Licochalcone A is a candidate for breast cancer prevention through its reprogramming of metabolic and antioxidant pathways

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BACKGROUND

• Less than 5% of women who could benefit from breast cancer risk reduction drugs report taking them, mainly due to the adverse effects of these medications.1 There is no drug for preventing ER- cancer.
• Prevention strategies with optimal efficacy, less toxicity, and greater acceptance are needed.
• Natural products with significantly lower toxicity and sufficient efficacy to shift the breast microenvironment to a tumor preventive milieu are ideal candidates.2
• Previously, we have shown that licochalcone A (LicA) from licorice inhibits aromatase activity and has antioxidant potential.3,4,5
• We now report on the response of high-risk postmenopausal human breast tissue, breast pre-malignant and malignant cells to LicA treatment in vitro and in vivo.

OBJECTIVE

LicA modulates metabolic and antioxidant pathways in the breast leading to a tumor preventive environment.

METHODS

• Contralateral unaffected breast tissue of 6 postmenopausal women, who had bilateral mastectomy due to unilateral breast cancer were obtained and processed to microstructures.
• Microstructures were treated with DMSO and LicA (5 μM) for 24 h, prior to RNA extraction and total RNA sequencing.
• Differential gene expression was determined. Gene ontology (GO) pathway analysis was performed. The enriched pathways with combined enrichment scores > 4 and FDR < 0.05 were considered statistically significant. The differential gene expression results were further analyzed with computational metabolic flux analysis and NanoString metabolism panel. Modulated pathways with P < 0.05 were considered significant.
• Live cell imaging/proliferation was analyzed in DCIS.COM/ER+ PR+, DCIS.COM, MCF-7, and MDA-MB-231 cells treated with single and repeated doses of LicA.
• Female athymic nude mice inoculated with luminal or triple negative breast cancer cells, received LicA or vehicle for 28 days at the dose of 80 mg/kg/day and tumor volume was evaluated.

RESULTS

Can a natural product protect high risk women from breast cancer?

Licochalcone A is a good candidate

• In high-risk women’s breast microstructures
• In ER+ and ER- pre-malignant and malignant breast cells
• In xenograft mouse models of luminal BC and TNBC

LicA modulates metabolic and antioxidant pathways

Upregulated

WikiPathway 2021 Human

NRF2 Pathway

P value: 7.537e-11

Ferrophotosis

P value: 2.392e-5

NRF2 transcriptional activation

P value: 6.380e-4

Pentose phosphate pathway

P value: 1.567e-3

Downregulated

Cholesterol metabolism

P value: 6.855e-6

PI3K-Akt signaling

P value: 5.626e-14

Neovascularisation process

P value: 2.383e-4

Mevalonate pathway

P value: 5.800e-5

Autophagy biosynthesis

P value: 8.347e-12


REFERENCES

5. bioRxiv, doi:10.1101/2022.05.06.490855.