

# **Lycium Barbarum Inhibits Growth of Hormone Responsive Human Breast Cancer Cells by Down-regulating C16 $\alpha$ -hydroxylation Pathway of Estradiol Metabolism**

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## Study Rationale

- Selective estrogen receptor modulators and aromatase inhibitors represent targeted endocrine therapy for estrogen receptor positive clinical breast cancer.
- Endocrine therapy is frequently associated with acquired therapy resistance and/or unacceptable toxicity profile, limiting patient compliance and leading to disease recurrence.
- Toxicity issues with endocrine therapy have rationalized the use of herbal medicines independently or in combination with clinical therapy to enhance efficacy and reduce toxicity.
- Phytoestrogen containing Chinese herbs have received increasing attention in the management of estrogen related health issues, and may also represent a relatively non-toxic alternative for breast cancer therapy.

## Study objectives

- To optimize a preclinical cell culture model for hormone responsive breast cancer.
- To demonstrate the growth inhibitory effects of the Chinese herb *Lycium barbarum* (LB) on the developed cell culture model for hormone responsive breast cancer.
- To identify possible mechanistic leads responsible for the efficacy of LB.

## Cell Culture Model and Herbal Extract

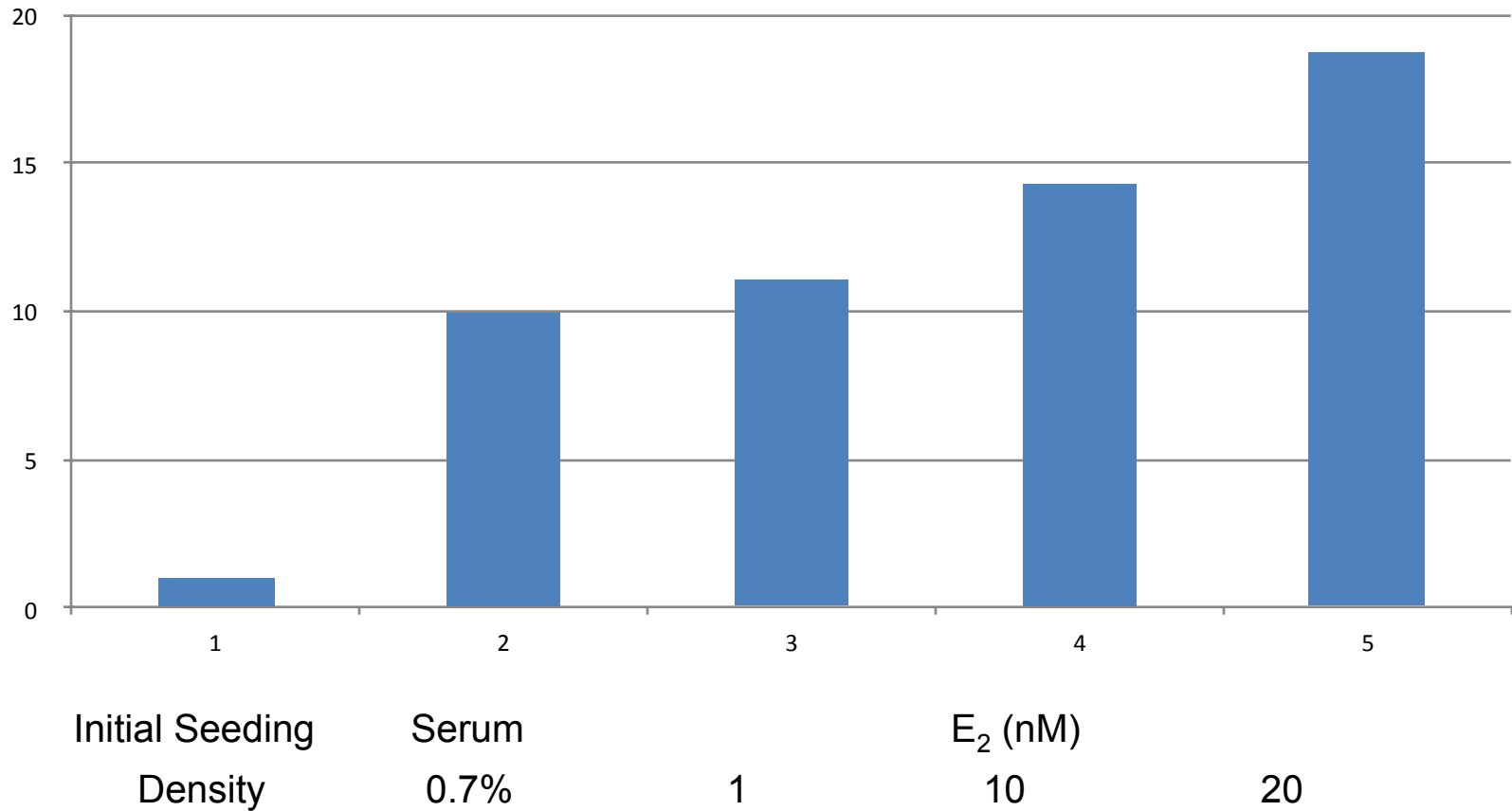
**Model:** Human mammary carcinoma derived Estrogen receptor positive MCF-7 cells adapted for growth in a chemically defined serum-depleted culture medium to evaluate the response of  $17\beta$ -estradiol ( $E_2$ ) and of Lycium barbarum (LB).

**Herbal Extract:** Non-fractionated aqueous extract from LB.

- 20 g of LB boiled in 200 ml of distilled water to reduce the volume to 100 ml (Extract # 1). Residue from this extract boiled in 100 ml of distilled water to reduce the volume to 50 ml (Extract # 2).
- Two extracts (150 ml) combined and boiled to reduce the volume to 25 ml.
- The combined extracts centrifuged (5,000 rpm, at room temperature) to collect the supernatant (20 ml). This aqueous supernatant served as the stock solution (100%). Stock solution serially diluted with the culture medium to obtain 1% 0.5% and 0.1% of LB used for evaluating the dose response.

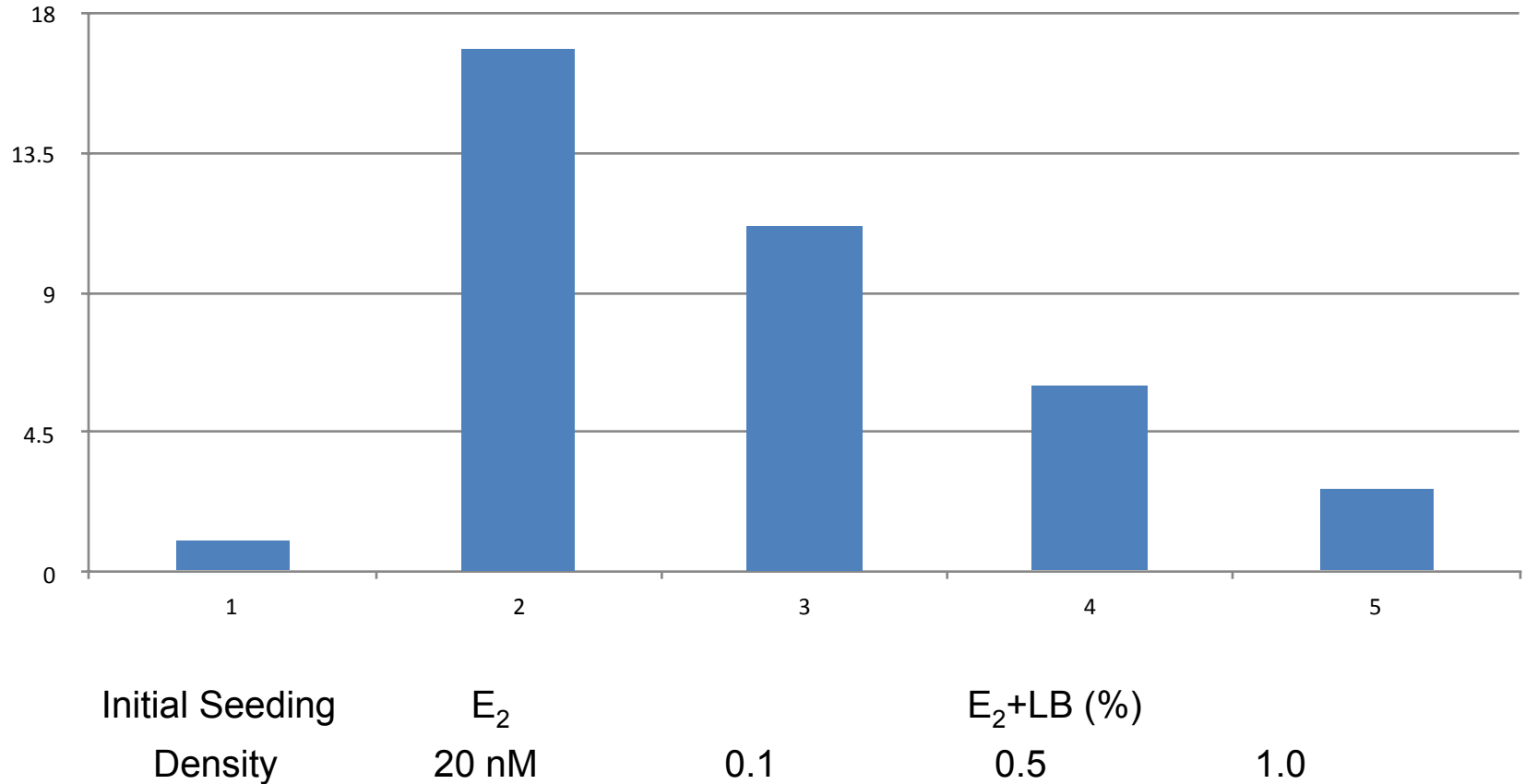
# Growth Promotion of Serum-depleted Human Mammary Carcinoma MCF-7 Cells by $17\beta$ -estradiol ( $E_2$ )

Viable Cell Number ( $\times 10^5$ )



# Dose Response of *Lycium barbarum* (LB) on Human Mammary Carcinoma MCF-7 Cells

Viable Cell Number ( $\times 10^5$ )



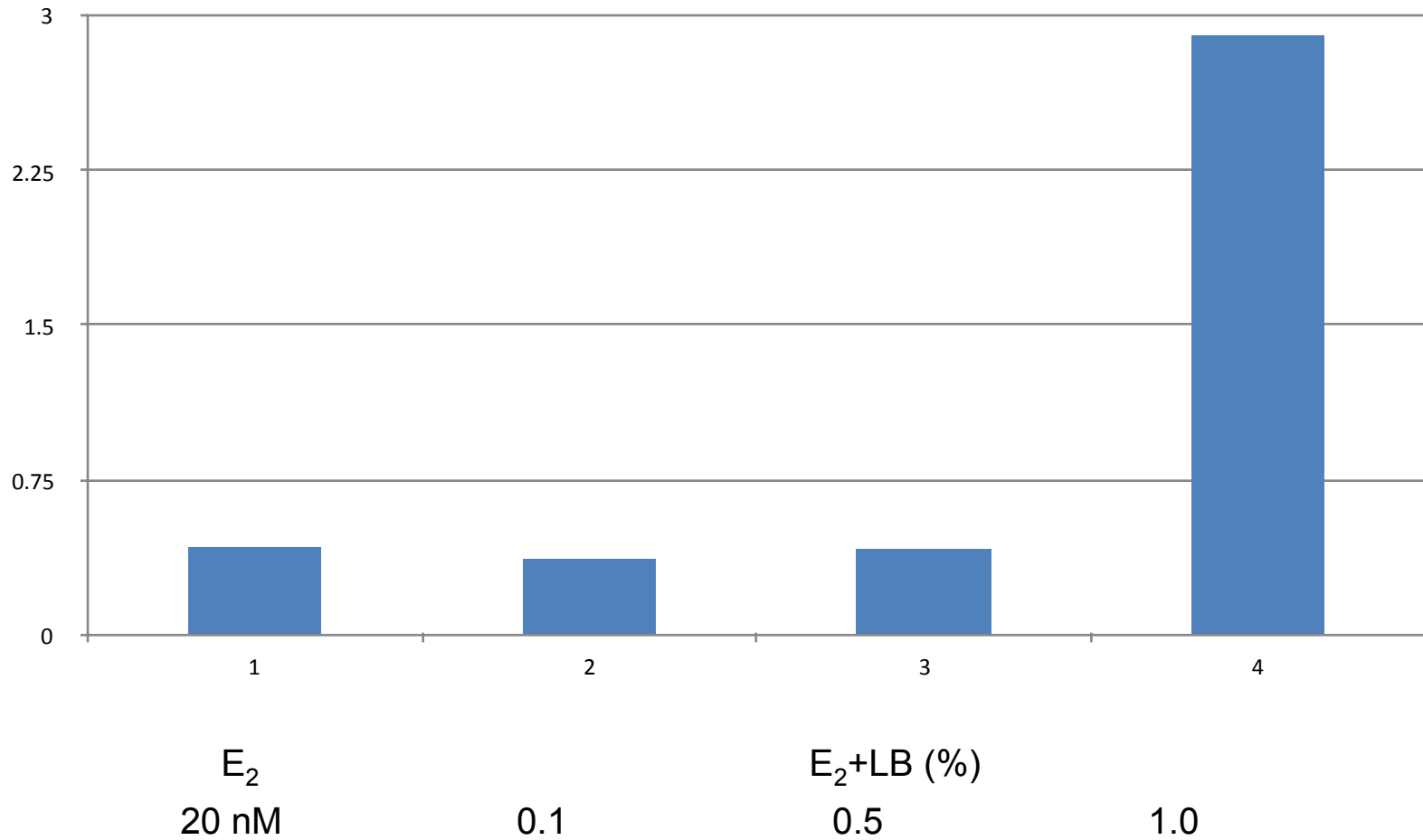
# Effect of Lycium Barbarum (LB) on Estradiol metabolism in Human mammary Carcinoma MCF-7 Cells

Treatment	Concentration	E <sub>2</sub> metabolite <sup>a</sup> (ng/10 <sup>6</sup> Cells)			
		E <sub>1</sub>	2-OHE <sub>1</sub>	16α-OHE <sub>1</sub>	E <sub>3</sub>
E <sub>2</sub>	20 nM	4.6±0.9	1.9±0.3 <sup>c</sup>	4.5±0.2 <sup>e</sup>	0.45±0.09 <sup>g</sup>
E <sub>2</sub> +LB	0.1%	6.8±2.2	1.6±0.4	4.3±0.4	2.1±0.1 <sup>h</sup>
	0.5%	7.0±2.4	1.8±0.9	4.4±0.3	6.5±1.0 <sup>i</sup>
	1.0%	8.5±0.4	8.7±0.4 <sup>d</sup>	3.0±0.3 <sup>f</sup>	4.6±0.7 <sup>j</sup>

<sup>a</sup> determined at day 3 post-seeding by stable isotope dilution and GC-MS analysis. Mean ± SD, N=3 per treatment group. <sup>c<d, e>f, g<h, g<l, g<j</sup> 1-way analysis of variance and Dunnett's multiple comparison test (α=0.05).

# Modulation of Cellular Metabolism of 17 $\beta$ -estradiol

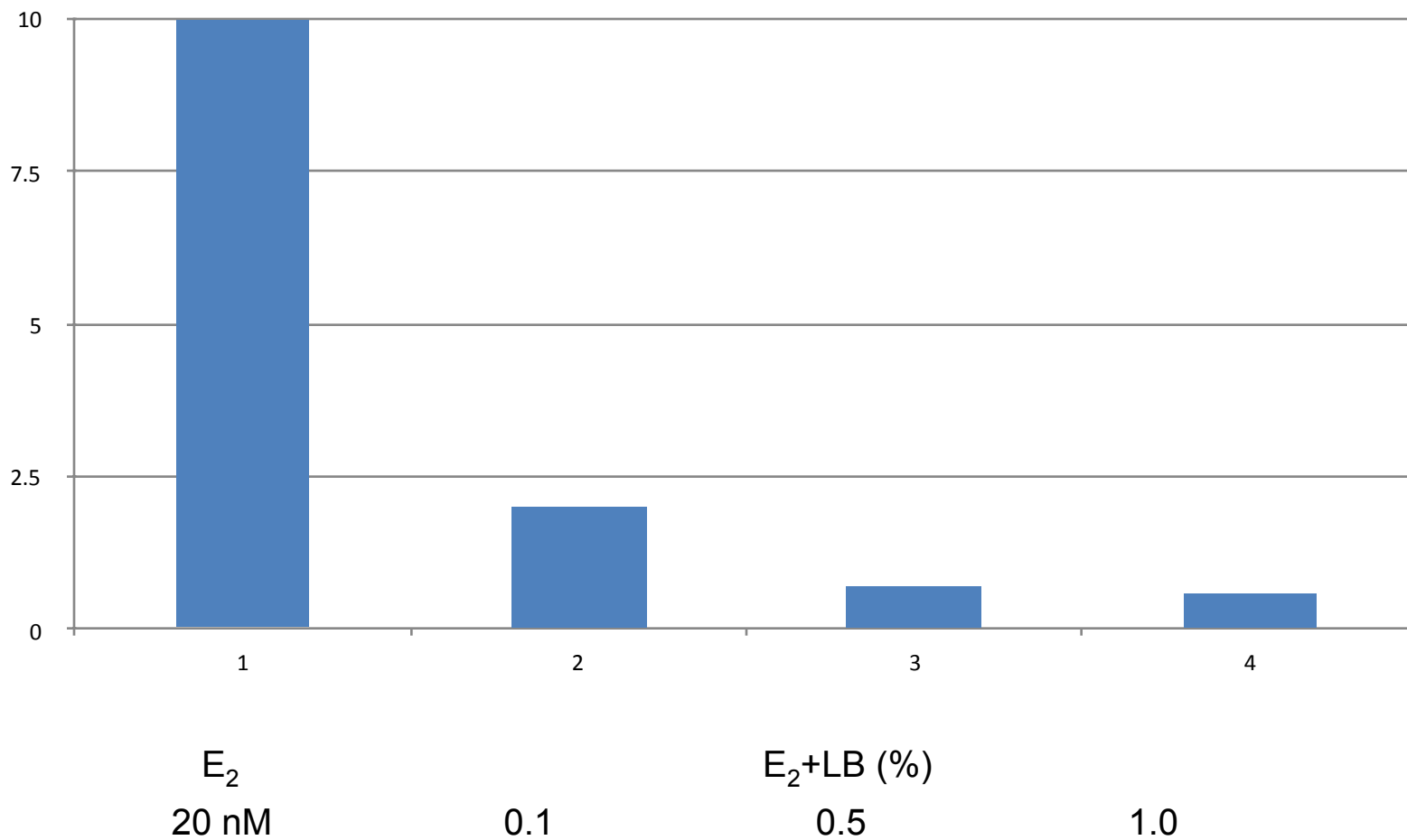
2-OHE<sub>1</sub>: 16 $\alpha$ -OHE<sub>1</sub> Ratio





# Modulation of Cellular Metabolism of $17\beta$ -estradiol ( $E_2$ )

$16\alpha$ -OHE<sub>1</sub>: E<sub>3</sub> Ratio



## Study Outcome

- Estrogen receptor positive human mammary carcinoma derived MCF-7 cells adapted for growth in a serum depleted medium ( $E_2 < 1\text{nM}$ ) retained their responsiveness to  $E_2$  (growth promotion and  $E_2$  metabolism).
- Lycium barbarum (LB) down-regulated  $E_2$  promoted growth in a dose dependent manner.
- Growth inhibitory effects of LB are associated with increased formation of the anti-proliferative  $E_2$  metabolite 2-OHE<sub>1</sub>, and with accelerated conversion of mitogenic 16 $\alpha$ -OHE<sub>1</sub> to inert  $E_3$ .
- LB at its maximum cytostatic concentration up-regulated 2-OHE<sub>1</sub>:16 $\alpha$ -OHE<sub>1</sub> ratio, and down-regulated 16 $\alpha$ -OHE<sub>1</sub>: $E_3$  ratio.

## Publications

1. Telang NT, Li G, Sepkovic DW, Bradlow HL and Wong GYC: Chinese herb *Lycium barbarum* inhibits growth of hormone responsive human breast cancer cells by down-regulating C16 $\alpha$ -hydroxylation pathway of estradiol metabolism. *Breast Cancer Res. Treat.* 94: S121 (Abst. # 2108), 2005.
2. Li G, Sepkovic DW, Bradlow HL, Telang NT and Wong GYC: *Lycium barbarum* inhibits growth of estrogen receptor positive human breast cancer cells by favorably altering estradiol metabolism. *Nutrition and Cancer* 61: 408-414, 2009.
3. Telang NT, Li G, Sepkovic DW, Bradlow HL and Wong GYC: Comparative preventive efficacy of aqueous extracts from *Lycium barbarum* bark and fruit on estrogen receptor positive human mammary carcinoma MCF-7 cells. *Cancer Res.* 71: 379S, 2011.
4. Telang NT, Li G, Katdare M, Sepkovic DW, Bradlow HL and Wong GYC: Comparative preventive efficacy of select Chinese herbs in breast carcinoma derived isogenic cells with modulated estrogen receptor functions. *Cancer Res.* 72: 190S, 2012.