Licochalcone A from licorice reprograms metabolic and antioxidant pathways in the breast leading to a tumor preventive environment.

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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]
- Prevention strategies with optimal efficacy, less toxicity, and greater acceptance are needed.
- Natural products with significantly low toxicity and sufficient efficacy to shift the breast microenvironment to a tumor preventive milieu are ideal candidates.[2]
- Previously, we have shown that licochalconeA (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 and breast pre-malignant and malignant cells to LicA treatment in vitro.

OBJECTIVE

- We hypothesize that 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 which maintain the architectural features and protein expression patterns of the tissues of origin.
- Microstructures were treated with DMSO and LicA (5 uM) 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 metabolism flux. Modulated pathways with P < 0.05 were considered significant. We performed live cell imaging/proliferation on DCIS.COM/ER+ PR+, DCIS.COM, MCF-7, and MDA-MB-231 cells treated with various doses of LicA.

REFERENCES

1. Mol. Cell. Endocrinol. 2021, 530: 111284.
2. Pharmacol. Rev. 2016, 68: 1026.
3. Chem. Res. Toxicol. 2015, 28: 2130.
4. Cancer Prev. Res. 2018, 11: 819.
5. *bioRxiv,* doi:10.1101/2022.05.06.490985.
6. Genome Biol. 2019, 20: 49.

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

Licochalcone A is a good candidate

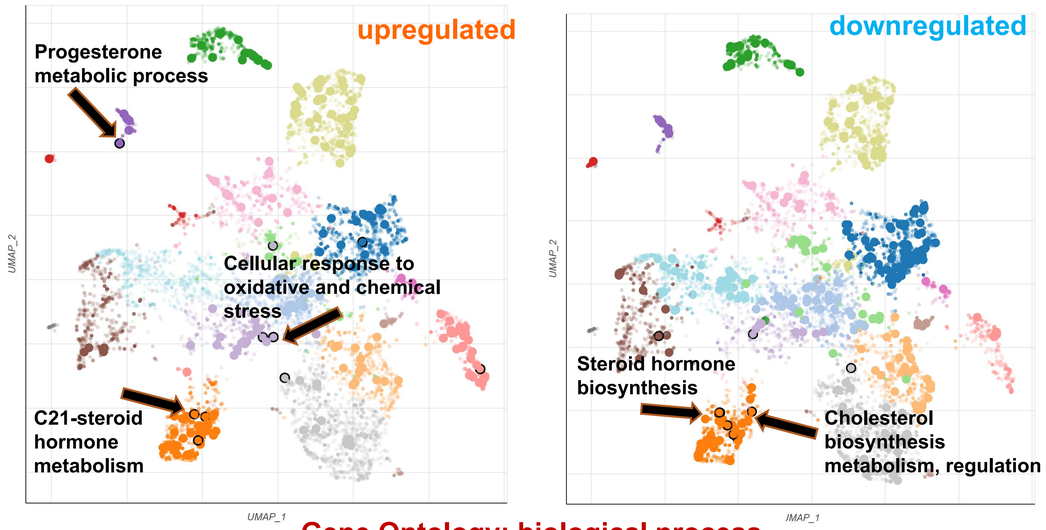
In high-risk breast microstructures:

- **Enhances antioxidant/anti-inflammatory responses**
- **Suppresses pro-adipogenic pathways**

In pre-malignant and malignant breast cells:

- **Retards proliferation, with a single dose.**

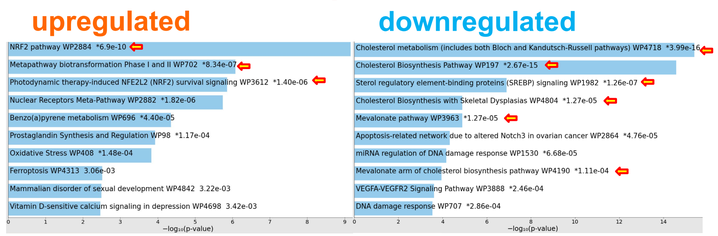
RESULTS

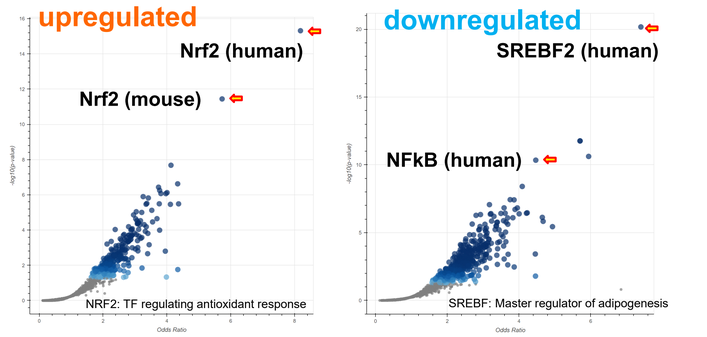


Gene Ontology: biological process

The scatterplot is organized so that similar gene sets are clustered together. Larger, black-outlined points represent significantly enriched terms.

WikiPathway 2021 Human





Metabolic flux analysis supports antioxidant and anti-adipogenic effects.

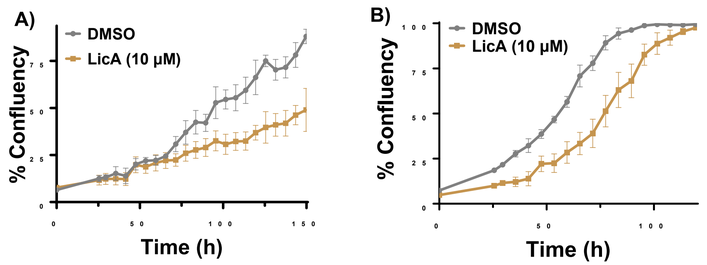
Pentose Phosphate Pathway, (PPP)
Cholesterol Homeostasis
Fatty Acid Synthesis
One Carbon Metabolism

→ **NADPH** →

Antioxidant/Anti-inflammation Pathways

Computational Metabolic Flux analysis showed increased flux through pathways leading to enhanced NADPH production (P < 0.05).[6]

LicA retards proliferation in malignant breast cell lines.



Live cell imaging using IncuCyte showed that a single dose of LicA can retard proliferation of (A) MCF-7 and (B) MDA-MB-231 cells.