1. **Effect of P2Et extract alone or in combination with chemotherapy in ex-vivo derived tumor organoids from breast cancer patients.**

**Global Integrative Oncology: Use in Cancer Treatment & Patient Management**

**Background:** The main cause of death by cancer is metastasis rather than local complications of primary tumors. Recent studies suggest that breast cancer stem cells (BCSCs), retaining the ability to self-renew and differentiation to repopulate the entire tumor, have been associated with resistance to chemotherapy (chemo) and tumor recurrence, even after tumor resection. Naturally occurring compounds, especially phytochemicals such as P2Et (polyphenol-rich extract from *Caesalpinia spinosa*), can target populations of cancer cells as well as BCSC, favoring the activation of an immune response through immunogenic tumor death induction**.**

**Aim:** Evaluate the presence of BSCS in tumor patients who had received (or not) chemo before surgery and the ex vivo response of the tumor-derived from these samples to chemo alone or in conjunction with P2Et extract.

**Methodology:** We evaluated the presence of BCSC as well as markers related to drug resistance in tumors obtained from 78 patients who had received (or not) chemo before surgery. We evaluated an ex-vivo response of the tumor-derived from these samples to chemotherapy alone or in conjunction with P2Et, and immunogenic cell signals released from triple-negative breast cancer cells (TNBC) lines. A xenotransplant model engrafted with MDA-MB-468 was used to evaluate in vivo the activity of P2Et.

**Results:** We show that patients with luminal and TNBC, and patients who received neoadjuvant therapy before surgery have a higher frequency of BCSCs. Further, the treatment with P2Et in organoids and human breast cancer cell lines improves the in vitro tumor death and decreases the viability and proliferation together with the release of immunogenic signals. P2Et extract also initially retards primary tumor growth of TNBC.

**Conclusions:** P2Et could be a good co-adjuvant in antitumor therapy in these patients, retarding the tumor growth and enabling the activation of the immune response.

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