Disrupting PXR Signaling Overcomes Temozolomide Resistance in Glioblastoma via Succisa pratensis–Derived Metabolites

Francesca Servidio [1-2], Fabio Pirovano [1-2], Sofia Remedia [1, 2, 3], Chiara Pellizzer [1], Martina Nespoli [1], Bruno Giovanni Galuzzi [1-2], Marcella Bonanomi [1], Sara Mallia [1-2], Mauro Commisso [2, 4], Flavia Guzzo [2, 4], Clarissa Gervasoni [1-2], Daniela Gaglio [1-2], Manuela Moriggi [5], Daniele Capitanio [5], Gloria Rita Bertoli [1-2], Alessandro Giammona*# [1-2] and Alessia Lo Dico#+ [1-2].

*** Alessandro.giammona@cnr.it**
 # *These authors contributed equally to this work.*
+ *Corresponding author: Dr Alessia Lo Dico,* *via Fratelli Cervi, 93, 20054 Segrate, Milan, Italy,* ***alessia.lodico@cnr.it***

[1] Istituto di Bioimmagini e Sistemi Biologici Complessi (IBSBC) - National Research Council (CNR), 20054 Segrate, Milan, Italy. [2] NBFC, National Biodiversity Future Center, 90133 Palermo, Italy. [3] Department of Earth and Marine Sciences (DISTEM), University of Palermo, Via Archirafi, 22, 90123 Palermo, Italy. [4] Department of Biotechnology, University of Verona, 15, Strada Le Grazie, 37134, Verona, Italy. [5] Department of Biomedical Sciences for Health, University of Milan, 20054 Segrate, Italy

Glioblastoma (GBM) remains a highly aggressive and therapy-resistant brain tumor, with limited benefit from the current standard-of-care regimen combining surgery, radiotherapy, and temozolomide (TMZ). Overcoming chemoresistance therefore represents a critical unmet clinical need.
Here, we investigate the anticancer potential of hydroalcoholic extract from leaves of Succisa pratensis and its ability to enhance TMZ efficacy in GBM models. Treatment with *Succisa pratensis* markedly reduced cell proliferation and migration while significantly increasing sensitivity to TMZ. Integrated multi-omics analyses revealed extensive metabolic rewiring, characterized by suppression of central carbon metabolism and activation of stress-adaptive pathways.
Mechanistically, we identify the Pregnane X Receptor (PXR), a key regulator of drug metabolism and chemoresistance, as a central node affected by treatment. Although *Succisa pratensis* increased PXR expression, this was not accompanied by induction of canonical downstream targets, including *MDR1* and *ALDH1A1*, indicating a functional impairment of PXR transcriptional activity. Consistently, pharmacological inhibition of PXR using the antagonist SPA70 further potentiated the cytotoxic effects of *Succisa pratensis* and TMZ.
Docking analyses suggest that specific secondary metabolites, including apigenin-derived compounds, may interact with the PXR ligand-binding domain, providing a potential molecular basis for this effect.
Collectively, our findings indicate that *Succisa pratensis* enhances TMZ efficacy by inducing metabolic vulnerability and functionally impairing PXR signaling. These results highlight the therapeutic potential of plant-derived metabolites as adjuvant strategies to overcome chemoresistance in glioblastoma.