Licochalcone A is an excellent candidate for preventing luminal and non-luminal breast cancers

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BACKGROUND

- Proven breast cancer prevention drugs have side effects that are not acceptable to 85% of women at high risk for breast cancer.[1] There is no drug for preventing ER- cancer.
- **Prevention strategies with optimal efficacy, less toxicity, and greater acceptance are needed.**
- Natural products are ideal candidates[2] if demonstrated to shift the breast microenvironment to a tumor preventive milieu with lower toxicity.
- Licochalcone A (LicA) from licorice inhibits aromatase activity and has antioxidant potential.[3,4,5]

OBJECTIVES

1. **Does LicA reprogram metabolism and antioxidant pathways in high-risk human breast tissue?**
2. **Does LicA retard cell proliferation and reduce tumor growth *in vivo*?**
3. **Pharmacokinetics: is LicA orally bioavailable?**

METHODS

- **Microstructures** were prepared from **contralateral unaffected breast tissue** of two cohorts of 6 postmenopausal women with unilateral breast cancer.
- They were **treated** with DMSO and **LicA (5 uM)** for 24 h, prior to RNA extraction and total RNA sequencing.
- **Differentially expressed genes (DEGs)** were identified. **Gene ontology** (GO) pathway analysis identified pathways with combined enrichment scores >4 and FDR<0.05. DEGs were analyzed with computational metabolic **flux analysis. Six additional subjects** were studied with the **NanoString metabolism panel.**
- **Live cell imaging/proliferation** was analyzed in DCIS.COM/ER+ PR+, DCIS.COM, MCF-7, MCF-7aro, HCC1937, HCC-3153, and MDA-MB-231 cells treated with single and repeated doses of LicA.
- **Western blot** was performed on MCF-7 and MDA-MB-231 cells treated with LicA (10 μM) for 24 h.
- **Xenografts** in female **athymic nude mice** were created using luminal or triple negative breast cancer cells, LicA was administered for 28 days at the dose of 80 mg/kg.day and rate of tumor growth was evaluated.
- **Oral bioavailability** in plasma, liver, and mammary tissue of BALB/c female mice was studied using LicA at a dose of100 mg/kg.

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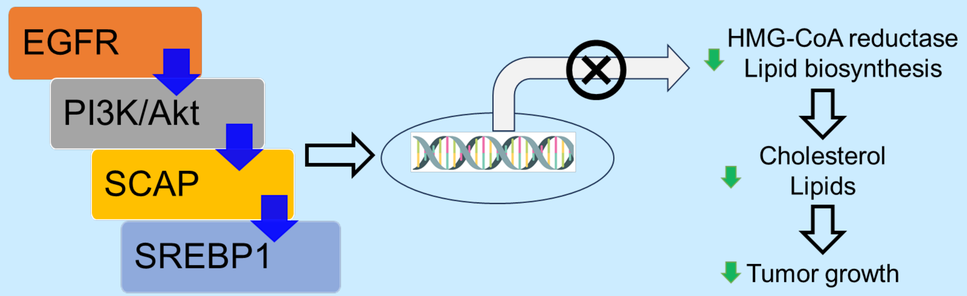
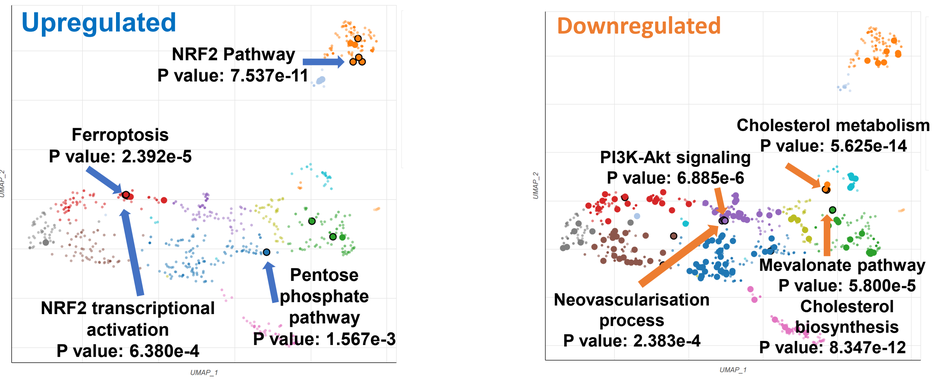
Licochalcone A (LicA): good candidate for preventing breast cancer



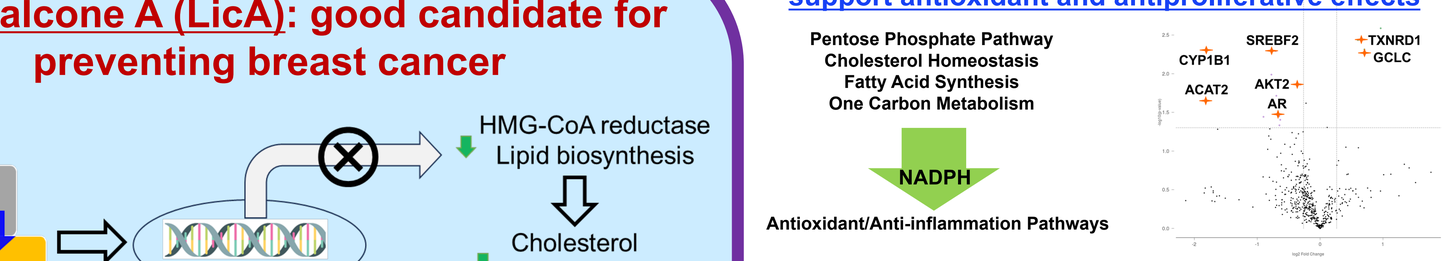
- ✓**In high-risk women's breast microstructures**
- ✓**In ER+ and ER- pre-malignant and malignant breast cells**
- ✓**In mouse models of luminal and TNBC**

RESULTS

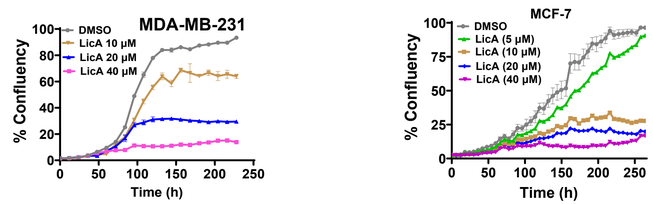
Breast Microstructures treated with LicA



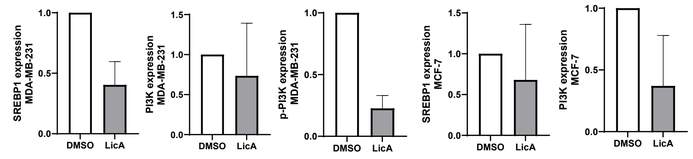
Metabolic flux (left) and NanoString metabolism (right) support antioxidant and antiproliferative effects



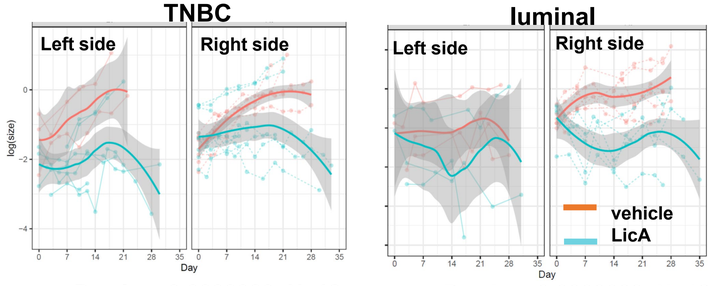
LicA retards proliferation in ER+ and ER- breast cells



LicA lowers SREBP1 protein expression



LicA reduces the growth of mammary tumors



P-value: 0.0000000, N=18 **P-value: 0.0000033, N=12**

The graphs demonstrate the changes in tumor sizes as a function of LicA treatment (blue) in comparison to vehicle control (orange)

LicA is orally bioavailable; but can improve

Tissue	Tmax (hr)	Cmax (ng/mL)	AUCall (hr*ng/mL)	AUCINF_obs (hr*ng/mL)	Lambda_z (1/hr)
Plasma	2	295.52	2448.24	2433.07	0.23
Mammary	2	413.54	1910.4	1912.58	0.29

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