Neolignans from *Callistemon lanceolatus*

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Unveiling the cytotoxic potential of four *Callistemon* fruit extracts against breast and colon cancer: a combined metabolomic and in silico approach

Amira Y. Eissa[1], Kamilia F. Taha[1], Abeer Dahab[2], Usama R. Abdelmohsen[3,4], Khayreya A. Youssif[5], Mona H. Ibrahim[6], Seham S. El-Hawary[7] and Manal M. Sabry[7*]

Abstract

Background Breast cancer and colon cancer are among the most prevalent malignancies worldwide, representing significant public health challenges. This study aimed to evaluate the potentially cytotoxic effect of fruit ethanol extracts of four selected *Callistemon* species: *Callistemon citrinus* (Curtis) Skeels, *Callistemon macropunctatus* (Dum. Cours.) Court, *Callistemon viminalis* (Sol. ex Gaertn) and *Callistemon subulatus* Cheel against breast (MCF-7) and colon (Caco-2) cancer cell lines in order to investigate the mechanism of action.

Methods metabolic profiling of the four selected *Callistemon* species was assessed using UPLC-ESI-MS/MS analysis. The in vitro cytotoxicity effects of the tested ethanol extracts against breast (MCF-7) and colon (Caco-2) carcinoma cell lines were assessed by means of 3-(4,5-dimethylthiazol-2- yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The most active extract cell cycle analysis was subjected to flow cytometry. In-silico docking analysis of the most abundant metabolites against cell cycle regulatory enzymes was conducted, followed by molecular docking simulations for top binders.

Results Among the four tested *Callistemon* species, the extract derived from *C. macropunctatus* exhibited the most potent cytotoxic activity, with IC_{50} values of 5.45 ± 0.34 µg/mL against MCF-7 breast cancer cells and 10.24 ± 0.59 µg/mL against Caco-2 colon cancer cells. These values indicate a higher cytotoxic potency compared to the reference drug staurosporine (IC_{50} = 7.72 ± 0.46 µg/mL for MCF-7 and 5.16 ± 0.2 µg/mL for Caco-2). As a result, *C. macropunctatus* was selected for further analysis related to its ability to induce apoptosis and mechanistic effects. In total, sixteen compounds were tentatively identified, with flavonoids, lignans, and meroterpenes emerging as the dominant metabolites.Specifically, the extract caused S-phase arrest in MCF-7 breast cancer cells while both G0/G1 and S-phase arrest in case of Caco-2 colon cancer cells, indicating a broad-spectrum efficacy in disrupting cell cycle progression across different cancer types. To elucidate the underlying mechanisms, in-silico docking simulations were conducted to assess the binding affinities of the identified compounds towards CDK6, a critical regulator of the cell cycle.

*Correspondence:
Manal M. Sabry
manal.sabry@pharma.cu.edu.eg

Full list of author information is available at the end of the article

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