	% Sub G0	Modulation (Relative to serum)
Serum	0.7%	1.9±0.4	----
E2	20 nM	0.3±0.1	-84.2%
PRG	20 nM	3.9±0.4	+2.0x

0.7% serum E2, PRG < 0.01nM, E2, 17β-estradiol, PRG, progesterone.

Consistent with this evidence, modulation of cellular apoptosis is associated with the altered expression of anti-apoptotic BCL2 and pro-apoptotic BAX proteins in MCF-7, T47D and ZR75-1 cellular models for breast cancer[18]

EFFECT OF NUTRITIONAL HERBS ON ESTRADIOL (E2) METABOLISM

Nontoxic nutritional herbs are widely used in traditional Chinese medicine for hormone- related health issues in women and for treatment of breast cancer[20, 21]. Traditionally, herbal formulations are prepared as aqueous decoctions and herbal tea is used for patient consumption. To simulate patient consumption, non-fractionated aqueous extracts are commonly used in experiments. Documented human consumption and preclinical efficacy of provide rationale for testing nutritional herbs as therapeutic alternatives for breast cancer. Conceivably, non-fractionated aqueous extracts may contain multiple bioactive agents that may synergize for the growth inhibitory efficacy. Documented bioactive agents for *Epimedium grandiflorum* (EG), *Lycium barbarum* (LB) and *Cornus officinalis* (CO) include prenylflavones, flavones, terpenes and anthocyanin, respectively[22]. These bioactive agents may represent potential drug candidates.

Inhibition of breast cancer growth by nutritional herbs involves anti-proliferative and pro-apoptotic effects. These biological effects are associated with modulated expression of cell cycle regulatory and apoptosis specific proteins. Published evidence for possible mechanistic leads responsible for growth inhibitory efficacy of nutritional herbs on a cellular model for the Luminal A breast cancer examined their effects on cellular metabolism of E2 as quantified by the 2-OHE1: 16α-OHE1 ratio. The data on treatment of MCF-7 cells with nutritional herbs are summarized in Fig.1.

Effects of Nutritional herbs on Cellular Metabolism of Estradiol

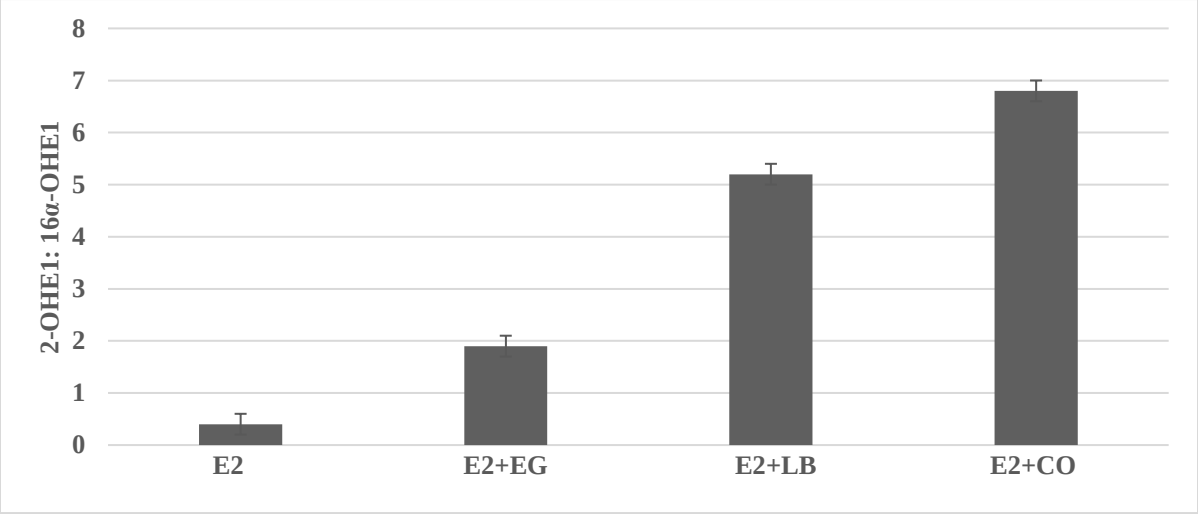

Figure 1: Nutritional herbs increase cellular metabolism of estradiol.MCF-7 cells were treated with E2 alone or with E2+EG, E2+LB and E2+CO. Data expressed as 2-OHE1: 16α-OHE1 ratio.

DRUG-RESISTANT STEM CELL MODEL

Pharmacological therapeutics are utilized as mainstream options for conventional or targeted treatment of breast cancer. Spontaneous or acquired resistance to endocrine therapy leads to the emergence of cancer stem cells. These chemo-resistant stem cells initiate cancer growth and facilitate progression of metastatic disease. Reliable drug-resistant stem cell models provide valuable experimental systems to investigate stem cell targeting effects of testable drug candidates. Expression of nuclear transcription factors OCT-4, Klf-4, SOX-2 and c-Myc is critical for maintenance of induced pluripotent stem cells and cancer stem

cells[23, 24]. Additionally, expression status of select cellular and molecular stem cell markers represent quantitative endpoints to characterize drug-resistant stem cell models.

Long-term treatment with selective estrogen receptor modulator tamoxifen (TAM) eliminates the drug sensitive phenotype. However, surviving minor cell population exhibits phenotypic drug resistance and progressive growth in the presence of cytotoxic concentrations of TAM. Progressive growth of cells leads to selection of TAM resistant (TAM-R) phenotype.

Stem cell specific cellular marker such as tumor spheroid formation and molecular markers such as stem cell membrane marker CD44 and nuclear transcription factors NANOG and OCT-4 represent established quantitative endpoints for model characterization. The expression status of these endpoints in TAM sensitive and TAM resistant cells is summarized in Table 4.

Table 4: Drug-resistant Stem Cell Model

Phenotype	Treatment	Stem Cell Marker			
		TS	CD44	NANOG	OCT-4
TAM-S	10 μM TAM	2.5±0.7	3.0±0.5	2.2±0.7	2.8±0.8
TAM-R	10 μM TAM	7.2±0.8	8.1±0.9	4.6±0.7	5.3±0.6
Modulation (Relative to TAM-S)		+4.7x	+5.1x	+1.8x	+2.5x

TAM-S, Tamoxifen sensitive; TAM-R, Tamoxifen resistant; TS, tumor spheroid; CD44, cluster of differentiation; NANOG, DNA binding transcription factor; OCT-4, octamer binding protein-4. Data expressed as TS number and as relative fluorescent units (RFU) for CD44, NANOG and OCT-4.

Conclusions

The published evidence discussed in the present review has provided mechanistic leads for growth modulatory effects of E2 and PRG, growth modulatory effects of E2 and PRG metabolites and functional significance of the ratios of anti-proliferative and proliferative metabolites of E2 and PRG, altered E2 metabolism by nutritional herbs and applicability of relevant drug-resistant breast cancer stem cell model to these elements identify anti-proliferative metabolites and bioactive agents as potential drug candidates. Positive data on these agents may represent a paradigm shift for novel treatment options for breast cancer therapy.

Future Research

Published evidence provides scientifically robust rationales for future research directions that identify novel therapeutic targets and experimental approaches to extend the preclinical evidence for its clinical relevance and translatability.

Network pharmacology and molecular docking experiments represent valuable initial research directions to identify bioactive agents as putative drug candidates. Promising agents are selected using high throughput screening assays specific for susceptible mechanistic pathways and molecular targets. The selectivity of mechanism of action is confirmed by genomic and proteomic assays. Thus, network pharmacology, transcriptomic analysis and subsequent mechanistic validation assays may provide additional leads for structure-function relationships of anti-proliferative metabolites of E2 and PRG, as well as for herbal bioactive agents.

Unlike ER-α, ER-β signal transduction functions as a negative growth regulator in estrogen responsive breast cancers, phytoestrogens influence the binding to estrogen response element and modulate ER-β target gene expression [3, 25, 26]. Naturally occurring flavones, lignans and saponins represent major bioactive agents in nutritional herbs including in those functioning as phyto-estrogens[20]. These bioactive agents functioning as ER-β agonists may represent testable drug candidates.

Breast carcinoma derived immortalized cell lines and cancer initiating stem cells universally express human telomerase reverse transcriptase (hTERT). This ribonucleo protein adds hexameric 5' TTAGGG 3' repeat nucleotide sequences to chromosomal telomeres and is responsible for the persistent replicative potential of the cancer phenotype. Thus, hTERT represents an attractive cancer therapeutic target[27-29]. Anti-proliferative hormone metabolites and herbal bioactive agents functioning as telomerase inhibitors may represent testable drug candidates. In this context it is notable that natural products are documented as telomerase inhibitors and function as anti-cancer agents[30].

Breast carcinoma derived cell lines may not faithfully represent patient characteristics because of long-term in vitro maintenance. Thus, preclinical

data from these models are dependent on extrapolation for their clinical relevance. In contrast, investigations on tumor explant models[31] or tumor organoid models[32-35] developed from endocrine therapy-resistant patients may reduce extrapolation and provide clinical relevance and translatability of preclinical evidence.

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