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Discovery of Chemosensitizing Flavonoids from *Eriobotrya japonica* Using *in silico* and HPLC-SPE-NMR Techniques

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Mimetics of the second mitochondria-derived activator of caspases (Smac) increase the sensitivity of tumor cells towards chemotherapeutics in cancer therapy [1]. Our aim was the discovery of naturally derived small molecule Smac-mimetics from the medicinal plant *Eriobotrya japonica* Lindl. (Rosaceae), which is known to contain cytotoxic constituents [2]. Using a previously generated and validated pharmacophore model [3] 122 3D-molecules (ERIO-database) of known constituents from the leaves of *E. japonica* were subjected to virtual screening. We focused on acylated flavonol monorhamnosides (AFMR) as promising phytochemical class due to the statistical evaluation of the virtual hits. AFMR were identified in the methanol extract by LC-MS and enriched by different chromatographic methods. In the Nicoletti test [4], the combination of the AFMR-mixture with sub-optimal concentrations of the chemotherapeutic etoposide strongly induced cell death in S-Jurkat and XIAP overexpressing Jurkat cells. Since the AFMR-mixture was not separable by conventional methods, we used an HPLC-SPE-NMR approach for the structural identification of single compounds. The combination of the *in silico* and HPLC-SPE-NMR techniques enabled the insight into ligand-target interactions of single compounds from a complex mixture.

[1] Schimmer AD, Dalili S, Batey RA, Riedl SJ. Targeting XIAP for the treatment of malignancy. Cell Death Differ. 2006; 13: 179-188. doi:10.1038/sj.cdd.4401826
[2] Ito H, Kobayashi E, Li SH, Hatano T, Sugita D, Kubo N, Shimura S, Itoh Y, Tokuda H, Nishino H, Yoshida T. Antitumor activity of compounds isolated from leaves of Eriobotrya japonica. J Agric Food Chem. 2002; 50: 2400-2403. doi:10.1021/jf011083l
[3] Bliem CB, Schyschka L, Rollinger JM, Langer T, Vollmar AM, Stuppner H. Pharmacophore modelling on the apoptosis regulating target XIAP-BIR3. Planta Med. 2006; 72: 1008. doi:10.1055/s-2006-949884
[4] Nicoletti I, Migliorati G, Pagliacci MC, Grignani F, Riccardi C. A rapid and simple method for measuring thymocyte apoptosis by propidium iodide staining and flow cytometry. J Immunol Methods. 1991; 139: 271-279. doi:10.1016/0022-1759(91)90198-O

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