The potential role of licorice and its bioactive compounds in promoting a tumor preventive environment in the breast

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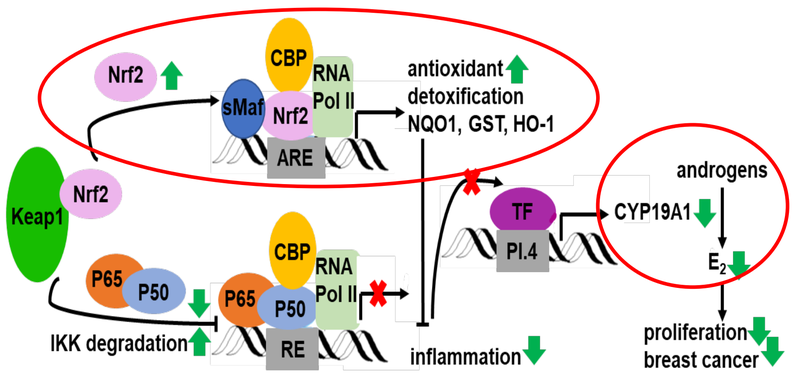
Introduction

- Estrogen (E_2) dependent breast cancer risk continues to rise post menopause.[1]
- Increased E_2 production in the postmenopausal breast through the increased aromatase expression and activity is implicated.[2, 3]
- Local E_2 production is in part regulated by the factors modifying breast microenvironment; enhanced Nrf2 antioxidant responses limit inflammation which can otherwise elevate aromatase expression.[4]
- Preventing breast cancer using strategies modulating the microenvironment and with greater acceptability than endocrine therapies among at risk but healthy women is desired.
- Botanicals such as three licorice species (GG, GU, GI), and their bioactive compounds, LigF, 8-PA, LicA, and LigC might have chemopreventive potential through limiting E_2 exposure and promoting antioxidant response in the breast.[5, 6]

Objective

To evaluate how licorice and its bioactive compounds limit aromatase and promote Nrf2 dependent pathways which could lead to a tumor preventive environment in the breast. The outcome could suggest a basis for future studies establishing an alternative breast cancer prevention approach with greater acceptability among high-risk but otherwise healthy postmenopausal women.



Green arrows represent the potential effects of licorice species and their bioactive compounds.

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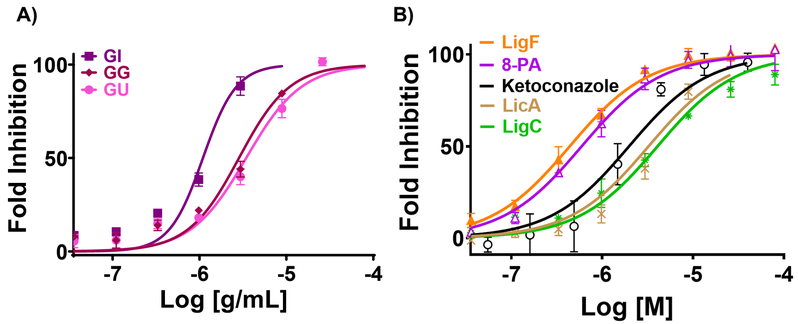
Results

Figure 1. Licorice species and their bioactive compounds inhibit aromatase activity.

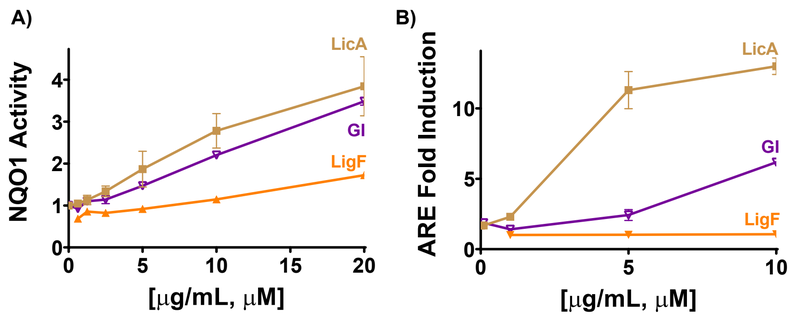


Inhibition of aromatase enzymatic activity after incubation of supersomes with A) licorice species: and B) their compounds for 40 min. Fluorescence intensity was measured at Ex/Em of 409 nm/530 nm. Data represents mean ± SD of at least three independent measurements.

Figure 2. Phytoestrogens of GI, LigF and 8-PA bind to aromatase like letrozole.

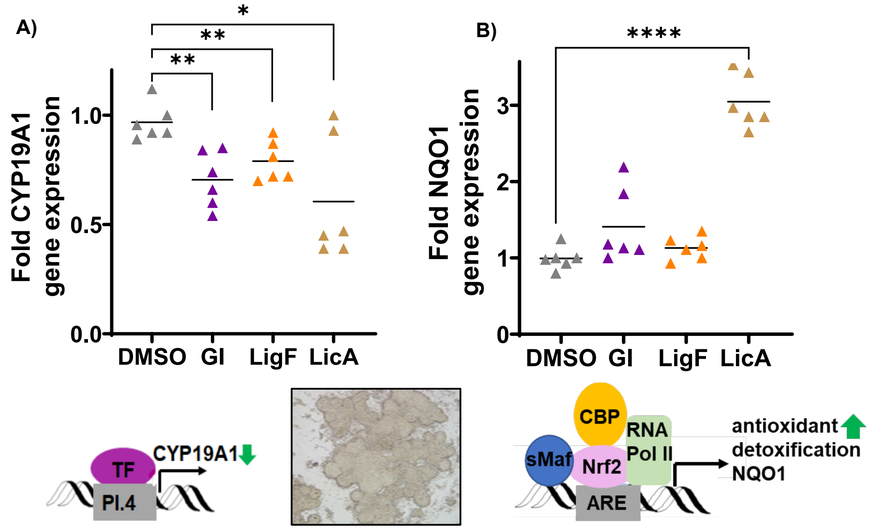
Compounds were docked to the binding site of aromatase (pdb: 3eqm) + heme, using the Molecular Operating Environment (MOE) computational platform..

Figure 3. Licorice and LicA activate Nrf2-dependent NQO1.



Induction of A) NQO1 activity in hepa1c1c7 cells after 48 h and B) antioxidant response element (ARE) in HepG2 cells after 24 h incubation. Results represent mean ± SD of at least 3 independent observations.

Figure 4. GI and its bioactive compounds suppress aromatase and enhance NQO1 expressions in breast microstructures.



Microstructures prepared from surgically removed breast tissue of high-risk postmenopausal women were treated for 24 h with GI (5 μg/mL) and its compounds LigF (5 μM) and LicA (5 μM). qPCR analysis of A) aromatase (CYP19A1) and B) NQO1 were performed. Data represents mean ± SD of replicate observations from 6 subjects. ($p < 0.05$).

Conclusions

- **Licorice GI and its phytoestrogens are potent aromatase inhibitors, behaving like letrozole.**
- **GI and its marker compound LicA enhance NQO1 activity through the Nrf2 dependent antioxidant pathway in cells.**
- **They also suppress aromatase and enhance NQO1 in the breast tissue of high-risk postmenopausal women.**
- **These effects could lead to a tumor preventive environment in the breast through limiting E_2 exposure, oxidative damage, and inflammation.**
- ***In vivo* MIND model studies can further elucidate their efficacy in preventing breast tumor formation, suggesting a potential prevention approach with better acceptability among high-risk but healthy postmenopausal women.**

References

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