Abstract

Fejtková Martina: Biological activity of *Peganum harmala* L. alkaloids and their semi-synthetic derivatives II. Diploma thesis 2022. Charles University, Faculty of Pharmacy in Hradec Králové, Department of Pharmacognosy und Pharmaceutical botany.

This diploma thesis deals with the preparation of semi-synthetic derivatives of the alkaloid harmine and the study of their biological activity. The alkaloid harmine was isolated by preparative TLC from an alkaloid extract, exactly from its subfraction PH-F1. Semi-synthetic derivatives were prepared by incorporation of different substituents in the N^9 position of harmine. For the purposes of this diploma thesis were prepared 17 derivatives, which were subsequently identified on the basis of LC-MS, ESI-HRMS and NMR analysis. After structural elucidation of prepared derivatives, their biological activity was studied. The prepared substances were tested for their inhibitory effect on human acetylcholinesterase (AChE), human butyrylcholinesterase (BuChE), glykogen synthase kinase 3β (GSK-3β) and their cytotoxic activity was also measured on selected tumor and leukemia lines and one healthy cell line.

Some of the prepared derivatives showed interesting selective inhibitory potencial against human BuChE, the most active derivative was 9-*N*-(4-isopropylbenzyl)harmine (IC_{50} BuChE 2,50 ± 0,78 μM). Neither harmine nor any of its derivatives showed significant AChE or GSK-3β inhibitory activity. The most active derivatives from the cytotoxic activity screening were 9-*N*-(3-methylbenzyl)harmine, 9-*N*-(2-chlorobenzyl)harmine, 9-*N*-(3-methoxybenzyl)harmine a 9-*N*-(3,5-dimethoxybenzyl)harmine, whose cytotoxic activity was highest on the Jurkat tumor line (acut T-cell leukemia). The most active derivative was 9-*N*-(3,5-dimethylbenzyl)harmine, which showed significant cytotoxic potencial in several tumor lines, namely Jurkat (viability after 48 hours 5 %), MOLT-4 (acute lymphoblastic leukemia) (viability 20 %) and HeLa (cervical adenocarcinoma) (viability 38 %). Many of the prepared derivatives showed a certain biological activity and we can therefore state that harmine represents an interesting pharmacophore with high potencial for further study.

Key words: *Peganum harmala,* harmala alkaloids, harmine, Alzheimer‘s disease, AChE, BuChE, GSK-3β, cytotoxicity