FACULTY OF PHARMACY
IN HRADEC KRÁLOVÉ
Charles University

12th Postgraduate and Postdoc Conference

1. – 2. February 2022

Abstracts

Section 6 - Pharmacognosy and Toxicology of Natural Compounds

EFSA-CDN

This conference is supported by the EFSA-CDN project (Reg. No. CZ.02.1.01/0.0/0.0/16_019/0000841) co-funded by the European Union

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European Structural and Investment Funds
Operational Programme Research,
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PG1

CYTOTOXICITY OF VARIOUS STRUCTURAL TYPES OF ALKALOIDS AND THEIR SEMISYNTHETIC DERIVATIVES

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Cancer is an extensive group of diseases which are generally characterized by rapid and uncontrollable cell division and growth of abnormal cells. According to the most current WHO report, more than 19 million new cases of cancer were diagnosed worldwide in 2020 and almost 10 million deaths were reported in the same year.[1] Between 1981 and 2019, 1881 drugs were newly approved of which over 49% were somehow associated with natural compounds and in group of small-molecule drugs it takes almost 67%.[2] This fact verifies natural compounds, their derivatives or moieties as an essential and important source where new active compounds should be sought. Among the natural substances that are already used in cancer treatment are paclitaxel, omacetaxine, *Catharanthus* alkaloids or derivatives of podophyllotoxin and camptothecin.

Considering the natural compounds, amaryllidaceae alkaloids with over 600 identified compounds[3] are attractive and intensively studied – e.g. pancracine showed interesting activity and was studied regarding the mechanism of its action on MOLT-4 and A549 cell lines. On the other hand, in many bioactive compounds and their derivatives the cytotoxicity is monitored as a side effect to their main way of action and it is necessary to calculate the selectivity index to establish if there is a possibility to avoid the undesirable toxicity.

The study was supported by Pre-application research into innovative medicines and medical technologies project (Reg. No. CZ.02.1.01/0.0/0.0/18_069/0010046).

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PG2

ANALYSIS OF THE EFFECT OF FLAVONOIDS ON COPPER-TRIGGERED FENTON REACTION

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Flavonoids are a large family of polyphenolic compounds that appear naturally in plants as secondary metabolites. As a dietary component, they are generally considered to be beneficial. Their positive effects are mostly attributed to their antioxidant activity, which include both scavenging of free radicals, chelation of metals as well as interference with enzymes forming reactive oxygen species.[1] On the other hand, they can cause as well pro-oxidation, which could be based on their reducing potential.[2] Since, it is difficult to assess theoretically the effect of a compound having both metal reducing and chelating properties on the Fenton chemistry, 24 flavonoids were tested experimentally *in vitro* on copper-based hydroxyl radical generation via HPLC with coulometric detection. Four types of behaviour were observed: antioxidant (a gradual decrease in hydroxyl radical production), pro-oxidant (a gradual increase in hydroxyl radical production), bell-shaped (pro-oxidant effect was followed by antioxidant one) and neutral. Only two flavonoids (3-hydroxyflavone and 5-hydroxyflavone) were able to block the copper-based Fenton reaction (purely antioxidant effect). In the case of diosmin and rutin, bell-shaped behaviour was demonstrated. The others had a predominantly neutral effect and in seven cases, a pro-oxidant effect was observed.

The study was supported by the project entitled "Grant Schemes at CU" (reg. no. CZ.02.2.69/0.0/0.0/19_073/0016935).

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PG3

ISOLATION OF ALKALOIDS FROM *NARCISSUS POETICUS* VAR. RECURVUS

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Alkaloids are a very important group of secondary metabolites with a number of interesting biological effects (anticancer, anticholinesterase, antimalarial, …). Amaryllidaceae family is source of structurally unique compounds, Amaryllidaceae alkaloids. For this reason, the Amaryllidaceae family is interesting goal in searching for active substances with various biological activities.[1]

Several interesting alkaloids were isolated from some species of the genus *Narcissus*. For example, alkaloid with anticholinesterase activity narcimatuline from *Narcissus pseudonarcissus* cv. DUTCH MASTE.[2] In one previous study, the alkaloid extracts of *Narcissus poeticus* var. recurvus also showed significant inhibitory activity against human acetylcholinesterase ($IC_{50HuAChE}$) = 6.0 ± 0.1 μg/ml. For this reason, it was selected for a more detailed phytochemical study. [3]

About 29 kg of fresh bulbs were ground and extracted by ethanol. Extract was separated by Flash chromatography. The obtained fractions were subjected to preparative TLC. Four pure substances were isolated: lycorine, cherylline, pancracine and galanthine.

The study was supported by project EFSA CDN, reg. č. CZ.02.1.01/0.0/0.0/16_019/0000841.

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PG4

ALKALOIDS OF NORBELLADINE TYPE FROM *NARCISSUS PSEUDONARCISSUS* CV. CARLTON AS INSPIRATION FOR DEVELOPMENT OF HIGHLY SELECTIVE BUTYRYLCHOLINESTERASE INHIBITORS

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The most important group of secondary metabolites in the plant family Amaryllidaceae are alkaloids. *Narcissus pseudonarcissus* cv. Carlton (NPC) is one of the abundant species of Amaryllidaceae family, exclusively used for the commercial extraction of galanthamine, which is used as a drug for the treatment of mild to moderate stages of Alzheimer's disease (AD). Novel alkaloids carltonine A, and B have been isolated from the alkaloidal extract of NPC, demonstrated highly selective *in-vitro* butyrylcholinesterase (BuChE) inhibition potency in the nanomolar range (IC_{50}, 910 nM, and 31 nM, respectively) [1]. Unfortunately, these alkaloids are present in plant material only in trace amounts. Therefore, we have synthesized a pilot series of compounds (1–20), structurally inspired by carltonine A, and B, and evaluated their acetylcholinesterase (AChE) and BuChE inhibition properties [2]. Seven compounds were found to possess *h*BuChE inhibition profile, with IC_{50} values below 1 μM. The most significant inhibition activity was demonstrated by compound 6 with value of IC_{50} 72 nM and an excellent selectivity pattern over *h*AChE, reaching a selectivity index of almost 1400. The next part of the current study was design of total synthesis of carltonine A, and B.

The study was supported by Charles University grant SVV UK 260 548

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PG5

AMARYLLIDACEAE ALKALOIDS AS INSPIRATION FOR THE DEVELOPMENT OF HIGHLY SELECTIVE BUTYRYLCHOLINESTERASE INHIBITORS: THE RELATIONSHIP BETWEEN STRUCTURE, EFFECT, AND TOXICITY

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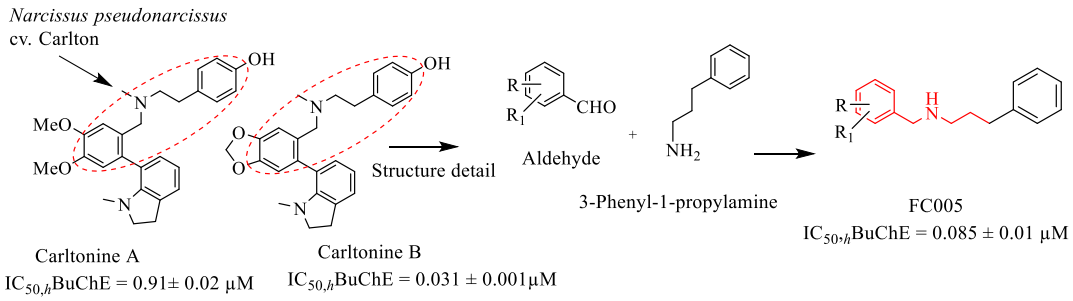
Alzheimer's disease is a serious irreversible progressive neurodegenerative age-dependent disorder characterized by memory loss and progressive cognitive impairment.[1] As reported by the cholinergic hypothesis, damaged nerve cells in the AD brain lead to an abnormal decrease in acetylcholine (ACh) and, at the same time, low enzyme levels are a symbolic pathological feature strongly associated with cognitive function. As AD progress levels of acetylcholinesterase in the brain are decreased sharply by 90%, while butyrylcholinesterase (BuChE) is increased to 165% of normal levels, taking over the hydrolysis of ACh. On this basis, BuChE is a potential target for the treatment of advanced AD.[2] Carltonine A and B alkaloids demonstrated an exceptional selective inhibition potential of BuChE in tens of nanomoles (IC_{50} = 0.031 ± 0.001μM). The aim of this work is the preparation of synthetic compounds inspired by alkaloids of the belladin-type with a subsequent study of the structure and biological activity relationship. Cytotoxicity against human SH-SY5Y neuroblastoma and the ability to cross the BBB using the PAMPA assay was measured for selected derivatives.



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PG6

ALKALOIDS OF THE DICRANOSTIGMA FRANCHETIANUM HOOK F. ET THOMSON (PAPAVERACEAE) HERB ABOVE-GROUND AND THEIR INHIBITION OF ACETYL- AND BUTYRYLCHOLINESTERASE

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Dicranostigma franchetianum (Prain) Fedde, syn. *Chelidonium franchetianum* Prain (Papaveraceae) is one of the representatives of the scanty genus *Dicranostigma* Hook.f. & Thomson. This annual plant grows endemically in the Himalayas and western China and is used as an ornamental plant in Europe. In the primary screening of the alkaloid extract for cholinesterases inhibition, the inhibitory value was high (hAChE/hBChE, IC_{50} μg/ml; 1.67 ± 0.11/3.85 ± 0.31) and together at least 25 alkaloids were found in the extract. The primary ethanol extract was prepared from 11.8 kg of dry above-ground part, from which alkaloid extracts with different solvents with increased polarity (n-hexane, diethyl ether, ethyl acetate, chloroform, chloroform-ethanol) were prepared. The purified diethyl ether extract of the alkaloidal bases (93 g) was separated by flash chromatography on silica to give 12 combined fractions. From these fractions after purification with TLC chromatography, obtained 17 pure alkaloids which are **1** dihydrosanguinarine, **2** dihydrochelerythrine, **3 (**±) protopine, **4** isocorydine, **5** corydine, **6** bis [6-(5,6-dihydrochelerythrinil)]ether, **7** 6-ethoxydihydrochelerythrine, **8** oxyhydrastinine, **9** doryanine, **10** scoulerine, **11** 6-methoxydihydrochelerythrine, **12 (**±) cryptopine, **13** isoboldine, **14** isocorytuberine acetate, **15** laudanosine, **16** norisocorydine, and **17** corydamine based on NMR structure elucidation. So far, their inhibitory activity on AChE and BChE was determined by using of recombinant human brain cholinesterases resulted **2** dihydrochelerythrine and **13** isoboldine were active against AChE and BChE, **17** corydamine was active only against BChE, and the other compounds was not active against both cholinesterases.

The study was supported by projects SVV 260 548 and PROGRES Q42.

PG7

SEMISYNTHETIC DERIVATIVES OF AMARYLLIDACEAE ALKALOID HAEMANTHAMINE AS POTENTIAL DRUGS IN THE TREATMENT OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is the most prevalent neurodegenerative disease worldwide with complex etiology and multifaceted pathophysiology and data indicate an exponential rise in the number of cases of this disease. The well-known Amaryllidaceae alkaloid (AA) galanthamine is marketed drug for AD therapy under the commercial name Reminyl© (galanthamine hydrobromide).

Studies also pointed out various pharmacological properties of semisynthetic derivatives of some AA, such as alkaloid haemanthamine (HMT), which is widely distributed through Amaryllidaceae plants. Based on our previous results, where several HMT derivatives demonstrated promising *h*AChe/*h*BuChe inhibition potency, we continued the preparation of further HMT semisynthetic derivatives.[1]

Several new esters showed interesting inhibition of both studied cholinesterases, thus structure-activity relationship (SAR) was also studied.[2] Newly prepared compounds were identified by 1D-, 2D- NMR and ESI-MS methods. The most active compounds were studied in more detail (e.g. type of inhibition, docking studies, logBB etc.).

This project was supported by Charles University grant SVV UK 260 548.

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PG8

ALKALOIDS OF *VINCA MINOR* L. – IDENTIFICATION OF NEW ANTI-ALZHEIMER'S STRUCTURAL SCAFFOLD

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Based on our previous research, alkaloids of *Vinca minor* L. possess a selective inhibition activity against human butyrylcholinesterase (*h*BuChE), a less known but crucial enzyme in the pathology of Alzheimer's disease (AD). One of the compounds, namely 2-ethyl-3[2-(3-ethylpiperidinyl)-ethyl]]-1*H*-indole, isolated from this species for the first time, exerted unusual inhibitory *h*BuChE activity (IC_{50} 0.65 μM). The alkaloid also exhibited a good inhibition of prolyloligo-peptidase (IC_{50} 58 μM), another enzyme involved in AD's pathogenesis. These results led us to further examination. The enzyme kinetics study revealed the binding mode to the active site of the *h*BuChE to be as reversible competitive, while *in silico* simulations, such as molecular docking and dynamics, clarified the binding pose. Parallel artificial membrane permeability assessment *in vitro* predicted this compound's ability to penetrate the blood-brain barrier by passive diffusion. This alkaloid also tentatively seemed non-cytotoxic, as showed by a cytotoxicity test on the panel of ten tumorous cell lines. Since this structure can be prepared synthetically, these compelling results support the future exploration of potentially better analogues.
This study was supported by projects SVV 260 548, Progres Q42, InoMed, Czech Science Foundation project No. 20-29633J, Long-term development plan (Faculty of Military Health Sciences), and by University of Hradec Kralove (Faculty of Science, no. VT2019-2021).

PG9

ISOLATION OF AMARYLLIDACEAE ALKALOIDS FROM *NERINE BOWDENII* BY PH-ZONE REFINING CENTRIFUGAL PARTITION CHROMATOGRAPHY

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Nerine bowdenii (Amaryllidaceae) is a flowering plant native of South Africa. In order to investigate the rich alkaloid content, the ether extract of fresh bulbs was subjected to pH-zone refining centrifugal partition chromatography (CPC), a technique used for the fast and efficient isolation of alkaloids with varying pKa. The biphasic system used consisted of methyl *tert*.-butyl ether, acetonitrile and water (4:1:5, v/v), while triethylamine (8mM) was added to the organic phase and hydrochloric acid (10mM) was added to the aqueous phase. The separation was performed by eluting the column with the organic phase (ascending mode), while the aqueous phase was used as the stationary phase. In this one-step procedure, two alkaloids were isolated in high purity, while all the fractions were analysed with the aid of various techniques such as HPTLC, HPLC-DAD, HPLC-ELSD, and HPLC-HRMS.

The study was supported by GA UK/B-BIO328121 (2021-2023) and Project No. CZ.02.2.69/0.0/0.0/16_018/0002736.

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PG10

ANTIMICROBIAL ACTIVITY OF SEMISYNTHETIC DERIVATIVES OF MONTANINE-TYPE ALKALOIDS

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The Amaryllidaceae plant family is one of the most important alkaloid-containing plant families with potent biological properties such as antitumor, antimicrobial, antimalarial, and significant anti-neurodegenerative activities. Among all Amaryllidaceae alkaloids, montanine-type alkaloids are characterized by 5,11-methanomorphanthridine ring system and are known for their antiproliferative, antimalarial, antirheumatic, anticholinesterase and most recently for their antimicrobial activity.[1] Montanine itself, demonstrated activity against pathogenic *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *S. epidermis*, giving values of 5, 20, 5 and 15 μg respectively, as minimum quantities for inhibitory activity.[2]

In the current study, 40 new derivatives of montanine-type alkaloids were synthesized and evaluated for their antibacterial and antimycobacterial activity on a panel of 4 Gram-positive, 4 Gram-negative and 3 avirulent strains of mycobacterium (*Mycobacterium smegmatis*, *M. aurum* and *M. tuberculosis* H37Ra). Among all, 2 derivatives demonstrated significant activity against *Klebsiella pneumoniae* with MIC less than 32 μM and 8 derivatives showed MIC less than 8 μM on *M. tuberculosis* H37Ra while 3 of them demonstrated activity against all investigated mycobacterium strains with MIC less than 15.68 μM.

The study was supported by SVV 260548 and 260549 project.

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PG11

PREFERENCE OF DIETARY SUPPLEMENTS IN CANCER PATIENTS

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Cancer survivors show increasing interest in accessing information on cancer using internet.[1] Due to high availability of dietary supplements (DS) to European population, DS are available also to cancer patients. The prevalence of herbal medicine use in cancer patients was found to be 19,7%. Such considerable percentage of cancer patients, who use this kind of DS, stresses an urgent need to better understand the self-medication behaviour of these individuals.[2]

The aim of this research study was to analyse attitudes towards use of DS in users that accessed online health information about breast cancer, lung cancer, colorectal cancer, or prostate cancer.

As a survey tool, an automated conversation system (chatbot) was created. This chatbot was added to selected websites Linkos.cz and Anamneza.cz. Namely, the chatbot was placed on websites covering topics of breast cancer, colorectal cancer, lung cancer, and prostate cancer. The chatbot was displayed on the selected websites to 15.431 users between the 1st of May and the 31st of December. However, only 198 users (1,28 %) completely filled in the entire survey (n=198, 100 %). Patients with cancer (78 respondents) and past cancer patients (13 respondents) were asked which DS were taking in the past. Respondents whose relatives are cancer patients (60 respondents) or respondents visiting websites for educational purposes (48 respondents) were asked about their recommendations of DS to cancer patients.

The respondents chose vitamin C , vitamin D, omega-3 fatty acids, magnesium, and zinc. From herbal medicines dominated garlic, curcuma, seaberry, and ginger. The most frequently chosen medicinal mushrooms were oyster mushroom and reishi mushroom.

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