Cytotoxic effects of hellebrigenin and arenobufagin against human breast cancer cells

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To gain a novel insight into therapeutic approaches to fight against breast cancer, the cytotoxic effects of hellebrigenin (Helle) and arenobufagin (Areno) were investigated in MCF-7 (ER positive) and MDA-MB-231 (ER negative) human breast cancer cell lines. Helle exhibited more potent cytotoxicity than Areno in both cancer cells, and MCF-7 cells were more susceptible to both drugs. The downregulation of the expression level of Bcl-2 and Bcl-xL, the upregulation of the expression level of Bad, and the activation of caspase-8, caspase-9, along with the cleavage of PARP were observed in Helle-treated MCF-7 cells. Helle-mediated necrosis-like phenotype and G₂/M cell cycle arrest were further observed. Upregulation of the expression level of p21 and downregulation of the expression level of cyclin D1, cyclin E1, cdc25C and survivin were observed in MCF-7 cells treated with Helle and occurred in parallel with G₂/M arrest. The addition of wortmannin or 3-MA, two well-known autophagy inhibitors, slightly but significantly rescued the cells, and further inhibited necrosis induction in Helle-treated MCF-7 cells. In addition, Helle-triggered G₂/M arrest was significantly corrected by wortmannin, suggesting autophagy induction contributed to Helle-induced cytotoxicity of breast cancer cells by modulating necrosis and cell cycle arrest. Collectively, our results suggested potential usefulness of both Helle and Areno in developing therapeutic strategies to treat patients with different types of breast cancer, especially ER-positive breast cancer.