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Ability of Flavonoids to Mimic the Estrogen Receptor to Drive Myeloid Derived Suppressor Cell Differentiation

Megan Bland
Longwood University

Cecilie Elliott
Longwood University

Kathryn Kosiorek
Longwood University

ABILITY OF FLAVONOIDS TO MIMIC THE ESTROGEN RECEPTOR TO DRIVE MYELOID DERIVED SUPPRESSOR CELL DIFFERENTIATION

Kathryn Kosiorek, Cecilie Elliott, Megan Bland

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BACKGROUND

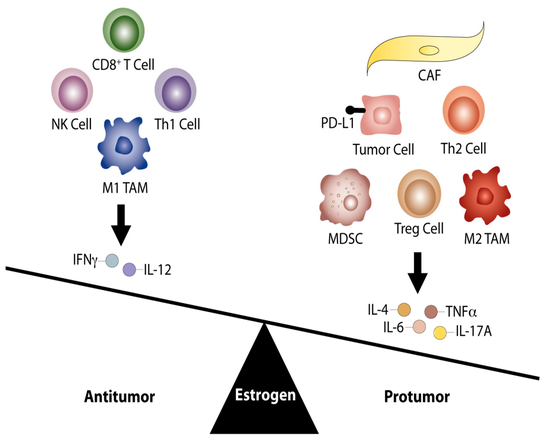


Figure 1. Estrogen antitumor and protumor immune responses. Antitumor responses include IFN_{γ}, while protumor responses utilize MDSC and IL-4.

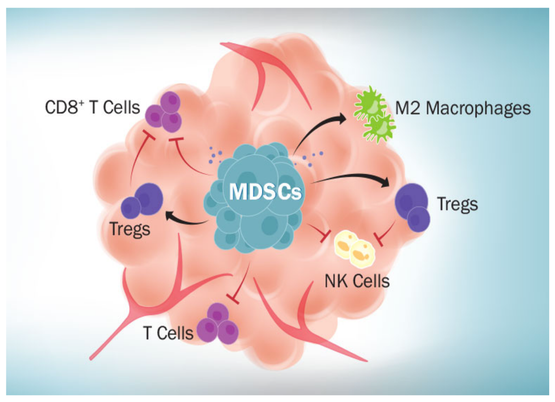


Figure 2. Targeting MDSCs in the tumor microenvironment. MDSCs inhibit the production of CD8 T cells and NK cells, while activating Tregs and macrophages.

- Phytoestrogens are natural compounds found in dietary products, such as green tea.[1]
- They have the ability to bind the estrogen receptor, causing increased activity and estrogen production.[4]
- Increased estrogen levels have been shown to increase the risk of breast cancer development.[4]
- Myeloid-derived suppressor cells (MDSCs) increase in abundance in cancer, inflammation and infection.[2]
- In healthy cells, MDSCs help regulate the immune response.[2]
- Flavonoids, like Genistein and Daidzein, play a role in the suppression of cancer because they compete with naturally occurring estrogens.[3]

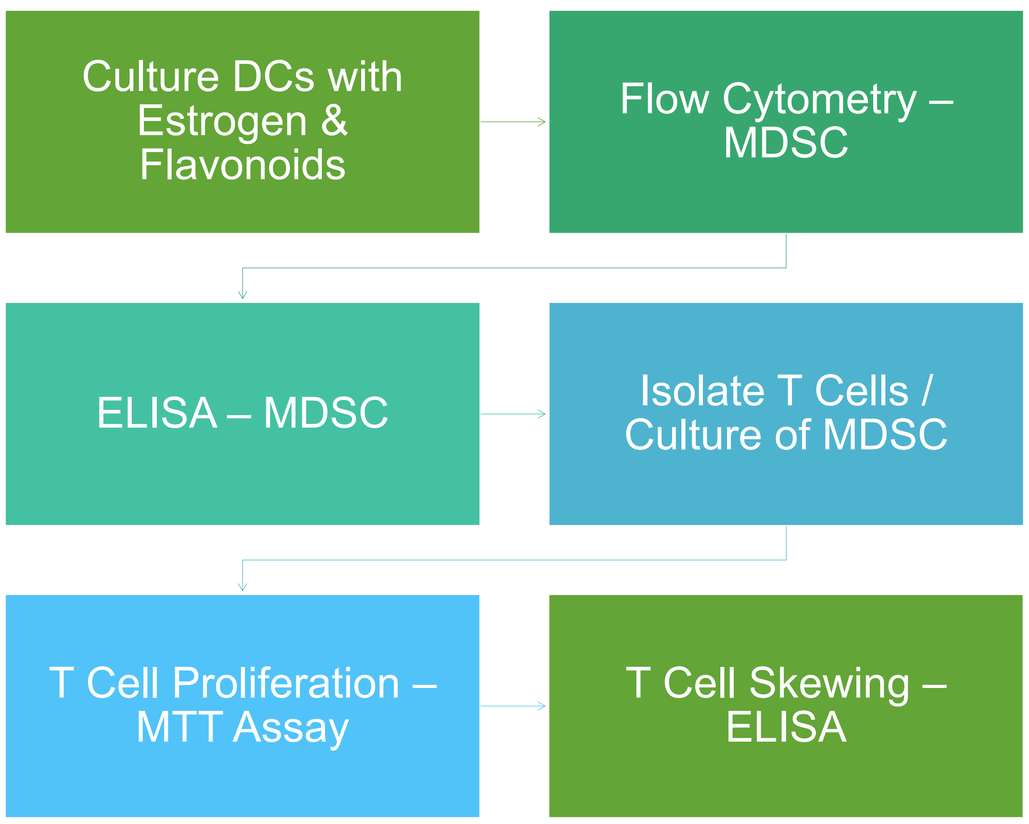
SPECIFIC AIM

- In this experiment, we are investigating phytoestrogens, specifically the family of compounds known as flavonoids, to learn more about how they mimic estrogen.

Hypothesis

- We suspect that when testing compounds with these flavonoids, there will be increased MDSC differentiation as well as cytokine expression.

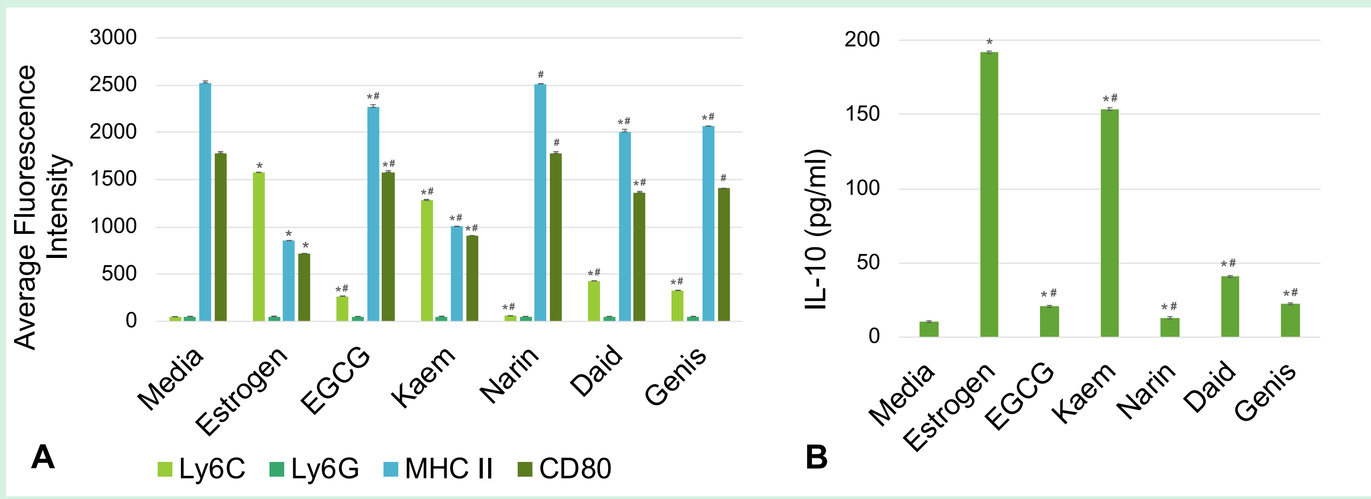
METHODS



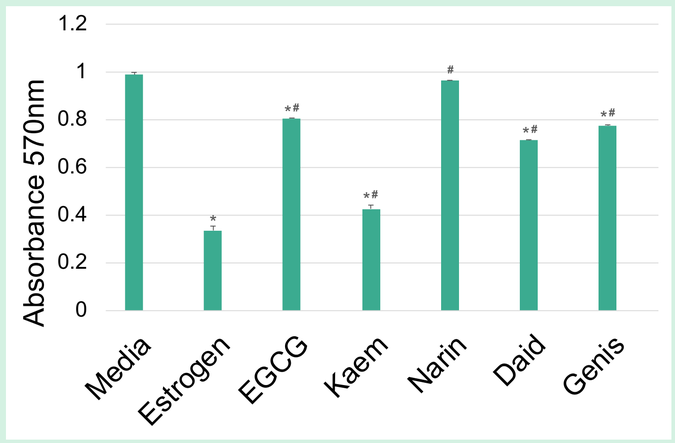
Tested Flavonoids

- Epigallocatechin-3-Gallate (EGCG)
- Kaempferol
- Naringenin
- Daidzein
- Genistein

RESULTS

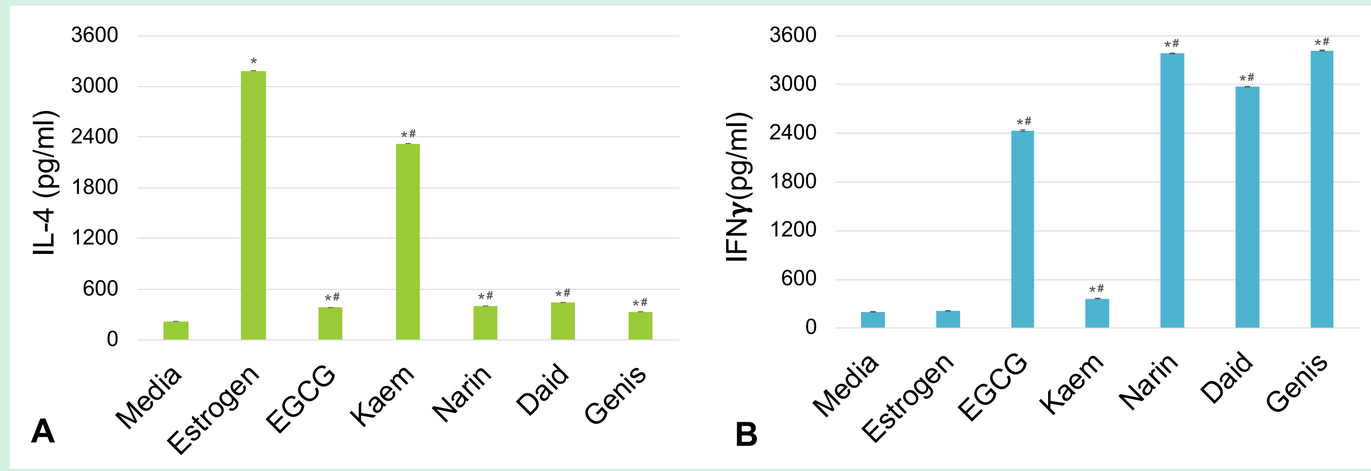


▲ **Figure 3. Estrogen and certain flavonoids support differentiation of MDSCs. A.** Flow cytometry was used to measure the average fluorescence intensity of Ly6C, Ly6G, MHC II, and CD80 in each of the tested flavonoids. **B.** IL-10 expression from ELISA for each flavonoid. *Significant results when compared to media (P<0.01). #Significant results when compared to estrogen (P<0.01).



◀ **Figure 4. Flavonoids display reduced rates of T cell proliferation.** Results of T cell proliferation after MTT Assay at 570nm. Each flavonoid displayed absorbance values lower than that of the media and higher than that of estrogen. Naringenin was not significantly different when compared to media. *Significant results when compared to media (P<0.01). #Significant results when compared to estrogen (P<0.01).

▼ **Figure 5. Cytokine expression increases with estrogen and flavonoid introduction. A.** IL-4 expression after ELISA for each flavonoid. *Significant results when compared to media (P<0.01). #Significant results when compared to estrogen (P<0.01). **B.** IFN expression from ELISA per each flavonoid. *Significant results when compared to media (P<0.01). #Significant results when compared to estrogen (P<0.01).



DISCUSSION

- When compared to media and estrogen, all five compounds showed statistical significance in increased expression of the cytokines IL-10, IL-4 and IFN_{γ}.
- Each flavonoid except Kaempferol showed high IFN_{γ} expression, skewing a Th1 response and thus an increased potential for anti-cancer effects.
- Kaempferol drove high IL-10 and IL-4 expression, skewing a MDSC and Th2 response therefore not inducing an anti-cancer effect.
- ECGC showed the opposite effects in the expression of cytokines IL-10, IL-4 and IFN_{γ}. This compound may be better at halting tumor growth and progression.
- Our hypothesis was partially supported, in that it depended on the type of flavonoid tested. Specifically, kaempferol mimicked estrogen more closely than the other tested flavonoids.

Future Studies

- Put into a model organism for more accurate results
- Run different statistical analysis on the compounds
- Use more compounds within the flavonoid family to see if results are similar
- Potential for flavonoids to be used in drug therapies to decrease tumor suppression

REFERENCES

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4. Svoronos N et al. Tumor Cell-Independent Estrogen Signaling Drives Disease Progression through Mobilization of Myeloid-Derived Suppressor Cells. Cancer Discov. 2016; 7(1): 72-85.