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 cancer, 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, 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.

RESULTS

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Intervention</th>
<th>Dietary Counterpart</th>
<th>Mechanism</th>
<th>Author(s)</th>
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<th>Dietary Counterpart</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moussoutinan (2019)</td>
<td>DHA</td>
<td>DHA</td>
<td>↓ HIF-1a expression, ↓ LDHA, ↑ lactate, ↑ glucose uptake</td>
<td>Lin (2020)</td>
<td>Ispaghul-husk</td>
<td>Lecithin</td>
<td>↓ mTOR phosphorylation, ↓ p-AKT, ↓ p-S6K, ↓ p-70S6K, ↓ 70S6K, ↓ p-4EBP1, ↓ 4EBP1, ↓ p-PI3K, ↓ PI3K, ↓ p-ERK, ↓ ERK, ↓ cell proliferation</td>
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<td>Zuo (2016)</td>
<td>DHA + Vitamin E</td>
<td>DHA, Vitamin E</td>
<td>↓ Lipid droplet formation, ↓ Lipid droplet turnover, ↓ G6PD activity, ↓ GSH accumulation, ↓ ROS production</td>
<td>Guo (2011)</td>
<td>Selenium Yeast</td>
<td>Selenium Yeast</td>
<td>↓ cell proliferation, ↓ mitochondrial membrane potential, ↓ apoptosis, ↓ calpains, ↓ caspase-3</td>
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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


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METHODS

- Initial Covidence search with key terms
- Focusing on TNBC and nutraceutical therapy
- Specific metabolic outcomes measured

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, the lack of targeted therapies has highlighted the need for further investigation into therapies that work by targeting cellular metabolism, including nutraceutical therapy.

METABOLIC DISTURBANCES

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