INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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SHORT ABSTRACT

Enterolactone, a mammalian enterolignan, is a gut microbe-generated plant-lignan derivative, known for its estrogen receptor α -modulating activity. Although observational data are controversial, meta-analyses have affirmed that plant lignan-rich diets, or high serum enterolactone, reduce breast cancer risk, or the associated mortality in post-menopausal women. However, the mechanistic basis remains poorly understood. The study assessed enterolactone's impact on the proliferation of estrogen receptor α-positive and estrogen receptor α-negative breast cancer cell lines, revealing estrogen-like effects in estrogen receptor α-positive cells. In MCF-7 cells, it significantly increased the expression of *trefoil factor 1* mRNA, an estrogen-induced transcript. The binding of estrogen receptor α to the estrogen response element within the *trefoil factor1* locus further demonstrated the pro-estrogenic effect of enterolactone. Using RNA-sequencing (RNA-seq), genome-wide transcriptional changes were characterized upon treatment of MCF-7 cells with vehicle (0.1% DMSO) or 10 μM enterolactone. Analysis of RNA-seq data revealed modulation of expression of diverse sets of functionally related genes, which reflected cell cycle progression. Notably, enterolactone downregulated Cytochrome P450 1A1 (*CYP1A1*) mRNA, a xenobiotic-metabolizing enzyme regulated by the aryl hydrocarbon receptor. Intriguingly, it increased CYP1A1 protein, a mediator of xenobiotic response, which is frequently expressed in breast tumors and implicated in cell proliferation and survival. Enterolactone's effect on CYP1A1 expression was similar to estrogen and mediated via estrogen receptor α. But, by virtue of partial estrogen receptor α agonism/antagonism, enterolactone attenuated estrogen-mediated increase in CYP1A1 protein. These data suggest potential mechanisms underlying enterolactone's beneficial effects in breast cancer. In the face of xenobiotic exposure, its aryl hydrocarbon receptor antagonism, on one hand, may reduce the generation of cancer-inducing genotoxic agents. While, on the other hand, with the declining levels of estrogen in post-menopausal women, enterolactone may antagonize estrogen-mediated induction of CYP1A1 protein, and the associated proliferation of mammary epithelial cells. The study may motivate investigations using *in vivo* models, or clinical trials to explore whether increased intake of lignan-rich diet or supplementation of enterolactone will confer protection against breast cancer.