Withaferin A Inhibits the Pro-Inflammatory Effect of Active Breast Adipocytes

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Breast cancer is a leading cause of cancer-related deaths among women, with over 2.3 million new cases diagnosed worldwide each year. Obese breast adipocytes secrete pro-inflammatory cytokines such as IL-6, IL-8, GRO and downregulate the tumor suppressor P16INK4A, fostering a pro-tumorigenic microenvironment. The purpose of this study is to determine the effects of Withaferin A, a bioactive compound from Withania somnifera, on breast adipocytes from obese women (BMI =30). ELISA was conducted to quantitatively measure secreted pro-inflammatory cytokines in conditioned media. To assess transcriptional changes in pro-inflammatory genes and tumor suppressors qRT-PCR (relative mRNA expression) was conducted. Immunoblotting was done to validate protein-level restoration of p16 confirming transcriptional findings from qRT-PCR. To functionally evaluate angiogenesis inhibition by quantifying capillary-like tube formation HUVEC cell assay was conducted. qRT-PCR (EMT/stemness) was done to analyze EMT and stemness) transcripts in luminal cells. Results show that Withaferin A significantly reduced the secretion of pro-inflammatory cytokines IL-6, IL-8, and GRO in breast adipocytes. Additionally, Withaferin A increased the expression of p16, normalizing cytokine levels in obese and lean adipocytes. Withaferin A also repressed the pro-EMT and pro-stemness capabilities of Obadi cells and inhibited the angiogenic capability of breast adipocytes. These results demonstrate Withaferin A's dual anti-inflammatory and anti-cancer properties, highlighting it as a promising novel therapeutic agent to disrupt obesity-driven breast cancer progression.

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