A Review of Metabolic Targets of Anticancer Nutrients and Nutraceuticals in Pre-Clinical Models of Triple-Negative Breast Cancer

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ABSTRACT

Triple-negative breast cancer (TNBC) is a subtype of breast cancer that is notoriously aggressive and has poorer outcomes as compared to other breast cancer subtypes. Due to a lack of targeted therapies, TNBC is often treated with chemotherapeutics as opposed to hormone therapy or other targeted therapies available to individuals with estrogen receptor positive (ER+) breast cancers. Because of the lack of treatment options for TNBC, other therapeutic avenues are being explored. Metabolic reprogramming, a hallmark of cancer, provides potential opportunities to target cancer cells more specifically, increasing efficacy and reducing side effects. Nutrients serve a significant role in metabolic processes involved in DNA transcription, protein folding, and function as co-factors in enzyme activity, and may provide novel strategies to target cancer cell metabolism in TNBC. This article reviews studies that have investigated how nutrients/nutraceuticals target metabolic processes in TNBC cells alone or in combination with existing drugs to exert anticancer effects. These agents have been shown to cause perturbations in many metabolic processes related to glucose metabolism, fatty acid metabolism, as well as autophagy and oxidative stress-related metabolism. With this information, we present the potential of nutrients as metabolism-directed anti-cancer agents and the potential for using these agents alone or in cocktails as a new direction for TNBC therapy.[1]

INTRODUCTION

- In the US, TNBCs make up about 10-15% of all breast cancers diagnosed, and are most common in women under 40 years of age, women with a BRCA1 mutation, and rates are disproportionately higher in African American women
- TNBCs are generally detected later in development and have a shorter 5 year survival rate than ER+ breast cancers
- TNBCs are treated with surgery and chemotherapy while ER+ breast cancers respond to hormone therapy, which is typically more tolerable.
- While previous studies have shown links between diet and breast cancer,[2] the lack of targeted therapies has highlighted the need for further investigation into therapies that work by targeting cellular metabolism, including nutraceutical therapy.

METHODS

Initial Covidence search with key terms

→ 915

Focusing on TNBC and nutraceutical therapy

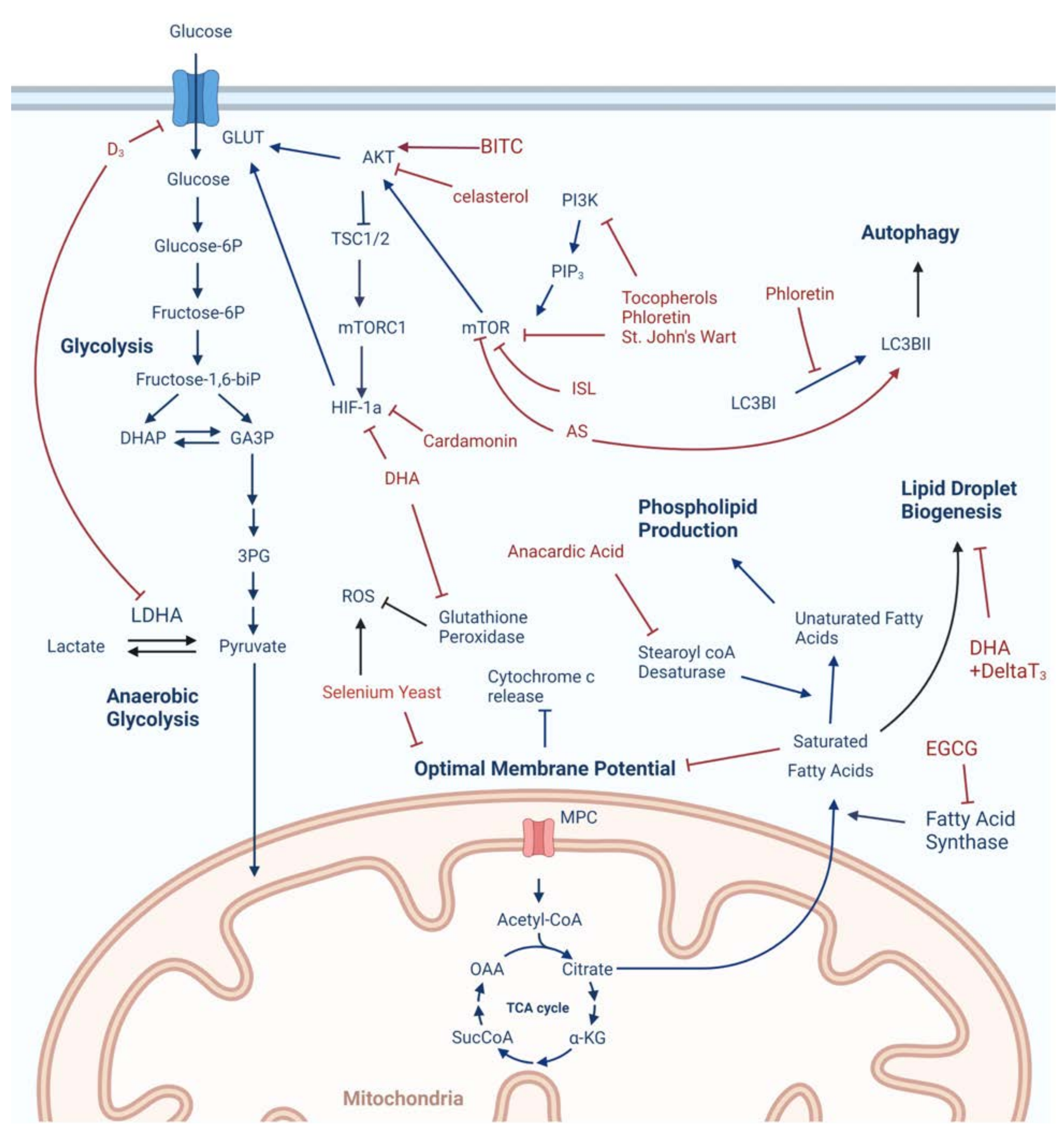
→ 111

Specific metabolic outcomes measured

→ 19

RESULTS

Author (Year)	Intervention	Dietary Counterpart	Mechanism	Author (Year)	Intervention	Dietary Counterpart	Mechanism
Roy (2019)	Benzyl Isothiocyanate	Mustard Family	↑: GLUT-1 localization, AKT activity	Vibet (2011)	DHA+Anthracyclines	DHA	↓: GPx activity; ↑: GSH accumulation, ROS
Shrivastava (201	Celasterol	Tripterygium wilfordii and Tripterygium regelii	↓: AKT activity; ↑: apoptosis	Tran (2015)	Tocotrienols, Tocopherols	Vitamin E	↓: mTOR and PI3K activity, cell proliferation; ↑: autophagy, apoptosis
Jin (2019)	Cardamonin	Alpiniae katsumadai	↓: HIF-1a expression, glucose uptake, lactic acid production; ↑: ROS production	You (2020)	St. John's Wort	Hypericum perforatum	↓: mTOR and PI3K phosphorylation; ↑: pro-death autophagy
Mouradian (2014	DHA	DHA	↓: HIF-1a expression, LDHA, lactic acid, glucose uptake	Lin (2020)	Isoliquiritigenin	Licorice	↓: mTOR phosphorylation, Cyclin D1 expression, Bcl-1 protein; ↑: Bax protein expression
Santos (2018)	Calcitriol	Vitamin D3	↓: GLUT-1 expression, LDHA expression, HKII expression, lactate concentration	Chang (2017)	Antrodia Salmonea	Fungus	↓: Cyclin B1, cyclin A, cyclin E, CDC2, COX protein expression; ↑: LC3B-II, caspase-3
Xiao (2016)	Leucine	Amino Acid / Protein	↓: FAS expression, Sterol Response Element Protein CII, Palmitate	Chang (2017)	Antrodia Salmonea	Fungus	↓: mTOR phosphorylation, ↑: LC3-II, AVOs formation, apoptosis
Crous-Maso (20	EGCG	Green Tea, fruits	↓: FAS expression, palmitate	Chen (2021)	Phloretin	Apples	↓: LC3-I to LC3-II conversion, ULK1 expression; ↑: mTOR and AMPK phosphorylation, sensitivity to doxorubicin
Schultz (2018)	Anacardic Acid	Cashews	↓: Stearoyl coA desaturase expression	Hardy (2003)	Saturated Free Fatty Acids	Fatty Acids	↓: cell proliferation, mitochondrial membrane potential; ↑: apoptosis, cytochrome c relase, caspase-3 activity
Pizato (2019)	DHA + Vitamin E Delta-T3	DHA, Vitamin E	↓: Lipid droplet formation; ↑: Lipid droplet lipophagy	Guo (2015)	Selenium Yeast	Selenium Yeast	↑: apoptosis; ↓: disruption of mitochondrial membrane potential
Vibet (2011)	DHA+Anthracyclines	DHA	↓: GPx activity; ↑: GSH accumulation, ROS				



Metabolic Disturbances

- Anaerobic Glycolysis
- Fatty Acid Metabolism
- Phospholipid Production
- Lipid Droplet Biogenesis
- Pro-Death Autophagy
- Mitochondrial Function
- Oxidative Stress

CONCLUSIONS

- Metabolic adaptations showed to be targets for nutraceutical therapies
- Certain nutraceutical compounds showed to have several metabolic targets or to increase sensitivity to chemotherapeutic drugs
- Many of these compounds showed selective toxicity towards cancer cells, indicating the potential for less severe side effects
- Using nutraceutical therapy as part of a nutrient cocktail or in combination with current treatments may allow for more effective and tolerable TNBC treatment options.

REFERENCES

1. Wiggs, Alleigh; Molina, Sabrina; Sumner, Susan' Rushing, Blake. A Review of Metabolic Targets of Anticancer Nutrients and Nutraceuticals in Pre-Clinical Models of Triple-Negative Breast Cancer. *Nutrients.* **2022** (14). *Under review.*
2. Wiggs, Alleigh; Chandler, Justin; Aktas, Aynur; Sumner, Susan; Stewart, Delisha. The Effects of Diet and Exercise on Endogenous Estrogens and Subsequent Breast Cancer Risk in Postmenopausal Women. *Frontiers in Endocrinology.* **2021** doi:10.3389/fendo.2021.732255

ACKNOWLEDGEMENTS

Thank you to Dr. Blake Rushing, Dr. Susan Sumner, Dr. Delisha Stewart and the Nutrition Research Institute as a whole for your wonderful mentorship and the opportunity to work on these projects with you.

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