ABSTRACT

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Title of diploma thesis: Screening of selected alkaloids of *Fumariaceae* and *Amaryllidaceae* families on the farnesoid X receptor and the G protein coupled receptor 1

Farnesoid X receptor (FXR) and bile acid receptor associated with G protein 1 (TGR5) significantly affect metabolic processes in the human body. The role of FXR in neuronal apoptosis in Alzheimer's disease (AD) has also been discovered. The possible structural similarity of the small lipophilic molecules binding to these receptors and the alkaloids found in the plants *Corydalis cava* and *Narcissus pseudonarcissus*, as well as the richoften use of these plants in traditional medicine, represent a potential therapeutic intervention for these molecules. In our screening methods, we performed tests using a luciferase gene reporter assay to determine the ability of the alkaloids to interact with FXR and TGR5 in the HepG2 cell line. Many derivatives have shown a strong ability to antagonize FXR and TGR5 activated by obethicholic (OCA) or litocholic (LCA) acids in this assay. Some of the compounds also demonstrated the ability to potentiate the effects of OCA or LCA. Cytotoxicity assays were performed to exclude the cytotoxic effects of tested substances on living cells. Based on these tests, the toxicity or effects on viability of many derivatives were confirmed, which we excluded from the subsequent testing. We also performed a TR-FRET (Time-Resolved Fluorescence Resonance Energy Transfer) cell-free assay on FXR to determine the ability of alkaloids to bind directly to the ligand-binding domain of recombinant FXR, where the antagonistic properties of (-)-canadine and (+)-corydalin were confirmed. We subsequently evaluated their IC_{50} (mean inhibitory concentration) based on CRC (concentration-dependent curves). For hippeastrin, which was able to potentiate the effects of LCA in a gene reporter assay, we performed tests to determine these abilities in other bile acid derivatives and proposed subsequent testing procedures. These data warrant further studies to demonstrate potential therapeutic utility.

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