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Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer

Abstract

Fresh organically grown pomegranates (*Punica granatum* L.) of the Wonderful cultivar were processed into three components: fermented juice, aqueous pericarp extract and cold-pressed or supercritical CO_2-extracted seed oil. Exposure to additional solvents yielded polyphenol-rich fractions ('polyphenols') from each of the three components. Their actions, and of the crude whole oil and crude fermented and unfermented juice concentrate, were assessed *in vitro* for possible chemopreventive or adjuvant therapeutic potential in human breast cancer. The ability to effect a blockade of endogenous active estrogen biosynthesis was shown by polyphenols from fermented juice, pericarp, and oil, which inhibited aromatase activity by 60–80%. Fermented juice and pericarp polyphenols, and whole seed oil, inhibited 17-β-hydroxysteroid dehydrogenase Type 1 from 34 to 79%, at concentrations ranging from 100 to 1,000 μg/ml according to seed oil ≫ fermented juice polyphenols > pericarp polyphenols. In a yeast estrogen screen (YES) lyophilized fresh pomegranate juice effected a 55% inhibition of the estrogenic activity of 17-β-estradiol; whereas the lyophilized juice by itself displayed only minimal estrogenic action. Inhibition of cell lines by fermented juice and pericarp polyphenols was according to estrogen-dependent (MCF-7) ≫ estrogen- independent (MB-MDA-231) > normal human breast epithelial cells (MCF-10A). In both MCF-7 and MB-MDA-231 cells, fermented pomegranate juice polyphenols consistently showed about twice the anti-proliferative effect as fresh pomegranate juice polyphenols. Pomegranate seed oil effected 90% inhibition of proliferation of MCF-7 at 100 μg/ml medium, 75% inhibition of invasion of MCF-7 across a Matrigel membrane at 10 μg/ml, and 54% apoptosis in MDA-MB-435 estrogen receptor negative metastatic human breast cancer cells at 50 μg/ml. In a %% murine mammary gland organ culture, fermented juice polyphenols effected 47% inhibition of cancerous lesion formation induced by the carcinogen 7,12-dimethylbenz[*a*]anthracene (DMBA). The findings suggest that clinical trials to further assess chemopreventive and adjuvant therapeutic applications of pomegranate in human breast cancer may be warranted.