Modulation of hydroxytyrosol of oxidative stress and antitumor activities of paclitaxel in breast cancer

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Summary
Breast cancer represents the most common cancer in women and is associated with the most number of cancer-related deaths in women (2, 3). It is associated with an increasing incidence however, due to advanced treatments and early diagnosis, mortality rates are decreasing; although this issue remains contentious (4). Nevertheless, the conventional chemotherapeutics such as the taxane, paclitaxel, remain a mainstay in chemotherapy for advanced breast cancer (5, 6). In this study, the aim was to investigate whether the key olive phenolic hydroxytyrosol could potentially improve anticancer effects of paclitaxel in cell culture and an in vivo model of breast cancer. The widely used MCF-7 and MDA-MB-231 breast cancer cell lines were utilised for this study, and mammary tumors were induced in rats.

Key points and implications
Firstly, the findings from conventional cell culture studies indicated that hydroxytyrosol alone (up to 100 µM), reduced the proliferation of MCF-7 and MDA-MB-231 breast cancer cells following treatment for 72 hours. Similarly, paclitaxel (up to 10 nM) significantly reduced the proliferation of both cell lines. It was shown that hydroxytyrosol potentiated paclitaxel-mediated reductions in cell proliferation, particularly at the relatively higher doses (50 and 100 µM) in the MCF-7 cell line. Similarly, paclitaxel administered intravenously at 2 mg/kg/week for six weeks, resulted in a significant reduction in tumour volume in the in vivo rat mammary tumour model. This effect was augmented with combinations of hydroxytyrosol and paclitaxel. Importantly, the findings that hydroxytyrosol alone administered by gavage at 0.5 mg/kg for five day per week, for six weeks, significantly reduced tumor volume. Further, the number of Ki-67 (marker of cellular proliferation) positive cells was significantly reduced with hydroxytyrosol alone, and this reduction was also observed in the paclitaxel-hydroxytyrosol combination group; paclitaxel alone also reduced the number of Ki-67 positive cells but not as effectively as hydroxytyrosol. To determine whether hydroxytyrosol can influence the
oxidative stress induced by paclitaxel therapy, total plasma antioxidant capacity and plasma protein oxidation was measured. The findings indicated that hydroxytyrosol could rescue oxidative stress induced by paclitaxel. The findings highlight that combination therapy with hydroxytyrosol and paclitaxel could potentially reduce side effects associated with oxidative stress, while enhancing anticancer effects. More generally, these types of combination therapies represent an exciting direction for further research.

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