



Joint Conference
of Pharmacological
and Toxicological Societies

BOOK OF ABSTRACTS

SEPTEMBER 9–11, 2026

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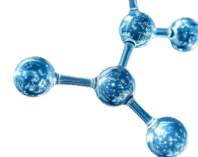
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PREFACE

It is our great pleasure to welcome you to Brno for **the Joint Conference of Pharmacological and Toxicological Societies**, held from 9 to 11 September 2026 at the University Campus Bohunice.

This joint scientific meeting brings together the 73rd Czech-Slovak Pharmacological Days, the 31st TOXCON Conference, the 25th Czech Conference of Clinical Pharmacology, and the 29th Czech Conference on Therapeutic Drug Monitoring.

The conference connects the Czech Society of Experimental and Clinical Pharmacology and Toxicology of the Czech Medical Association J. E. Purkyně, the Czech Society of Clinical Pharmacology of the Czech Medical Association J. E. Purkyně, the Slovak Pharmacological Society of the Slovak Medical Society, and the Slovak Toxicological Society.

We hope that this meeting will provide an opportunity for professional exchange and discussions among colleagues.

We extend our sincere thanks to all participants, speakers, organising and scientific committees, and institutional partners whose efforts and dedication made this event possible.

Welcome to Brno and to the Joint Conference of Pharmacological and Toxicological Societies.

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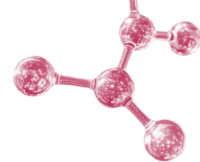


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INFORMATION FOR POSTER PRESENTATIONS

Please find your poster number and the corresponding installation and presentation times below:

P1–P14: Thursday, 10 September

- Poster display: 08:30–12:30
- Poster session: 10:00–10:30

P15–P32: Thursday, 10 September

- Poster display: 13:00–17:15
- Poster session: 14:45–15:15

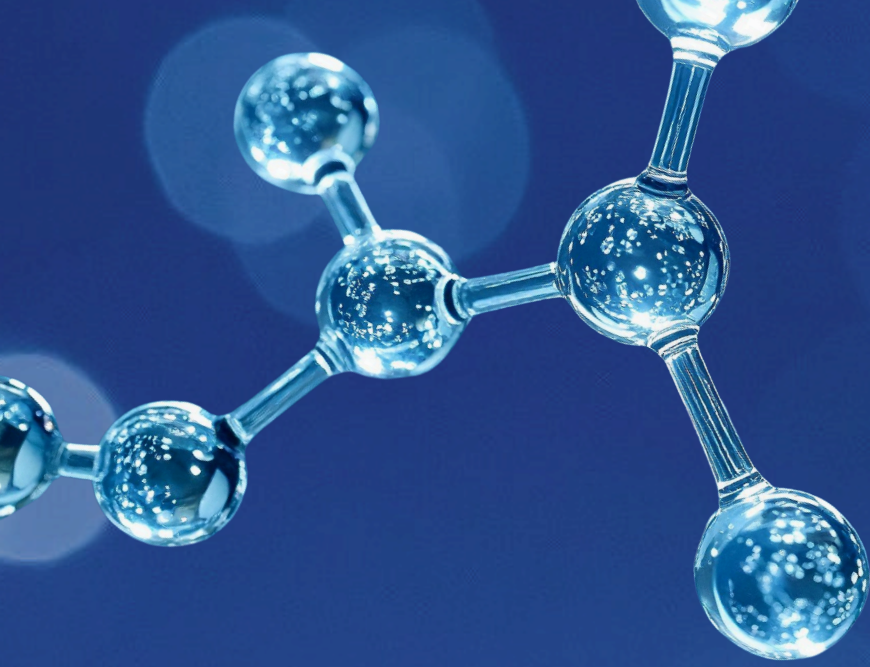
P33–P51: Friday, 11 September

- Poster display: 08:30–13:00
- Poster session: 10:00–10:30

Authors are kindly requested to mount their posters before the beginning of the designated display period and to be present at their poster during the assigned poster session.

Authors are kindly requested to remove their posters immediately after the end of the designated display period.

Posters remaining on the boards after the scheduled removal time may be removed and disposed of by the organizers.



ORAL PRESENTATIONS

EXPLORING THE PHARMACOLOGICAL POTENTIAL OF NATURAL BIOACTIVE COMPOUNDS, EXTRACTS AND THEIR COMBINATION THERAPIES ON IL-17A-MEDIATED INFLAMMATION IN EXPERIMENTAL ARTHRITIS

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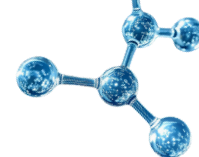
Introduction: The pathogenesis of rheumatoid arthritis (RA) is driven by a network of pro-inflammatory cytokines including TNF- α , IL-1 β , IL-6 and especially IL-17A, which induces synovial inflammation, osteoclastogenesis and bone destruction. Elevated levels of IL-17A is associated with disease severity and poor therapeutic response.

Aim: To examine IL-17A as a therapeutic target in experimental arthritis by studying the effects of selected natural bioactive compounds and extracts alone and in combination with methotrexate (MTX) on IL-17A inflammatory activity.

Methods: Plasma samples from induced experimental arthritis – adjuvant arthritis (AA) treated with β -cryptoxanthin (CRY), crocin (CR), lotus leaf extract (LEX), beetroot extract (REP), apisimin (API), hyaluronan (HA) and melittin (MEL) administered alone and in combination with MTX were analyzed to quantify IL-17A levels and to evaluate their therapeutic effects.

Results and Discussion: IL-17A level was extensively elevated in arthritic rats throughout the experiment. IL-17A was significantly reduced with the combinations treatments (CTs) as compared to monotherapies. The CTs with MTX showed the greatest reduction in IL-17A on day 14 for these substances: CRY, CR, LEX, REP and API, while their monotherapies alone had limited efficacy. Moreover, the plasma levels of IL-17A were significantly suppressed by SHA (medium molecular weight HA), VHA (high molecular weight HA) and their combinations and notably this inhibitory effect was sustained during the trial. MEL had minor influence on IL-17A levels when used alone. All these results propose that CTs are more efficacious than monotherapies in the inhibition of IL-17A mediated inflammatory response in experimental arthritis.

ACKNOWLEDGMENT: VEGA 2/0079/24, VEGA 2/0091/23, VEGA 2/0126/23, SAS-VAST bilateral project, SAIA project (Elisabeth Ndjengue Mindang), APP0689, and APP0840.



MODERN TREND IN PHARMACOTHERAPY OF PATIENTS WITH DIABESITY

Renata Blechová¹

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Introduction: The prevalence of Diabetes in the Czech Republic is approx. 10 % of the population (more than 1 million registered patients). Annually, there are around 60,000 newly diagnosed patients, 92 % of which with Type 2 Diabetes (T2D). Over 90% of T2D patients are overweight or obese. The rest always have some accumulation of fat in the abdominal area. Hence the name Diabetesity. The patient's age and genetic predisposition are risk factors, with the incidence of T2D increasing significantly with the aging of the population, lifestyle and nutritional style. The advent of incretin therapy changes the paradigm of current treatment.

Aims: Observational cohort pharmacoepidemiologic study targeted on geriatric T2D patients and drug consumption analysis, focused on the use of weight reducing drugs in the treatment of Diabetesity.

Methods: Prescription analysis of a group of 70 patients, 39 females (55,71 %), 31 males (44,29 %), aged 65+ (from 67 to 87), 28 patients in age cohort 65–74 (40,00 %), 40 patients in age cohort 75–84 (57,14 %) and 2 patients in age cohort 85+ (2,86 %). BMI Categories (overweight and mostly obese) and HbA1C were among the other examined values. All values were gathered in the first half of 2026.

Results and Discussion: A total of 17 agents were used in medication. Metformin was predominately used (in 61 cases), mostly in combination with other agents. Such results follow modern trends in T2D treatment. Incretins were the most combined agents with metformin; semaglutide was the most prominent agent. Patients with Class 2 Obesity and Class 3 (Severe) Obesity benefited from the incretin therapy. Incretin-based agents do not only promote weight loss (or are weight-neutral), but have significant glucose-lowering effects, pleiotropic effects such as cardiovascular protective effects and benefits. Caution must be taken regarding medication-related hypoglycemia effects and sarcopenic obesity risks. In addition, Beers Criteria and the FORTA list must be observed in the treatment of Diabetesity.

WHAT HAVE WE LEARNED FROM FIFTEEN YEARS OF ADJUVANT ARTHRITIS RESEARCH?

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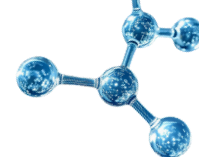
Introduction: Rat adjuvant arthritis (AA) is a robust model of inflammatory arthritis, but translation to rheumatoid arthritis (RA) requires reproducible effects across independent domains and explicit recognition of model limits. Our fifteen-year programme tests both the value and boundaries of this platform.

Aims: To identify reproducible findings across 18 publications, assess adjunctive activity beyond methotrexate (MTX), and benchmark the programme against international AA research.

Methods: Publications from 2010–2025 (at Scopus) were qualitatively synthesised. Most studies used male Lewis rats, healthy and untreated AA controls, low-dose MTX, monotherapy, and MTX combinations. Interventions comprised endogenous and plant-derived compounds, a probiotic, carotenoids, and glycosaminoglycan-related macromolecules. Outcomes included paw volume, arthritic score, body-weight change, inflammatory and oxidative biomarkers, tissue γ -glutamyl transferase, and selected structural or signalling measures. Related overviews were not treated as independent replications. Findings were benchmarked for validity, bias control, biomarker interpretation, and translation.

Results and Discussion: Repeated controls, longitudinal measurements, and MTX benchmarking created a stable comparative platform. Increased paw volume and arthritic score, impaired weight gain, and inflammatory and oxidative abnormalities were the most reproducible findings. Paw volume was the most consistently treatment-sensitive endpoint; score and body weight were supportive but partly overlapping or nonspecific. Biomarkers were less consistent: IL-17A was most informative earlier in disease, whereas MMP-9, tissue γ -glutamyl transferase, and oxidative indices varied with sampling time, tissue, and intervention. None was validated as a surrogate, prognostic, or predictive biomarker. Selected coenzyme Q10, N-feruloylserotonin, Lactiplantibacillus plantarum LS/07, carotenoid, saffron, and 0.99-MDa hyaluronan regimens improved particular endpoints beyond MTX. Conversely, carnosine mainly affected redox measures and early swelling, while quercetin, pinosylvin, and robinin produced molecular or tissue effects without consistent added clinical benefit. Overall, efficacy was compound- and endpoint-specific, and biomarker improvement did not invariably parallel clinical benefit. The programme aligned internationally in longitudinal paw assessment, active MTX comparison, combination designs, and mechanistic breadth. Major deviations were short follow-up, mostly induction-proximal treatment, male-only cohorts, limited independent replication, and incomplete reporting of blinding and statistical planning. Pain, function, structural protection, durability, PK/PD, biological diversity, complementary models, and human validation were not systematically addressed. AA therefore supports compound prioritisation and mechanistic testing, but not direct proof of human efficacy. Future studies should use prespecified outcomes, post-onset treatment, phase-appropriate biomarkers, and independent structural, functional, or pain-related confirmation in blinded, adequately powered, sex-inclusive designs.

ACKNOWLEDGMENT: This study was supported by VEGA 2/0091/23.



MATERNAL DEPRESSION: NOVEL EXPERIMENTAL APPROACHES AND CHALLENGES

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Maternal depression represents a serious risk factor for fetal and neonatal development. It is estimated that approximately 10-20% of women experience clinically significant depression during pregnancy or lactation. The pharmacotherapy of maternal depression is a highly relevant issue because antidepressant drugs may affect developmental processes during the prenatal and early postnatal periods, particularly the highly vulnerable stages of brain development. Therefore, the safety of antidepressants for the treatment of maternal depression remains controversial. Most antidepressants are classified as pregnancy category C drugs, indicating that there is insufficient evidence from well-controlled studies to adequately assess the risks associated with their use during pregnancy and breastfeeding. Several studies have shown that antidepressant treatment during gestation is associated with an increased risk of spontaneous abortion, preterm birth, low birth weight, neonatal adaptation difficulties, and neurobehavioral disorders later in life. Experimental studies using relevant animal models of maternal depression are essential for elucidating the underlying mechanisms of these adverse outcomes. In our experimental research, maternal depression is induced in pregnant laboratory rats using a chronic mild unpredictable stress protocol. The dams and their offspring of both sexes undergo comprehensive evaluation, including assessments of maternal behavior, reproductive outcomes, pup reflex and neuromotor development, hippocampal neurogenesis, in vivo and in vitro electrophysiology, neurochemistry, immune function, magnetic resonance spectroscopy and imaging, as well as behavioral testing. The results of our studies indicate that the adverse consequences of untreated maternal depression outweigh the potential risks associated with pharmacotherapy. Furthermore, the antidepressants investigated in our studies were found to be relatively safe with respect to fetal and neonatal development in rat offspring.

ACKNOWLEDGMENT: This work was supported by APVV-24-0391 and VEGA 2/0133/23.

EVALUATION OF TWO DOSES OF α -PHELLANDRENE AND ITS COMBINATION WITH METHOTREXATE IN AN ADJUVANT-INDUCED ARTHRITIS MODEL

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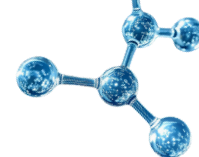
Introduction: α -Phellandrene (Ph) is a cyclic monoterpene with anti-inflammatory effects, suppressing cytokines (TNF- α , IL-6) and reducing cell migration/degranulation. However, its anti-arthritic properties, alone or in combination with methotrexate (MTX), have not yet been evaluated on the adjuvant arthritis (AA) model.

Aims: The present study aimed to compare the anti-arthritic effects of orally administered Ph at 25 and 50 mg/kg, as monotherapy or in combination with MTX, in Lewis rats with AA, using disease activity measures and selected systemic and local parameters.

Methods: Animals were randomised to 7 groups: Healthy; AA-untreated; MTX (0.3 mg/kg, 2x/week); Ph 25 mg/kg; Ph 50 mg/kg; Ph 25mg/kg+MTX and Ph 50 mg/kg+MTX. Ph was administered daily. Changes in hind paw volume (HPV), arthritic score (AS), and body weight (BW) were assessed longitudinally. Plasma MMP-9 was quantified by ELISA on day 28, along with spleen (SI) and liver indices (LI).

Results and Discussion: AA increased HPV and AS, particularly at later disease stages. Ph 25 mg/kg monotherapy significantly reduced HPV on days 21 and 28 and AS on days 14, 21, and 28, whereas its combination with MTX showed only non-significant trends. Ph 50 mg/kg monotherapy reduced HPV only on day 14, whereas Ph 50 mg/kg+MTX significantly reduced HPV on all days and was more effective than MTX on days 21 and 28; neither the 50 mg/kg regimen nor MTX significantly affected the AS. BW gain improved transiently with Ph 50 mg/kg+MTX on day 21. MMP-9 was not reduced but increased with Ph monotherapy at both doses and with Ph 25 mg/kg+MTX. SI confirmed AA-associated immune activation, but it was not normalised by treatment. LI showed no consistent treatment-related changes, except for a reduction with Ph 25 mg/kg+MTX compared with untreated AA. Overall, Ph showed dose- and endpoint-dependent anti-arthritic activity, with a profound effect on clinical score at 25 mg/kg and the strongest reduction in paw swelling with Ph 50 mg/kg+MTX.

ACKNOWLEDGMENT: This study was supported by VEGA 2/0091/23, 2/0079/24, and 2/0126/23; FaF/20/2025, FaF/28/2026, and FaF/26/2026; and APP0713, APP0689, and APP0840.



ROLE OF HEPATOCYTE GROWTH FACTOR IN STREPTOZOTOCIN-INDUCED DIABETIC NEPHROPATHY: EXPRESSION AND ACTIVITY

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Introduction: The role of hepatocyte growth factor (HGF) in diabetic nephropathy (DN) remains elusive. We have previously demonstrated that high glucose activates the HGF receptor (c-MET) independently of HGF in vitro.

Aims: The aim of the present study was to investigate the HGF/c-MET signalling pathway in an in vivo model of DN. As hyperglycaemia is a hallmark of diabetes mellitus, we hypothesised that c-MET is overactivated and that HGF plays an important role in the pathogenesis of DN.

Methods: Diabetes mellitus was induced in male Wistar rats by a single intraperitoneal injection of streptozotocin (60 mg/kg). Six weeks later, the animals were sacrificed, and the kidneys were evaluated for DN using PAS and Picro-Mallory trichrome staining, together with mRNA analysis of KIM1 and inflammatory markers. The expression of HGF, c-MET and their downstream signalling molecules was assessed by Western blotting and RT-qPCR. Immunohistochemistry (IHC) was performed to detect and localise HGF within kidney tissue sections. Plasma HGF concentrations were determined by ELISA.

Results and Discussion: Diabetic kidney injury was demonstrated by increased glomerulosclerosis and numerous fibrotic lesions. DN was further confirmed by elevated albumin-to-creatinine ratio and microalbumin levels, together with increased expression of inflammatory markers, including IL-1 β , ICAM-1, COX2 and LOX. Importantly, HGF protein expression was significantly increased in diabetic kidneys, whereas plasma HGF concentrations remained unchanged. IHC revealed increased HGF localisation in injured cortical tubules exhibiting tubular dilatation and epithelial simplification. Furthermore, phosphorylation of c-MET was significantly increased in diabetic kidneys. Enhanced phosphorylation was also observed for AKT, whereas ERK1/2 phosphorylation remained unchanged. In conclusion, the increased activation of c-MET observed in DN may result from both hyperglycaemia and upregulated HGF expression. Enhanced activation of the HGF/c-MET signalling pathway may represent a compensatory mechanism protecting against diabetic kidney injury.

ACKNOWLEDGMENT: This work was supported by the grant from Faculty of Pharmacy Comenius University GVRFaFUK/1/2025.

CHALLENGES IN THE PHARMACOLOGICAL MANAGEMENT OF PAEDIATRIC TUBERCULOSIS IN SLOVAKIA

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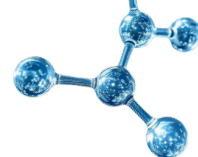
Introduction: Tuberculosis remains a global problem and in children with impaired cellular immunity can progress to severe multiorgan involvement. Defence against mycobacteria is supported by the interleukin-12/interferon-gamma axis, which activates macrophages, therefore, its loss of function, may lead to disseminated infection after administration of a live attenuated Bacillus Calmette–Guérin (BCG) vaccine.

Aims: The aim of this case report is to highlight severe complications of BCG vaccination in an immunodeficient child, the challenges of long-term pharmacotherapy, the need for lifelong antituberculous therapy (AT) in complete autosomal recessive interferon-gamma receptor 1 (IFNGR1) deficiency.

Methods: We retrospectively analysed the medical records of a patient with IFNGR1 deficiency and post-vaccination disseminated BCG infection, focusing on medical history, clinical course, microbiological/immunological results and therapeutic management.

Results and Discussion: The patient received the BCG vaccine shortly after birth. The family history revealed an immune disorder in the mother. Already in infancy, he developed left-sided axillary lymphadenitis with culture-confirmed detection of Mycobacterium (M.) bovis. Genetically confirmed IFNGR1 deficiency explained the dissemination to the lymph nodes, spleen, bones, skin, chest wall and lungs, as well as the need for lifelong AT. The patient required long-term, repeatedly modified combinations of first-line and reserve AT, guided by microbiological findings. The course was complicated by secondary non-tuberculous mycobacteriosis caused by M. intracellulare and by additional infections. Bone marrow transplantation was considered the only causal treatment modality, but it was refused by the parents. During the final hospitalisation, generalised exacerbation of the specific disease process, with specific pneumonia, left-sided pleural effusion, progression of pulmonary damage and the development of respiratory insufficiency was observed. Despite the 7-drug AT regimen in combination with other anti-infectives, oxygen and symptomatic support, the patient died at almost 13 years of age from respiratory failure due to progression disseminated BCG infection.

ACKNOWLEDGMENT: The study was supported by APVV-22-0342, VEGA- 1/0049/25.



KRÁTKÉ KAZUISTIKY K TERAPEUTICKÝM ÚČINKŮM KONOPÍ PRO LÉČEBNÉ POUŽITÍ

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Úvod: Prezentace několika krátkých kazuistik z algeziologické praxe reflektující terapeutické účinky konopí pro léčebné použití (dále KLP).

Cíle: Cílem prezentace bude ukázat možnosti použití KLP v léčbě bolesti na reálných případech z praxe.

Metody: Konopí se stalo v posledních 10 letech nedílnou součástí léčby bolesti. Šíře použití na různé typy chronické bolesti je velká. V příkladech bude prezentováno použití KLP s opioidy, kdy dokáže redukovat dávky opiodů. Použití v monoterapii léčby bolesti u 93leté pacientky a příklad běžného použití v kombinaci s jinými analgetiky. Použití KLP včetně lokální formy.

Výsledky a diskuse: Konopí je báječným lékem, ale není panacea. Jeho použití má však velké možnosti a budoucnost, nejen v léčbě bolesti.

ADVERSE EFFECT OF AMIODARONE IN PATIENT WITH GENETIC FORM OF DILATIVE CARDIOMYOPATHY

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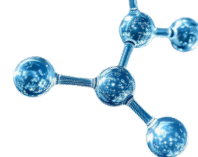
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Introduction: Treatment of ventricular arrhythmias in patients with genetically determined cardiomyopathies represents a significant therapeutic challenge, especially when catheter ablation is not feasible due to the multifocal nature of the arrhythmogenic substrate. We present the case of a patient in whom, after the initial assumption of a parainfectious etiology, a rare pathogenic genetic mutation was identified based on detailed diagnostic workup, which also led to the screening of first-degree relatives. In the above case report of a patient with genetically determined dilated cardiomyopathy, we point out the importance of pharmacovigilance and monitoring the safety of antiarrhythmic treatment.

Aims: A 63-year-old female patient was admitted to the Department of Internal Medicine for a sudden syncopal episode. After extensive non-invasive and invasive diagnostics, which included also magnetic resonance imaging, examination of late ventricular potentials and genetic analysis, a rare mutation was identified as the cause of cardiomyopathy. The mutation was also associated with an arrhythmogenic substrate. The heart failure treatment was optimized and patient was implanted a cardioverter defibrillator in the prevention of sudden death. In the further course of the disease, progression of mitral regurgitation was noted along with numerous multifocal ventricular extrasystoles. Both of them probably contributed to decompensation of heart failure with a significant increase in NTproBNP levels.

Methods: Due to the high burden of numerous multifocal ventricular extrasystoles and the impossibility of catheter ablation, treatment with amiodarone was initiated. After starting therapy, there was a prolongation of the QTc interval with subsequent development of polymorphic ventricular tachycardia of the torsades de pointes type, repeatedly terminated by adequate therapy with an implanted cardioverter-defibrillator. The severe form of arrhythmia was probably caused by the genetically determined microarchitecture disorder itself and the effects of amiodarone which was subsequently replaced by a beta-blocker in the treatment.

Results and Discussion: Dilated cardiomyopathy requires a meticulous diagnostic algorithm to precisely identify the underlying cause because it may reveal a previously unrecognized familial genetic disorder, the first manifestation of which could be sudden cardiac death in a family member. On the other hand, it also emphasizes the need for individual therapeutic management. Amiodarone is considered a relatively safe antiarrhythmic drug in therapy of heart failure with reduced ejection fraction. Its administration can in exceptional cases lead to serious, potentially life-threatening ventricular arrhythmias. The case report emphasizes the importance of individualizing drug therapy, especially in patients with hereditary myocardial diseases.



DUÁLNÍ OPIOIDNÍ ANALGEZIE V TERAPII NÁDOROVÉ BOLESTI

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Úvod: Současná opioidní analgetika účinkují jako agonisté nebo parciální agonisté opioidních receptorů μ , λ , δ a ORL1 (MOPr, DOPr, KOPr a NOPr). Při kombinaci agonistů a parciálních agonistů nebo dvou plných agonistů s rozdílnou receptorovou afinitou by teoreticky mělo docházet spíše ke snížení maximálního možného účinku, a tak se jejich kombinace nedoporučují. Vedle multimodální analgezie a nefarmakologických intervencí se v klinické praxi však tyto kombinace přesto osvědčují, a to zejména pro zvýšení analgetické účinnosti, lepší snášenlivost, lepší kontrolu intenzity bolesti během dne a pro oddálení tolerance.

Cíl: Zmapovat a statisticky popsat využití duální opioidní analgezie u pacientů Masarykova onkologického ústavu. Dalším dílčím cílem bylo ve vybraných případech analyzovat důvody vedoucí k nasazení druhého opioidu a zhodnotit přínos duální opioidní léčby.

Metody: Prospektivní analýza medikace s využitím nemocničního informačního systému při vstupní revizi medikace při příjmu pacienta na lůžkovou oddělení klinickým farmaceutem. Hodnocené období 2017-2024. Statistické zpracování pomocí MS Excel.

Výsledky: Ve sledovaném období bylo zaznamenáno 232 případů, kdy byl pacient léčen dvěma nebo více opioidními analgetiky současně. Při počtech hospitalizací na těchto lůžkových odděleních za rok vychází prevalence duální opioidní léčby na 1,3 %. Nejčastější kombinací byla kombinace fentanyl + oxykodon (resp. fentanyl + oxykodon + naloxegol), následovaná kombinací fentanyl + tramadol. Sporadicky byly používány i mnohé další kombinace. Důvody pro nasazení kombinace byly především potenciace účinku, ovlivnění kolísavé intenzity bolesti v průběhu dne, ovlivnění neuropatické složky bolesti a snaha omezit nežádoucí účinky.

Závěr: Četnost použití duální opioidní analgezie je i ve skupině hospitalizovaných onkologických pacientů relativně nízká. Častým důvodem bylo přidání kombinovaného přípravku obsahujícího oxykodon s naloxonem pro ovlivnění intenzity bolesti během dne a současně ovlivnění opioidy indukované zácpy. Zkušenosti z MOÚ s kombinací opioidních agonistů/parciálních agonistů jsou vesměs pozitivní a ve vybraných případech a po pečlivém zvážení poměru přínos/riziko může tento off-label postup přinášet benefit.

PODĚKOVÁNÍ: Práce vznikla za podpory specifického vysokoškolského výzkumu (MUNI/A/1819/2025).

THERAPEUTIC POTENTIAL OF KYNURENIC ACID IN A BILE DUCT LIGATION MODEL OF LIVER FIBROSIS

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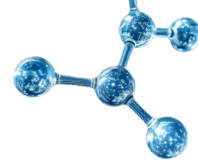
Introduction: Liver fibrosis is a consequence of chronic liver injury that frequently progresses to cirrhosis and ultimately to hepatocellular carcinoma. Kynurenic acid (KYNA) suppresses the immune response and has demonstrated beneficial antifibrotic effects in both dermal and renal fibrosis. Indoleamine 2,3-dioxygenase (IDO) catalyzes the degradation of the essential amino acid tryptophan (Trp) into kynurenines, including KYNA.

Aims: The aim of this study was to investigate the in vivo therapeutic potential of KYNA in liver fibrosis using genetically modified IDO knockout mice subjected to bile duct ligation (BDL). BDL induces cholestasis by obstructing bile flow from the liver, leading to inflammation and hepatic fibrosis progression.

Methods: Genetically modified IDO knockout mice were randomized into a SHAM group, a group that underwent BDL, and a BDL group treated with KYNA (400 mg/kg, p.o., every 24 h) for 14 days. On day 14, the animals were euthanized. Samples from the median and left liver lobe were collected for Western blot and histological analysis. Plasma levels of the liver enzymes were determined using biochemical assays.

Results and Discussion: Our results showed that plasma levels of liver enzymes were significantly elevated in both the untreated and KYNA-treated BDL groups. A non-significant trend toward reduced expression of α -smooth muscle actin (α -SMA) was observed in the KYNA-treated group, whereas α -SMA expression was significantly increased in the untreated BDL group. No significant differences were detected in the expression of collagens among the experimental groups. The expression of EMT-related proteins and MMP-1 was increased in both untreated and KYNA-treated BDL groups. However, KYNA treatment significantly reduced IL-6 expression, suggesting a potential protective anti-inflammatory effect.

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RIZIKA SPOJENÁ S UŽÍVÁNÍM KRATOMU

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Úvod: *Mitragyna speciosa* (běžně známá jako kratom) je tropický strom pocházející z jihovýchodní Asie. Zpracované listy se používají k úlevě od bolesti a léčbě únavy. V západních zemích si získal popularitu díky svým stimulačním a opioidním účinkům a jako alternativa použití při samoléčbě abstinenčních příznaků po opioidech. Hlavní účinnou látkou je alkaloid mitragynin.

Cíl: přednášky je podat přehled o farmakologicky účinných látkách obsažených v kratomu a dalších semisyntetických derivátech, dokumentovat nežádoucí účinky a lékové interakce a zhodnotit zdravotní rizika a společenský a ekonomický dopad spojený s užíváním kratomu.

Metody: Byla provedena rešerše odborné literatury v databázích PubMed, Scopus za období 2014–2026 s využitím následujících klíčových slov: ("*Mitragyna speciosa*" OR "kratom" OR "mitragynine") AND ("adverse effects" OR "" OR "drug metabolism" OR "toxicity" OR "semisynthetic derivatives"). Kritéria pro zařazení zahrnovala dostupnost úplného textu, informace o farmakologii, bezpečnostním profilu a užívání kratomu. Dále byly využity informace EMA, FDA, WHO, TIS (Toxikologické informační středisko, Praha), Policie ČR, Úřad vlády ČR.

Výsledky a diskuse: Z více než 400 relevantních vědeckých článků vyplývá, že užívání kratomu je spojeno s riziky akutních i dlouhodobých nežádoucích účinků. Jsou popsána úmrtí spojená s užíváním kratomu včetně České republiky. Případové studie přinášejí mimo jiné informace o zhoršení psychiatrických poruch. Kratom užívají miliony lidí, zejména mládež a mladí lidé. Je důležité, aby lékaři, ale i další zdravotnický personál, byli obeznámeni s účinky kratomu a přizpůsobili léčebné a ošetrovatelské přístupy k pacientům vyžadující léčbu. Tvůrci politik by měli omezit dostupnost, aby se předešlo závažným poškozením veřejného zdraví. V České republice byl v r. 2025 kratom zařazen mezi tzv. psychomodulační látky a jeho prodej je regulován.

TARGETING INTRACELLULAR SIGNALING PATHWAYS TO MODULATE PD-L1 EXPRESSION: A PRECLINICAL APPROACH FOR CHECKPOINT INHIBITOR POTENTIATION

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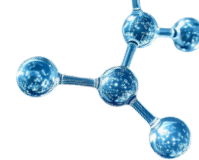
Introduction: The therapeutic success of immune checkpoint blockade is limited by low clinical response rates in certain tumor types and by the development of drug resistance. While anti-PD-L1 checkpoint inhibitor antibodies target PD-L1 on the cell surface, recent insights have shown that intracellular PD-L1 regulation also plays an important role in tumor survival. Thus, understanding the intracellular molecular pathways that regulate PD-L1 metabolism could help identify approaches to further improve the efficacy of checkpoint inhibitors.

Aims: The study evaluates strategies to regulate cancer PD-L1 expression using small-molecule inhibitors that target interfering pathways. These approaches were used to select candidate small-molecule inhibitors that may possibly affect PD-L1 expression in vitro. Additionally, the study focused on using co-culture models to assess whether targeting these intracellular pathways could increase cytotoxic T-cell activity when combined with checkpoint inhibitors.

Methods: An initial selection process was established to categorize and include candidate small-molecule inhibitors into a testing series based on their potential to interfere with PD-L1 regulation pathways in vitro. Furthermore, a functional PBMC-based co-culture model, supplemented with a selected anti-PD-L1 monoclonal antibody, was established to assess the immunomodulatory effects of the most promising substances.

Results and Discussion: In this study, we identified potential signaling pathways that influence PD-L1 expression. Agents targeting these pathways can modulate PD-L1 levels in vitro and, consequently, the resulting immunomodulatory effect of checkpoint inhibitors.

ACKNOWLEDGMENT: This work was supported by the project NW26-03-00542.



PHARMACOGENETICS AND THERAPEUTIC DRUG MONITORING IN PSYCHIATRY: CURRENT STATE AND FUTURE PERSPECTIVES

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Introduction: The considerable variability in treatment response and the occurrence of intolerable adverse drug reactions among psychiatric patients highlight the limitations of the traditional “one-size-fits-all” approach. These challenges have driven increasing interest in personalized psychiatry, with pharmacogenetics (PGx) and therapeutic drug monitoring (TDM) emerging as promising tools for optimizing psychopharmacotherapy.

Aims: To summarize the current evidence, discuss practical aspects of the PGx and TDM implementation into routine psychiatric practice, and outline future perspectives of precision psychiatry while presenting practical experience from Slovakia.

Methods: The presentation is based on the results of several research projects focused on the implementation of PGx and TDM in psychiatric practice. Our work included the use of pharmacogenetic panel testing and targeted PCR-based genotyping, the clinical application of developed LC–MS/MS method for TDM of venlafaxine, vortioxetine, and fluoxetine, the evaluation of the complementary role of PGx (primarily CYP2D6/CYP2C19 genotypes) and TDM in patients treated with venlafaxine, and the assessment of treatment response and adverse drug reactions.

Results and Discussion: PGx and TDM provide complementary information for individualized psychopharmacotherapy, each addressing different determinants of treatment response. Our experience highlights the importance of selecting the appropriate PGx methodology, identifying patients most likely to benefit from testing, and interpreting the findings within the broader clinical context. Although both tools have demonstrated clinical utility, several challenges remain before their widespread implementation.

ACKNOWLEDGEMENT: This project was supported by the EU NextGenerationEU through the Recovery and Resilience Plan for Slovakia under the project No. 09I03-03-V04-00207, APVV-22-0342, and VEGA 1/0707/25.

O6-BENZYLGUANINE TRIGGERS ACTIVATION OF THE ATR-CHK1 AND DNA-PKCS-CHK2 SIGNALING PATHWAYS ASSOCIATED WITH REDUCED PROLIFERATION AND VIABILITY OF HUMAN CANCER CELLS

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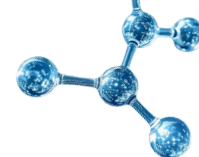
Introduction: Inhibitors of O6-methylguanine-DNA methyltransferase (MGMT) were developed to overcome resistance to alkylating agents (AAs), but their clinical use is limited by severe myelosuppression in combination therapies. We hypothesize that MGMT inhibition leads to the accumulation of endogenous DNA alkylation lesions, thereby reproducing the effects of alkylating agents while suppressing a key resistance mechanism.

Aims: The aim of this study was to investigate the antiproliferative effects of O6-benzylguanine (O6-BG), an MGMT inhibitor, in cancer cells in the absence of alkylating agents.

Methods: Human HepG2 and HeLa cancer cell lines were used for in vitro experiments. Cell proliferation and viability were assessed by CyQUANT and MTT assays, respectively. DNA strand breaks were analyzed using the Comet assay, and proteins involved in DNA damage response (DDR) signaling were examined by Western blotting.

Results and Discussion: O6-BG significantly reduced proliferation and viability of both HeLa and HepG2 cells. The Comet assay revealed double-strand breaks (DSBs) in HeLa cells after 5 days of treatment, whereas no DSBs were detected in HepG2 cells. In HepG2 cells, phosphorylation of ATR (Ser428) and Chk1 (Ser345) was significantly increased, indicating activation of the DDR pathway associated with single-strand breaks, while ATM (Ser1981) and Chk2 (Thr68) remained unchanged; however, inhibition of the ATR-Chk1 pathway significantly increased levels of Chk2 (Thr68). In HeLa cells, phosphorylation of DNA-PKcs (Ser2056), Chk1 (Ser345), and Chk2 (Thr68) was significantly elevated, suggesting activation of DSB-associated DDR signaling. These findings indicate that O6-BG exerts antitumor effects independently of AAs and may represent a promising therapeutic strategy.

ACKNOWLEDGMENT: This work was supported by UK/1070/2026, APVV-23-0399, VEGA 1/0297/26, VEGA 1/0513/24



TOPOBEXIN TARGETS THE TOPOISOMERASE II ATPASE DOMAIN FOR BETA ISOFORM-SELECTIVE INHIBITION AND ANTHRACYCLINE CARDIOPROTECTION

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Introduction: Anti-cancer efficacy of anthracyclines depends mainly on topoisomerase II α (TOP2A), whereas their dose-limiting chronic cardiotoxicity arises from effects on topoisomerase II β (TOP2B) present in cardiomyocytes. This side-effect significantly affects cancer survivorship, especially for pediatric cancer patients. Dexrazoxane mitigates anthracycline cardiotoxicity but inhibits TOP2A as well, motivating the search for cardioprotective agents with genuine TOP2 isoform selectivity.

Aims: Development of novel cardioprotective TOP2 catalytic inhibitors, and to obtain an agent that selectively targets TOP2B while preserving TOP2A-dependent anti-tumor activity.

Methods: A focused panel of compounds was synthesized and screened for protection against daunorubicin-induced injury in neonatal rat cardiomyocytes (NRCM) alongside ATPase and decatenation assays on recombinant human TOP2A and TOP2B. Lead structures were analyzed by X-ray crystallography of TOP2 ATPase domains, complemented by FRAP and RADAR assays in cells, and by a well-established rabbit model of chronic daunorubicin cardiotoxicity to assess in vivo cardioprotection and tolerability.

Results: By screening and rationally optimizing TOP2-targeting scaffolds for cardioprotection, we uncovered the obex pocket in the TOP2 ATPase domain and developed topobexin (first of new obexin class of TOP2 inhibitors) as a TOP2B-selective (25-fold), allosteric catalytic inhibitor that provides robust protection from chronic anthracycline cardiotoxicity while preserving TOP2A-mediated anti-cancer activity. Topobexin, supported by co-crystal structures and in vitro/in vivo characterization, offers both a promise for cardioprotective therapy and a well-defined chemical probe for selectively interrogating TOP2B biology in the topoisomerase field.

TAKING AN EXTREME DOSE OF BETA-BLOCKER WITH SUICIDAL INTENT

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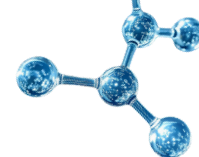
Introduction: A 91-year-old woman was found in her flat with no signs of life. Chemical-toxicological examination showed betaxolol in the blood at a concentration of 19.7 mg/l and ethanol at a concentration of 2.54 g/kg.

Aims: Explain the mechanism of interaction of betaxolol with alcohol and the possible consequence on the death of the above mentioned person.

Methods: Using information from the autopsy report and toxicology report, explain the possible interactions of both substances measured in the blood and, using a pharmacokinetic calculation, approximately to determine the dose of betaxolol that was taken by the above mentioned person.

Results and Discussion: The effects of alcohol alone in severe alcohol intoxication (2.54g/kg) in a 91-year-old occasional drinker could cause significant disorientation, unsteadiness of gait and inability to move independently, a drop in blood pressure and a decrease in consciousness. Alcohol is generally absorbed quickly. The onset of the effect of alcohol could occur in as little as 15–20 minutes, with a significant effect in 30–40 minutes. The effect of betaxolol in a toxic concentration (19.7mg/l) (purely mathematical calculation, 355 tablets of betaxolol 20 mg) could have caused a significant bradycardia, a sharp drop in heart pressure with the risk of sudden collapse. Maximum levels are usually reached within 2–4 hours after ingestion, with a massive dose and combination with alcohol, the clinical effect occurs much earlier. In conclusion, combination of alcohol (2.54 g/kg) and betaxolol (19.7 mg/l) could have caused loss of consciousness, probably within a time frame of approximately 1–2 hours after ingestion, or possibly even earlier. The dose of betaxolol was probably taken 2–6 hours before death.

ACKNOWLEDGMENT: This work was supported by the “Cooperatio” Program, research area Pharmaceutical Sciences.



THE EFFECT OF MEDICAL CANNABIS ON QUALITY OF LIFE IN PATIENTS SUFFERING FROM CHRONIC PAIN

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Introduction: Cannabis is an annual dioecious plant; it was domesticated several thousand years ago, and its therapeutic effects were known to people as far back as ancient civilizations (China, Persia). In recent years, significant progress has been made in the legal use and production of individually prepared medicinal products containing cannabis, leading to the widespread and common use of cannabis for medical purposes. Currently, pain management (regardless of the cause of the pain) is one of the main indications for medical cannabis.

Aims: Based on the above-described progress, we have decided to carry out this pilot study with the aim of assessing (preliminarily determining) the effect of medical cannabis on patients suffering from chronic pain of various origins, particularly in terms of pain intensity and quality of life in these patients.

Methods: The standardized EQ-5D-3L questionnaire (Czech Republic version) was used and administered to patients receiving cannabis treatment at the Centre for Pain Management (St. Anne's University Hospital, Brno). A total of 31 questionnaires were collected. The questions focused on subjective evaluation of overall health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The questionnaires were completed before the start of cannabis treatment and after six weeks of treatment. Patients were given cannabis orally in the form of capsules or via inhalation using a vaporizer.

Results and Discussion: In the subjective assessment of overall health, a clear (albeit non-significant) positive trend was observed, while a statistically highly significant improvement was noted in the assessment of pain intensity. The remaining parameters showed no changes. Thus, the results of this pilot study demonstrated positive effects of medical cannabis at least on pain perception whereas other monitored parameters were not affected significantly.

MULTIDRUG- AND PRE-EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS IN THE SLOVAK AND CZECH REPUBLICS: WHERE DO WE ENCOUNTER LIMITS?

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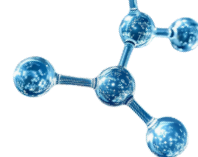
Introduction: Tuberculosis (TB) remains one of the leading infectious diseases worldwide. The emergence of multidrug-resistant (MDR) and pre-extensively drug-resistant (pre-XDR) *Mycobacterium* (M.) tuberculosis strains represents a major challenge for disease control.

Aims: The aim of this study was to evaluate the epidemiological trends of MDR- and pre-XDR-TB in the Czech Republic and Slovakia between 2013 and 2024. Drug resistance and M. tuberculosis lineages were further assessed using whole genome sequencing (WGS).

Methods: National surveillance data on adult MDR- and pre-XDR-TB cases were obtained from the national TB surveillance units, while clinical M. tuberculosis isolates were collected from the National Reference Laboratories for Mycobacteriology in the Czech Republic and Slovakia. Following WGS, genomic data were analysed using the MTBseq bioinformatics pipeline.

Results and Discussion: Overall TB incidence declined in both countries between 2013 and 2024, while MDR-TB cases increased in the Czech Republic but remained low in Slovakia. A total of 98 drug-resistant M. tuberculosis isolates were analysed, including 52 MDR-TB (53.1%) and 36 pre-XDR-TB (36.7%). Lineage 4 predominated among Slovak isolates (26/30, 86.7%), with sublineage 4.7 being the most common (11/30, 36.7%), whereas the Beijing lineage (Lineage 2) predominated among Czech isolates (51/68, 75.0%). The increase in MDR-TB in the Czech Republic was largely associated with cases among Ukrainian citizens after 2022. These findings highlight the role of WGS in rapid diagnostics and control of spread of MDR- and pre-XDR-TB.

ACKNOWLEDGMENT: This work was supported by APVV-22-0342 and VEGA- 1/0049/25.



INDIVIDUÁLNĚ PŘIPRAVOVANÁ LÉČIVA V PEDIATRII

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Pediatrická populace představuje velmi nehomogenní skupinu pacientů, u nichž rychlý růst a vývoj zásadně ovlivňují farmakokinetiku i farmakodynamiku léčiv. Děti nejsou „malí dospělí“, a proto nelze jednoduše extrapolovat dávkování a podávat lékové formy určené dospělým. Kvůli etickým překážkám je v pediatrii také nedostatek klinických studií, což vede k omezené dostupnosti registrovaných hromadně vyráběných léčivých přípravků (HVLP) určených dětem. V praxi se proto často setkáváme s off-label a unlicensed použitím léčiv, které však zvyšuje riziko nežádoucích účinků. Individuálně připravované léčivé přípravky (IPLP) tak hrají klíčovou roli při zajištění vhodné terapie pro dětské pacienty. Umožňují upravit dávku přesně podle věku a hmotnosti dítěte a vytvořit lékovou formu, kterou dítě dokáže bezpečně užít. IPLP jsou nezbytné také u dětí, které mají alergie na běžné pomocné látky, nebo když je potřeba přípravek dochutit. Lékárny mohou připravit i léčiva, která nejsou dostupná v odpovídající síle či formě, nebo zcela chybí na trhu. Přesná struktura preskripce a zásady latinské formulace zajišťují jednoznačnost a bezpečnost přípravy. Přestože legislativa omezuje přípravu IPLP v případech, kdy existuje dostupný HVLP stejné kompozice, zůstává magistraliter příprava nenahraditelným nástrojem dětské farmakoterapie. Umožňuje individualizovat léčbu tak, aby byla pro dítě účinná, bezpečná a dobře tolerovaná.

PODĚKOVÁNÍ: Tato práce byla podpořena projektem IGA_LF_2026_006.

CENTRUM CAATS: SYNERGIE KLINICKÉ MEDICÍNY A FARMAKOLOGIE V PERSONALIZOVANÉ LÉČBĚ DĚTÍ SE VZÁCNÝM ONEMOCNĚNÍM

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Úvod: Pokrok v molekulární diagnostice významně rozšířil možnosti odhalování vzácných onemocnění. Samotné stanovení diagnózy je ale jen prvním krokem při volbě vhodné terapie pro konkrétního pacienta. V oblasti vzácných onemocnění je často nevyhnutelné indikovat léčbu na základě empirie a nikoliv evidence, používat léčiva off-label, případně doporučit účast v klinickém hodnocení. Vyhledávání těchto možností klade na ošetřující lékaře vysoké časové nároky. Právě potřeba překlenout mezeru mezi stanovením diagnózy a přístupem k léčbě vedla ke vzniku Centra pro podporu přístupu k pokročilým terapiím (CAATS).

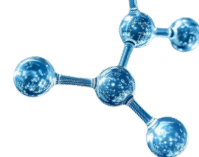
Cíl: Cílem přednášky je představit činnost CAATS jako modelu podpory personalizované medicíny.

Metody: Sdělení vychází ze zkušeností CAATS získaných při spolupráci s Centrem precizní medicíny FN Brno na identifikaci, posouzení a zprostředkování přístupu k inovativním léčebným možnostem u dětí se vzácnými onemocněními.

Výsledky a diskuse: Od zahájení činnosti CAATS konzultovalo 25 případů pacientů se vzácným onemocněním, u nichž nebyly dostupné standardní léčebné možnosti. Ve více než 50 % případů byla identifikována potenciální farmakoterapie, ať už formou off-label podání léčiva, použití neregistrovaného léčivého přípravku nebo pokročilé terapie (ATMP), a ve 20 % případů byla nalezena vhodná klinická studie v zahraničí. Zajištění přístupu k léčbě mimo ČR však zůstávalo na bedrech ošetřujícího lékaře. Proto se CAATS postupně rozhodlo lékařům nabídnout i podporu zprostředkování léčby v zahraničí, vč. pomoci při komunikaci s výzkumnými institucemi a specializovanými centry a při zpracování odborné dokumentace.

Dosavadní zkušenosti ukazují, že činnosti CAATS mohou podpořit ošetřující lékaře a léčbu dětí se vzácnými onemocněními. Model CAATS fungující ve spolupráci s Centrem precizní medicíny FN Brno tak představuje jeden z možných směrů dalšího rozvoje klinické farmakologie v péči o pacienty se vzácnými onemocněními.

PODĚKOVÁNÍ: Vytvořeno v rámci realizace projektu CREATIC financovaného z programu Evropské unie Horizon Europe Coordination and Support Action na základě grantové dohody číslo 101059788.



MOŽNOSTI VYUŽITÍ BIOMARKERŮ MÍRNÉHO POŠKOZENÍ MOZKU – MILD TRAUMA BRAIN INJURY (mTBI) V TOXIKOLOGII

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Úvod: Při vyšetření poškození mozku jsou nyní k dispozici nové, vysoce specifické biomarkery. Jedná se o GFAP (glial fibrillary acidic protein) a UCH-L1 (ubiquitin c-terminal hydrolase L1). V současné době je využití biomarkerů schváleno k vyloučení traumatického poškození mozku, diskutuje se ale další využití v neurologii, sportovní medicíně a v neposlední řadě i v toxikologii.

Cíl: Přednáška je zaměřena na uvedení do problematiky biomarkerů poškození mozku

Metody: klinické vyšetření, analýza modifikujících faktorů, laboratorní vyšetření – core laboratory platform, CT mozku

Výsledky a diskuse: K diagnostice poškození mozku se jako základní metoda již mnoho let používá CT mozku. Referenční metoda je NMR, ta ale pro akutní použití není všeobecně rozšířena. Zejména u mírného traumatického poškození mozku (mTBI) má CT mozku velmi malou výtěžnost a řada pacientů je tak zbytečně vystavena relativně vysoké dávce záření bez terapeutického výstupu. Vyšetření biomarkerů GFAP a UCH-L1 pro svou vysokou negativní prediktivní hodnotu tak vyplnilo mezeru v diagnostice a má ambice eliminovat aspoň část zbytečných CT mozku. To má význam i v situacích, kdy CT mozku nelze z různých důvodů provést. Toto může nastat i některých intoxikací pacienta, která může vyústit v intracerebrální krvácení nebo může toto krvácení zastřít. U intoxikovaných pacientů s úrazem hlavy, kteří jsou nebo byli v bezvědomí, se CT mozku provádí prakticky vždy, protože není jasné, jaký podíl na poruše vědomí má vlastní intoxikace. Také v těchto případech by při splnění kritérií k vyšetření mTBI bylo možné eliminovat některá nadbytečná CT mozku a nebo alespoň konfirmovat negativní výsledek CT vyšetření a neprovádět tak zbytečně druhé kontrolní CT mozku.

Vyšetření biomarkerů GFAP a UCH-L1 je ve světě i v ČR schváleno pro vyloučení mírného traumatického poškození mozku a v řadě států se již běžně používají. Další indikace jsou předmětem dalšího výzkumu. Předpokládáme, že v krátké budoucnosti dojde k většímu rozšíření těchto vyšetření i v ČR, v současnosti čekáme na schválení úhrady od ZP a na schválení guidelines dotčenými odbornými společnostmi.

TERAPEUTICKÉ MONITOROVÁNÍ LÉČIV: OD PLAZMATICKÝCH KONCENTRACÍ KE KLINICKÝM VÝSLEDKŮM

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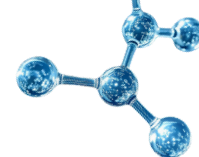
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Terapeutické monitorování léčiv (TDM) představuje nástroj personalizace farmakoterapie založený na stanovení koncentrací léčiv typicky v plazmě a následné individualizaci dávkování. Tradičně je využíváno především u léčiv s úzkým terapeutickým oknem, avšak v posledních letech dochází k významnému rozšíření analytických možností a setkáváme se s jeho použitím i u léčiv, pro která tato charakteristika neplatí. Příkladem mohou být beta-laktamová antibiotika či linezolid.

U antibiotik jsou za surrogáty účinnosti považovány farmakokineticko-farmakodynamické (PK/PD) parametry. Interpretace PK/PD parametrů je však zatížena značnou mírou aproximace. Na úrovni farmakodynamiky se jedná zejména o variabilitu a reprezentativnost hodnot minimální inhibiční koncentrace, na úrovni farmakokinetiky pak o dynamické změny distribučního objemu a clearance v průběhu času, nejviditelnější u kriticky nemocných pacientů, otázky korelace plazmatické koncentrace antibiotika a koncentrace v místě infekce. Stanovení plazmatických koncentrací umožňuje hodnotit pravděpodobnost dosažení terapeutického cíle (PTA, probability of target attainment), která je často používána jako hlavní výstup studií zaměřených na TDM antibiotik.

Zatímco publikací hodnotících PTA u antibiotik s širokým terapeutickým oknem rychle přibývá, data potvrzující přímý dopad TDM na klinické výsledky zůstávají ve srovnání s nimi vzácná. Moderní přístupy a budoucí výzkum by se proto měly zaměřit především na prospektivní studie hodnotící klinický outcome pacientů, což umožní přesněji definovat místo TDM v terapii.

PODĚKOVÁNÍ: Podpořeno ze státního rozpočtu prostřednictvím MŠMT projektem VVI CZECRIN (LM2023049).



EFFECT OF OREXIN SYSTEM MODULATION ON THE INFLAMMATORY RESPONSE

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Introduction: There is a growing body of evidence regarding the involvement of the orexin system in the modulation of the inflammatory response. Drugs that modulate the orexin system have emerged as a new class of treatments for insomnia, and other therapeutic classes are in advanced stages of development for neuropsychiatric indications.

Aims: this study investigated whether orexin agonism or antagonism influences inflammatory responses in vitro and in vivo, with relevance for autoimmune disease.

Methods: PBMCs were stimulated with LPS or TNF and treated with orexin agonists or antagonists. IL-6 and TNF levels were measured using immunoassays and gene expression by qPCR. Pharmacokinetic and pharmacodynamic studies in rats have been conducted to address pharmacokinetics of OXA 17-33 and its impact on adrenocorticotropin (ACTH) and corticosterone levels after i.v., s.c., or i.n. OXA 17-33 or placebo. In the collagen-induced arthritis (CIA) model study, rats were assigned to OXA 17-33, lemborexant, methylprednisolone, placebo, or untreated control groups.

Results and Discussion: OXA 17-33 exerted anti-inflammatory effect on PBMCs from 5 μ M, reducing IL-6 production to $33.4 \pm 12.3\%$ of the LPS control ($P < 0.001$). Pharmacokinetics of OXA 17-33 resembled orexin A, with half-life of 0.48 ± 0.07 h, volume of distribution of 1.84 ± 1.38 L/kg, and clearance of 103.74 ± 45.18 mL/min/kg. OXA 17-33 significantly increased ACTH and corticosterone after i.v. administration (57.6 ± 15.0 pg/mL and 256.6 ± 85.9 ng/mL vs 23.9 ± 10.0 pg/mL and 79.4 ± 39.5 ng/mL; both $P < 0.05$). After s.c. dosing, corticosterone rose significantly, while ACTH showed a nonsignificant trend. In CIA OXA 17-33 produced modest improvements compared to placebo: lower arthritis score (8.6 ± 0.5 vs 12 ± 3.4 ; $P = 0.08$), reduced STAT3 expression in synovia (-0.52 ± 0.16 vs 0.00 ± 0.18 ; $P < 0.05$), and decreased ERK1/2 and pERK1/2.

ACKNOWLEDGMENT: This work was supported by the GAUK project No. 140823 and by the Ministry of Health of Czech Republic projects MH CZ-DRO-VFN64165. DS would like to acknowledge support by The Parc platform (www.theparc.eu).

HEPATOTOXICITY OF TACRINE AND IMPLICATIONS FOR DRUG DISCOVERY

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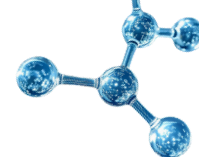
Introduction: Tacrine, used as anti-Alzheimer's disease drug, was withdrawn from clinical use in 2013, mainly due to drug-induced liver injury. The culprit of tacrine-associated hepatotoxicity is believed to be 7-OH-tacrine metabolite, a possible precursor of quinone methide, which binds to intracellular -SH proteins and or/depletes glutathione.

Aims: We aimed to assess the mechanism of tacrine hepatotoxicity and find out if rational structure modifications of tacrine are less prone to quinone methide formation and may hinder the formation of toxic species

Methods: Using incubation with various sources of liver microsomes our newly developed HPLC-MS/MS method, we identified and separated some unpublished tacrine metabolites and biologically evaluated.

Results and Discussion: Tacrine and 7-methoxytacrine are primarily hydroxylated to toxic precursor 7-OH-tacrine, whereas 7-phenoxytacrine formed only a trace amounts and 6-chloro-tacrine did not form it at all. Our results we suggest that 7-OH-tacrine and quinone methide formation is not the mechanism causing tacrine toxicity as previously hypothesized. In addition, via primary human hepatocytes, an alternative toxicity pathway which bring a new insight to further development of tacrine-based compounds was proposed. Finally, one of the 6-chloro-tacrine identified metabolite proved promising acetylcholinesterase inhibition and could therefore be considered as new potentially useful drugs in Alzheimer's disease therapy

ACKNOWLEDGMENT: This work was supported by the grant No GA23-07570S and by the Biomedical Indicators for Personalized Medicine project (BIPOLE), project ID CZ.02.01.01/00/23_021/0008439, co-funded by the European Union.



MERCURY – THE STORY OF A TOXIC ELEMENT

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It began at the end of the 1950s with the story of Minamata disease in Japan, and in this country at the beginning of the 1970s with the Marktredwitz case – the Skalka reservoir near Cheb (our own little Minamata). The principle: inorganic mercury compounds arriving in wastewater from chemical plants were converted by bacteria in the bottom sediment into the most toxic form – methylmercury. This was transferred through the aquatic food chain to fish and subsequently to animals (dancing cat disease) and to humans.

At the beginning of the 1970s, a methodology for the determination of mercury was developed in this country. Its author was Assoc. Prof. Miloš Hejtmánek, CSc., of the University of Chemistry and Technology, Prague, followed by his master's and doctoral student Ing. Jiří Doležal, CSc., who later, together with further colleagues, designed the unique single-purpose AMA 254 analyser for the determination of total mercury content.

The lecture will present cases involving the individual forms of mercury, i.e. metallic mercury and inorganic and organic compounds. A very serious case was addressed at the beginning of the 1980s, namely the toxic effects of phenylmercury. Phenylmercury was used as an excellent fungicide for the treatment of seed grain (1913–1990); surplus treated seed grain was fed to large farm animals, poultry and fish. This resulted in damage to the health of these animals and, above all, in the accumulation of mercury in the food chain. Moreover, seed grain treated with phenylmercury was exported from our country to Iraq, where it was used as bread grain (approximately 300 people died).

The issue of the most toxic form of mercury – methylmercury – remains highly topical, particularly in the aquatic environment. In fish muscle, methylmercury accounts for 80–85 % of the total mercury content. The methylation of mercury in the sediments of aquatic environments depends on a number of factors, especially on oxygen concentration (cf. newly flooded reservoir syndrome). The AWI for methylmercury is 0.3 µg/kg wet weight. At present, on the basis of the results of mercury analysis in the muscle of fish from a given locality, the amount of muscle tissue that may be consumed weekly is established (e.g. perch from the Skalka reservoir 0.5 kg, from the Lipno reservoir 2.5 kg of muscle). Mercury burden in humans and animals can be monitored by analysis of skin derivatives (hair, bristles, etc.).

ANTIFIBROTIC EFFECTS OF KYNURENIC ACID IN RENAL FIBROSIS: MODULATION OF FIBROTIC CROSSTALK AND INVOLVEMENT OF AHR

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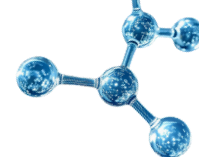
Introduction: Kidney injury activates TGF- β signaling and fibrotic pathway crosstalk, ultimately leading to the development of renal fibrosis (RF). Kynurenic acid (KYNA), an endogenous ligand of the aryl hydrocarbon receptor (AhR), exhibits immunomodulatory properties and may modulate RF progression.

Aims: To investigate the antifibrotic effects of KYNA in vitro and in vivo, and to determine whether these effects are mediated through AhR signaling. A secondary aim was to evaluate the effect of KYNA on fibroblast migration using an in vitro scratch wound (SW) assay.

Methods: Human dermal fibroblasts (HDF) were stimulated with recombinant TGF- β 1 (5 ng/ml) and treated with KYNA (50 or 150 μ mol/l) for 48 h. To investigate AhR involvement, NIH/3T3 fibroblasts were stimulated with TGF- β 1 and treated with KYNA (50 or 150 μ mol/l) with AhR inhibition using CH-223191 (10 μ M), 1 h prior to KYNA exposure. Cellular protein expression was analysed by Western blot. NIH/3T3 fibroblast migration after KYNA treatment (50 or 150 μ mol/l, 48 h) was evaluated by SW assay. The in vivo effect of KYNA was assessed in a rat model of unilateral ureteral obstruction (UUO), where treated rats received KYNA (100 mg/kg/day, p.o.) for 7 days, followed by histological, protein, and RT-qPCR analyses.

Results and Discussion: In vitro, KYNA reduced TGF- β -induced fibrotic signaling in HDF, as demonstrated by decreased phosphorylation of SMAD2, p38, JNK, ERK, accompanied by reduced levels of α -SMA, collagen III and N-cadherin. In NIH/3T3 fibroblasts, AhR inhibition attenuated KYNA effects on pSMAD2 and α -SMA; however, KYNA remained effective in reducing non-canonical TGF- β signaling and collagen expression, suggesting that AhR contributes but is not essential for its antifibrotic activity. KYNA also enhanced fibroblast migration under basal condition. In the UUO model, KYNA reduced fibrotic area, α -SMA-positive areas and tubular dilatation, accompanied by modulation of non-canonical TGF- β pathway and other fibrotic pathways, including JAK/STAT3, Wnt/ β -catenin, and NF- κ B. AhR activation was confirmed by increased Cyp1a1 expression. These results highlight the therapeutic potential of KYNA in renal fibrosis.

ACKNOWLEDGMENT: This work was supported by APVV-23-0399, VEGA 1/0121/2022, VEGA 1/0513/2024.



SERUM-TARGETED VANCOMYCIN DOSING DOES NOT ENSURE CONSISTENT CEREBROSPINAL FLUID EXPOSURE: A POPULATION PHARMACOKINETIC ANALYSIS

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Introduction: Vancomycin is widely used as part of empirical treatment for CNS infections; however, current dosing recommendations are primarily based on systemic PK/PD targets that may not adequately represent drug exposure within the infected CNS. Penetration of vancomycin into cerebrospinal fluid (CSF) is highly variable, and the association between serum and CSF concentrations has not been fully elucidated.

Aims: The objective of this study was to establish a population pharmacokinetic model describing vancomycin disposition in both serum and CSF using real-world TDM data and to evaluate the relationship between systemic and intrathecal exposure.

Methods: This retrospective observational study included 64 adult neurosurgical patients diagnosed with secondary meningitis. A total of 133 serum and 100 CSF vancomycin concentrations were analyzed using nonlinear mixed-effects modeling. Monte Carlo simulations were subsequently applied to investigate drug exposure across different dosing regimens and levels of renal function. Additional simulations were performed under controlled systemic exposure (target serum $AUC_{24} \sim 500$ mg·h/L) while minimizing interindividual variability in clearance to specifically assess variability in CSF exposure.

Results and Discussion: The observed data were best characterized by a two-compartment model representing serum and CSF. Vancomycin clearance was significantly influenced by estimated glomerular filtration rate. The median CSF-to-serum AUC ratio was 0.29, although considerable between-patient variability was observed. Model-based simulations showed that CSF concentrations remained highly heterogeneous despite comparable systemic exposure, yielding a median (5th–95th percentile) average CSF concentration of 6.2 (3.2–10.4) mg/L. Furthermore, the likelihood of attaining progressively higher CSF concentration thresholds decreased substantially as target concentrations increased.

Overall, vancomycin exposure in CSF demonstrated marked interindividual variability that could not be reliably inferred from serum pharmacokinetics, even when systemic exposure was standardized. These findings underscore the limitations of serum-based dosing approaches for CNS infections and emphasize the need for compartment-specific PK/PD targets and dosing strategies.

ACKNOWLEDGMENT: This work was supported by the Ministry of Health of Czech Republic project MH CZ-DRO-VFN64165 and by the Charles University project Cooperatio (research area PHAR).

THE FARNESOID X RECEPTOR (FXR) ANTAGONIST 7B-ISOPROPYLCHENODEOXYCHOLIC ACID IMPROVES GLUCOSE METABOLISM IN MICE ON A WESTERN DIET

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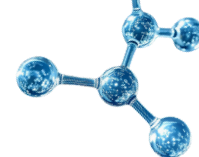
Introduction: Times New Roman 12 The significant roles of the farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5) in regulating metabolic pathways have recently been demonstrated. However, the precise effects of FXR inhibitors on glucose metabolism remain to be elucidated.

Aims: In this study, we examined the impact of 7β-isopropylchenodeoxycholic acid (7β-ipCDCA), a dual FXR antagonist and TGR5 agonist, on impaired glucose metabolism in mice fed a Western diet.

Methods: The dual FXR antagonistic/TGR5 agonistic activity of 7β-ipCDCA was confirmed through gene reporter assays. We evaluated its effects on glucose homeostasis using a glucose tolerance test in C57BL/6 mice fed a Western diet supplemented with sugar in drinking water for 24 weeks. The glucose-lowering mechanism was further investigated by measuring GLP-1 release, mRNA expression of glucose transporters, and relevant genes involved in glucose metabolism in intestinal, hepatic, white adipose, and kidney tissues, and in human NCI-H716 and murine GLUTag L cell lines. Additionally, bile acid metabolome and hepatic lipidome analyses were conducted.

Results and Discussion: Results showed that 7β-ipCDCA improves glucose homeostasis altered by a Western diet in mice via enhanced GLP-1 secretion and decreased expression of glucose transporters in the ileum and kidneys. While its impact on liver function was marginal, 7β-ipCDCA increased plasma taurocholic acid levels. Furthermore, 7β-ipCDCA elevated hepatic triacylglycerols in mice on a chow diet, whereas mice on the Western diet were protected from triacylglycerol accumulation. This study highlights the role of FXR in regulating intestinal glucose transporters and GLP-1 secretion, emphasizing the therapeutic potential of combined FXR antagonists/TGR5 agonists in managing hyperglycemia.

ACKNOWLEDGMENT: The project is funded by the NETPHARM project (ID CZ.02.01.01/00/22-008/0004607), Czech Academy of Sciences institutional support (RVO:61388963). Alzbeta Stefela is grateful for the financial support of the Martina Roeselova Memorial Fellowship granted by the IOCB Foundation.



FROM PHENOTYPE TO GENOTYPE: RESISTANCE OF MYCOBACTERIUM TUBERCULOSIS TO NEW-GENERATION ANTITUBERCULOSIS DRUGS

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Introduction: Multidrug-resistant tuberculosis remains a major global health problem. Although regimens containing pretomanid (PTM) and delamanid (DLM) have improved treatment options, resistance has emerged. It is mainly associated with mutations in genes involved in F420-dependent bioactivation, including *ddn*, *fgd1*, and *fbiA-D*.

Aims: To identify PTM/DLM resistance-associated variants, assess a potential PTM critical concentration from minimum inhibitory concentration (MIC) distribution, determine phylogenetic lineages, and investigate transmission.

Methods: Heat-inactivated *Mycobacterium tuberculosis* isolates (n=86), phenotypically tested for PTM and DLM susceptibility at the National Reference Laboratory for Mycobacteria in Prague, underwent whole-genome sequencing (WGS). Lineages, resistance-associated variants, and genomic clusters were analysed bioinformatically.

Results and Discussion: PTM MICs ranged from >0.007813 to >0.5 mg/L; 23 isolates (26.7%) belonged to the highest category. Growth at 0.5 mg/L and complete inhibition at ≥1 mg/L suggest a critical concentration between 0.5 and 1 mg/L. Beijing 2.2.1 was a predominant sub-lineage significantly associated with MIC >0.5 mg/L (Fisher's exact test, OR = 6.71, p < 0.001). Four isolates carried *ddn* nonsense mutations: Gln58* in three and Trp27* in one. All Gln58* isolates belonged to one genomic cluster, suggesting transmission of a PTM-resistant strain. The *fbiD* deletion (p.Val144fs) and other variants warrant further evaluation as PTM resistance determinants. Overall, WGS is crucial for linking MICs to PTM/DLM resistance determinants.

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MEDICINAL CANNABIS PRODUCTION OF ST. ANNE'S UNIVERSITY HOSPITAL IN BRNO

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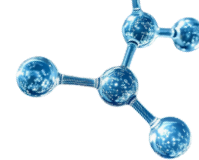
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Introduction: St. Anne's University Hospital in Brno (FNUSA) operates a globally unique facility for medicinal cannabis production. "The hospital's own medicinal cannabis production is supplied to FNUSA's in-house pharmacy, where it is processed into capsules — the form most commonly used by our patients. Part of the surplus production is distributed to pharmacies across the Czech Republic.

Aims: This work aims to describe the standardization and production process of medicinal cannabis at the FNUSA Cannabis Facility, from cultivation to the final product (capsules, ointments), and to present current output, quality assurance, and the facility's educational role.

Methods: Standardization is the cornerstone of production: constant growing conditions are maintained, and all plants share an identical genetic background through propagation of plant explants under sterile in-vitro conditions. Cultivation capacity is approximately 25–30 kg/year, about one third more than patients consume at the hospital pharmacy; this surplus is supplied to pharmacies nationwide. The facility also supports other growers by testing cannabis for hop latent viroid (HLVd), a virus that can devalue an entire crop.

Results and Discussion: A batch with a balanced THC:CBD ratio of 10:10, named "Johann", is currently available and is an ideal starting point once cannabis is prescribed. The next cycle focuses on higher-THC cannabis, for which demand from physicians and patients is high. The facility also plays a key educational role: in June–July it hosted a summer school for four students from Pennsylvania, USA, and two from Canada, reflecting the growing international interest in medicinal cannabis beyond the Faculty of Pharmacy of Masaryk University. Overall, this hospital-based standardized model achieves self-sufficiency, generates a nationwide supply surplus, supports crop-safety research, and serves as an educational platform.



NATURAL BIOACTIVE EXTRACT AND COMPOUNDS ENHANCE THE METHOTREXATE EFFICACY IN EXPERIMENTAL ARTHRITIS

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Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation, oxidative stress and progressive joint destruction. Methotrexate (MTX) belongs to DMARDs. However, MTX long-term use is associated with limited efficacy and adverse effects. Natural bioactive substances studied in adjuvant arthritis (AA) by our group have improved MTX effectiveness by complementary anti-inflammatory and antioxidant activities.

Aim: The aim of this work was to evaluate the therapeutic effects of MTX combined with beetroot extract (REP), β -cryptoxanthin (CRY) and apisimin (API) in AA.

Methods: Arthritis was induced in Lewis rats by incomplete Freund's adjuvant. Animals received MTX alone and in combination with CRY, REP and API. Disease progression was assessed by biometric parameters (change in body weight (CBW), change in hind paw volume (CHPV) and arthritic score (AS)). Different inflammatory markers were analyzed in plasma and tissues. The most important markers as the plasmatic levels of cytokines (IL-1 β , IL-17A), chemokines (MCP-1) and matrix metalloproteinases (MMP-9) were selected to compare the efficacy of the treatments.

Results and Discussion: In the present experiments, CRY + MTX significantly improved biometric parameters and reduced MCP-1 and MMP-9 comparative to AA. API + MTX mainly reduced significantly CHPV in comparison to monotherapy. Further, IL-1 β and MCP-1 showed slight effect when compare to AA. REP + MTX improved AS progression and reduced IL-1 β and MMP-9, however these changes were not statistically significant. All these results are supporting our previous studies with natural compounds, especially in combination with MTX, which speak in favour of using adjuvant therapy with natural substances in RA therapy.

ACKNOWLEDGMENT: VEGA 2/0079/24, VEGA 2/0091/23, VEGA 2/0126/23 and SAIA fellowship of E. Ndjengue Mindang.

NÁKAZA ŠKRKAVKOU MÝVALÍ (BAYLISASCARIS PROCYONIS) – MOŽNOSTI TERAPIE

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Úvodem je třeba zmínit že mýval severní je zvíře, které do evropské přírody nepatří. Ve svém trávicím traktu přenáší velice nebezpečného parazita – mývalí škrkavku (*Baylisascaris procyonis*). Její vajíčka o velikosti pouhých několika desítek mikrometrů jsou obsažena v obrovském množství ve trusu těchto zvířat. Jsou extrémně odolná. V přírodě, ve které přežívají i několik let, je nezničí nízké ani vysoké teploty. Jsou odolná proti běžným desinfekčním prostředkům. K jejich likvidaci slouží vroucí voda nebo žár.

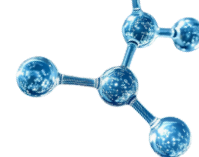
Po vniknutí do těla se z nich líhnou larvy, které jsou schopny cestovat po organismu. Nejčastějším cílem jsou svaly, oči nebo mozek. Mohou tak způsobit ztrátu zraku, nevratné poškození CNS, v krajním případě může infekce končit fatálně. Promořenost mývalů škrkavkami v Evropě je velmi vysoká. Hovoří se o 30 až 90 procentech, závisle na lokalitě.

Tuto škrkavku může ve svém trávicím traktu přenášet i pes, který se s infekcí setkal. Stane se tak producentem obrovského množství vajíček ve svém trusu, podobně jako mýval. Příznaky přitom nemusí být vůbec u zvířete patrné. Naprosto klíčové je v oblastech s přítomností mývalů časté pravidelné odčervování psů.

Jako základní prevence je nutné dodržování základních hygienických pravidel ohledně důkladného omytí všech plodin pěstovaných v místech výskytu mývala severního.

Z hlediska farmakoterapie je preferovaným lékem volby albendazol, který brání larvám v dalším růstu a množení. Často se podává preventivně i v případě pouhého podezření na požití kontaminované půdy nebo trusu. Současně s albendazolem (zejména u neurologických forem) se podávají kortikosteroidy pro zmírnění zánětlivé reakce organismu na pohybující se nebo odumírající larvy. Mezi alternativní léky (v případě okamžité nedostupnosti albendazolu) patří mebendazol nebo ivermektin, které mají být podávány pouze krátkodobě do doby možnosti podání albendazolu.

PODĚKOVÁNÍ: Tato práce byla podpořena vnitřním grantem Univerzity Palackého IGA_LF_2026_006.



Ah RECEPTOR AND ITS POTENTIAL ROLE(S) IN LIPID METABOLISM

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Introduction: Cancer development leads to significant alterations of cellular metabolism, including deregulation of fatty acid (FA), phospholipid and sphingolipid (SL), as well as glycosphingolipid (GSL) metabolism. The aryl hydrocarbon receptor (AhR) is a transcription factor, primarily known as xenobiotic sensor, that is often overexpressed in tumour cells. Potential links between the AhR and lipid metabolism deserve more attention.

Aims: We studied the functional role of AhR, which we found to be upregulated in tumour cells derived from colorectal carcinoma (CRC), in control of FA, SL and GSL metabolism, using a panel of CRC cell lines and their respective AhR knockout (AhR KO) variants, or, cells treated with AhR ligand(s).

Results and Discussion: AhR KO decreased cell proliferation rate, altered cell cycle progression, reduced ATP production, and it decreased mRNA levels of key enzymes of FA-biosynthetic pathway in AhR KO CRC cells, in particular of stearoyl-CoA desaturase 1 (SCD1), reduced activity of components of the PI3K/Akt pathway, which controls lipid metabolism, and reduced expression of lipogenic transcriptional regulator(s). AhR activation further led to a cell type-dependent upregulation of SLs, accompanied by increased expression of genes encoding serine palmitoyltransferase complex components. Ceramide levels remained largely unchanged, whereas sphingosine-1-phosphate (S1P) and S1P synthase SPHK2 were elevated, with implications for pro-survival signalling, while overall GSL changes were limited. Several SL/GSL metabolism genes (SPHK1, SPHK2, ST3GAL5) emerged as potential AhR-regulated targets. Overall, our findings highlight FA and SL metabolism as a possible target of toxic environmental ligands of AhR, which may impact cell proliferation and survival in a cell context-dependent manner.

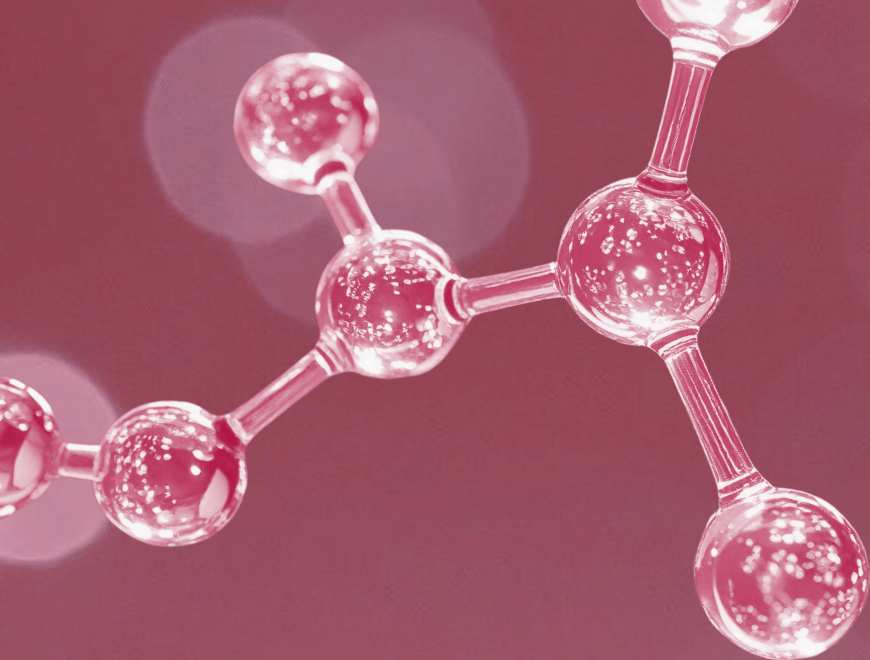
ACKNOWLEDGMENT: This work was supported by the Czech Science Foundation, project No. 24-10086S and the Czech Ministry of Health, project No. NU21-03-00421.

**POUŽITÍ CÍLENÉ SYNTETICKÉ LÉČBY V REVMATOLOGII – ÚČINNOST, BEZPEČNOST
A LÉKOVÉ INTERAKCE****Jan Voříšek¹, David Suchý¹**

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Inhibitory JAK jsou skupinou malých molekul, které působí na stejnou skupinu kináz, ale každá z nich se liší svou chemickou strukturou a farmakologickými vlastnostmi. Cílená terapie malými molekulami, která inhibuje proteiny Janusovy kinázy (JAK), je účinná možnost léčby autoimunitních a revmatických onemocnění, zejména u revmatoidní artritidy, spondyloartritidy, psoriázy, atopické dermatitidy či zánětlivých střevních onemocnění. Využití jednotlivých JAK závisí na jejich selektivních interakcích s konkrétními cytokinovými receptory. JAK inhibitory jsou narůstající skupinou cílených syntetických chorobu modifikujících léků (tsDMARD).

V současnosti jsou v České republice k dispozici čtyři JAK inhibitory (tofacitinib, baricitinib, upadacitinib, filgotinib) pro léčbu revmatoidní artritidy (RA). Část z nich je registrovaná i v dalších revmatologických indikacích. Selektivita k jednotlivým JAK definuje vlastnosti JAK inhibitoru jak účinnost, tak potenciální nežádoucí účinky. Bezpečnost JAK inhibitorů je do jisté míry srovnatelná s bDMARD, nicméně jsou zde určité rozdíly ve vyšším výskytu infekce herpes zoster, kardiovaskulárních onemocnění, tromboembolických příhod, dyslipidemie a dalších laboratorních abnormalit.



POSTER PRESENTATIONS

THE ROLE OF 5-HT_{2A} RECEPTORS IN SLEEP ARCHITECTURE AND MEMORY CONSOLIDATION IN AN ANIMAL MODEL

Kristýna Aleksić¹, Lucie Ladislavová¹, Klára Šíchová¹, Eva Lhotková¹, Čestmír Vejmla^{1,2},
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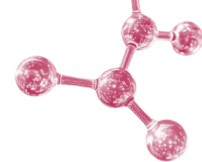
Introduction: Sleep plays a crucial role in cognitive functioning and memory consolidation. Psilocybin, a serotonergic psychedelic with high affinity for 5-HT_{2A} receptors, has attracted considerable attention because of its therapeutic potential in psychiatric disorders. However, the contribution of 5-HT_{2A} receptors to sleep regulation and sleep-dependent memory consolidation remains insufficiently understood.

Aims: To investigate the effects of psilocybin, the selective 5-HT_{2A} receptor antagonist MDL100907, and sleep deprivation on sleep architecture and hippocampus-dependent memory in rats.

Methods: Adult male Long-Evans rats were implanted with EEG/EMG telemetry devices. Animals received psilocybin (5 mg/kg), MDL100907 (0.5 mg/kg), their combination, or saline, followed by normal sleep or 8 h sleep deprivation. Sleep was recorded for 24 h. Memory consolidation was evaluated using the Object-Place Recognition and Morris Water Maze tests.

Results and Discussion: Psilocybin significantly increased wakefulness and reduced REM sleep by prolonging REM onset latency and decreasing REM duration, while NREM sleep was largely unaffected. Sleep deprivation effectively reduced both REM and NREM sleep. Neither psilocybin nor MDL100907 significantly influenced memory performance in either behavioural task. These findings suggest that acute modulation of 5-HT_{2A}-related signalling selectively affects REM sleep without producing measurable short-term changes in hippocampus-dependent memory consolidation. The results contribute to understanding the role of serotonergic signalling in sleep regulation and may be relevant for the therapeutic application of psychedelics.

ACKNOWLEDGMENT: This work was supported by the Czech Health Research Council (NU21-04-00307 and NW24-04-00413), the Czech Science Foundation (20-25349S and 23-07578K), the Ministry of the Interior of the Czech Republic (VK01010212), the Horizon Europe PsyPal project (Grant No. 101137378), the Charles University Cooperatio Neurosciences programme, and the Psychedelic Research Foundation (PSYRES).



EVALUATION OF THE ANTI-INFLAMMATORY ACTIVITY OF A PRENYLATED ISOQUERCITRIN IN A MODEL OF PAW EDEMA IN LABORATORY MICE

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Introduction: Prenylated phenolic compounds are promising group of natural substances with diverse biological activities, including antioxidant and anti-inflammatory effects. These findings provide a basis for further research. In this study, novel synthetic prenylated flavonoid was investigated.

Aims: The present study focuses on the first in vivo evaluation of the anti-inflammatory potential of selected 8-prenylisoquercitrin.

Methods: The anti-inflammatory activity was evaluated using a carrageenan-induced plantar edema model in ICR mice. Forty male mice were randomly assigned into four groups receiving 8-prenylisoquercitrin in two doses 2 mg/kg and 4 mg/kg, indomethacin 5 mg/kg as reference and vehicle by oral probe. Edema was induced by intraplantar injection of 0.1 ml of 1% carrageenan and paw volume was measured plethysmometrically at 0, 30, 60, 120, 240 and 360 min.

Results and Discussion: Both concentrations of prenylisoquercitrin reduced edema compared to the control group. The higher concentration (4 mg/kg) showed an effect at 60, 120 and 240 min, while the lower concentration (2 mg/kg) was more effective at later time points. At 240 min, prenylisoquercitrin 2 mg caused a statistically significant reduction of edema. These results suggest dose-dependent differences in the time course of the effect. Plethysmometric results were complemented by histological evaluation.

ACKNOWLEDGMENT: Role of prenylation and glycosylation patterns in anti inflammatory activity and metabolism of natural phenolic compounds (GA23-04655S).

DIFFERENCES IN PHYTOEXTRACTION EFFICIENCY AND STRESS TOLERANCE OF PLANTS EXPOSED TO PHARMACEUTICALS

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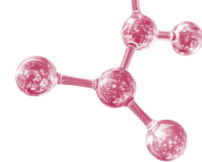
Introduction: Consumption of anti-inflammatory and psychotropic drugs is growing worldwide, while wastewater treatment plants cannot eliminate these diverse compounds, so their effluents remain a major source of pharmaceuticals in aquatic ecosystems.

Aims: To assess the suitability of maize for phytoremediation of pharmaceuticals of buspirone (B), dextromethorphan (D), ibuprofen (I), paroxetine (P), sulpiride (S) and the I+D combination, in terms of phytoextraction efficiency, oxidative stress, biotransformation enzymes and heat-shock proteins (HSP) as stress biomarkers.

Methods: Sterile-grown maize was grown hydroponically and exposed to 5 mg L⁻¹ of drugs for seven days. Drug content in the medium, leaves and roots was followed by HPLC-UV and LC-MS (Q-TOF); phytoextraction, translocation and bioaccumulation factors were calculated. NADPH-oxidase, superoxide dismutase (SOD), ascorbate-glutathione cycle enzymes were assayed spectrophotometrically and after native PAGE; HSP70 and HSP90 immunochemically.

Results and Discussion: I was extracted most efficiently and showed, with B, the highest translocation to shoots; hydrophilic S was absorbed least and P stayed in roots. S triggered the strongest response: higher NADPH-oxidase and root SOD activity. All drugs elevated HSP70 and HSP90, supporting their use as stress biomarkers, and GST activity rose up to fivefold after B and S. I+D acted synergistically on peroxidases, GST and HSP90, i.e. mixtures may be a greater threat than single drugs. Uptake of B, D and S by plants is reported for the first time. Maize combines efficient uptake with high stress tolerance, supporting its use in phytoremediation.

ACKNOWLEDGMENT: This project, SQ01020132, was funded in part by the Technology Agency of the Czech Republic as part of the program to support applied research and innovation in the fields of the environment, climate protection, and sustainable development—Environment for Life 2.



THROUGH THE LOOKING GLASS: D-AMINO ACIDS IN PSYCHIATRIC DISORDERS

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D-amino acids (D-AAs) were long deemed unnatural, and their presence in mammalian systems was overlooked for decades. However, recent analytical breakthroughs have dismantled this homochiral dogma, revealing D-AAs as an important class of signaling molecules. D-AAs (e.g., D-serine and D-aspartate) act as essential endogenous regulators of the central nervous system and are now recognized as key modulators of N-methyl-D-aspartate receptors (NMDARs), which play a complex role in neuronal function and are fundamental to synaptic plasticity and neurodevelopment. Furthermore, alterations in D-AA metabolism and levels appear to be associated with the onset and progression of some psychiatric disorders.

These findings have positioned D-AA signaling pathways as promising pharmacological targets; therapeutic approaches aimed at modulating D-AA homeostasis are being explored to restore NMDAR function, particularly in schizophrenia and other disorders characterized by glutamatergic system dysregulation. Since the DAAs represent less than 1 % of the total amino acid content, a highly sensitive, precise and accurate analytical platform is crucial for understanding the role of D-AAs in the neurobiology of psychiatric disorders and may facilitate translational research by enabling the identification of pharmacodynamic biomarkers and improving the evaluation of emerging therapies targeting D-AA metabolism.

Crucially, our research group seeks to address a knowledge and methodological gap by applying this platform to establish dynamic temporal trajectories. By moving beyond static measurements toward longitudinal profiling, this ongoing work aims to evaluate D-AAs as predictive biomarkers of disease progression and clinical relapse in selected neuropsychiatric disorders (schizophrenia, major depressive disorder, bipolar disorder), ultimately supporting the development of therapeutic strategies targeting D-AA pathways.

KVANTIFIKACE EMISÍ CO₂ KLINICKÉ STUDIE COL-ECMO2022: RETROSPEKTIVNÍ ANALÝZA

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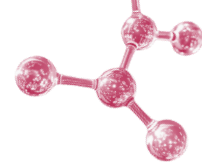
Úvod: Klinická hodnocení se podílejí na produkci CO₂ a tím přispívají ke globálnímu oteplování.

Cíl: Cílem této práce je zhodnocení celkových emisí CO₂ klinické studie COL-ECMO2022 a analýza podílu jednotlivých složek.

Metodika: Pro analýzu byla zvolena klinická studie COL-ECMO2022 – prospektivní, investigátorem iniciovaná, farmakokinetická, nerandomizovaná, otevřená, monocentrická studie fáze IV realizovaná v České republice po dobu 17 měsíců. Do studie bylo zařazeno 18 pacientů. Kalkulace jejích emisí CO₂ byla provedena pomocí Clinical Trial Carbon Calculator. Jedná se o retrospektivní analýzu.

Výsledky a diskuse: Uhlíková stopa studie byla odhadnuta celkově na 5520 kg CO₂, neboli 307 kg CO₂ na účastníka. Největší podíl (89 %) byl asociován s činnostmi a dopravou studijního týmu. Druhou nejvýznamnější položkou byla analýza vzorků a materiál. Příspěvky jsou nicméně odhadem, nikoli výsledkem jednoznačně dokumentovaných činností. Tyto výsledky se shodují s dříve publikovanými daty, přestože odlišností studie je zařazování hospitalizovaných pacientů a fakt, že použité léčivo nemělo charakter studijní medikace. Rovněž přípravná fáze a fáze po ukončení studie nebyla do výpočtu zahrnuta. Silnou stránkou je znalost pozadí realizace této klinické studie. Podobná analýza je důležitým krokem pro designování klinických studií budoucnosti.

PODĚKOVÁNÍ: Tato práce byla podpořena projektem Erasmus+ GREEN-TRIALS (2025-1-CZ01-KA220-HED-000355652) a ze státního rozpočtu prostřednictvím MŠMT projektem VVI CZECRIN (LM2023049).



ABNORMAL BREATHING PATTERN ASSOCIATED WITH CRYING AS THE FIRST MANIFESTATION OF A RARE CAUSE OF UPPER AIRWAY OBSTRUCTION IN THE NEWBORN

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Introduction: Epignathus is a rare teratoma of the oropharynx, that arises from the palate and, in most cases, results in death. This tumour is considered benign but life-threatening because of high risk of airway obstruction, which is the cause of death in 80-100% of the cases at the time of delivery.

Aims: To present the patient who was the 2nd child from 2nd pregnancy. Delivery was spontaneous in cephalic position (Apgar score: 8/9/10 points; birth weight: 2950 grams; birth length: 50 cm). Amniotic fluid with optimal volume was clear, GBS was negative. She was discharged from hospital home on the 3rd day of life. On 7th day of age she had clinical signs of severe dyspnoea. According to the mother, she had "strange" breathing since birth with sternum retraction when crying, she turned blue once, she cooed when drinking. She was admitted at the age of 7 days the Neonatal Department of Intensive Medicine due to development of the respiratory insufficiency for the purpose of specialized diagnostics and therapy.

Methods: Physical examination of the oral cavity after pressing on the root of the tongue revealed the spherical whitish-yellow resistance. Magnetic resonance imaging of the neck detected a soft-tissue pedunculated lipomatous lesion in the nasopharynx – oropharynx region with involvement in the supraglottic area paramedial on the left side with partial airway obstruction. An adequate flow signal of the displayed arterial structures, without demonstrable arterial supply structure to the lesion was confirmed in the Magnetic resonance angiography image. Surgery was performed on 13th day of age.

Results and Discussion: Histological examination confirmed diagnosis of epignathus. Prenatal detection of the lesion (sonography, magnetic resonance imaging) is most important. If undetected prenatally, postnatal manifestation depends on size, location and rate of growth of epignathus. Early detection and multidisciplinary cooperation are able to minimize the spectrum of complications in newborn.

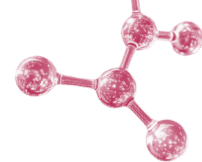
ACKNOWLEDGMENT: This work was supported by the Ministry of Education, VEGA No. 2/0133/23.

STUDIUM INTERAKCE VYBRANÝCH SEMISYNTETICKÝCH KANABINOIDŮ S CYP2C9
IN VITRO

Matyáš Crhák

Abstract not submitted.

Abstrakt nedodán.



ATMP V KLINICKÉ PRAXI V ČESKÉ REPUBLICE

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Úvod: Léčivé přípravky pro moderní terapii (Advanced therapy medicinal products, ATMP) zásadně mění paradigma současné medicíny. Umožňují převést léčbu některých vzácných, geneticky podmíněných či život ohrožujících onemocnění z dlouhodobé symptomatické péče na potenciálně kurativní jednorázový terapeutický zásah. Jsou jedním z pilířů personalizované medicíny.

Cíle: Cílem práce je představit skupinu ATMP a poskytnout aktuální přehled těchto přípravků podávaných pacientům v České republice (ČR).

Metody: Práce vychází z analýzy dat a přehledů Evropské lékové agentury, Státního ústavu pro kontrolu léčiv (SÚKL), odborné literatury a platné legislativy ČR k 30. červnu 2026.

Výsledky a diskuze: ATMP zahrnují přípravky pro genovou terapii, somatobuněčnou terapii, produkty tkáňového inženýrství a kombinované ATMP se zdravotnickým prostředkem. Vedle vzácných vrozených vad nacházejí uplatnění v hematoonkologii, v terapii solidních nádorů, v imunologii nebo regenerativní medicíně. V Evropské unii je v současnosti registrováno 23 ATMP, z nichž pouze devět je reálně dostupných pacientům v ČR. Ošetřující lékař může rovněž za specifických podmínek předepsat ATMP neregistrované. Nově je v ČR k dispozici jeden ATMP v režimu tzv. nemocniční výjimky, kterou povolil SÚKL v březnu tohoto roku. Tento přípravek je vyvíjen a vyráběn v Centru excelence CREATIC při Lékařské fakultě Masarykovy univerzity. Strategický význam má podpora národní akademické či nemocniční produkce ATMP, která umožňuje flexibilní vývoj a výrobu terapií na míru konkrétním pacientům a může přispět ke zvýšení dostupnosti nejmodernější léčby. Právě posílení institutu nemocniční výjimky a její integrace do systému úhrad představuje významný krok pro rozvoj ATMP, personalizované medicíny i dlouhodobou udržitelnost celého systému.

PODĚKOVÁNÍ: Tato práce byla vytvořena v rámci realizace projektu CREATIC, financovaného z programu Evropské unie Horizon Europe Coordination and Support Action na základě grantové dohody číslo 101059788.

EFFECTS OF HIGH-FAT-FRUCTOSE DIET AND FERULIC ACID TREATMENT ON LOCOMOTOR ACTIVITY AND RECOGNITION MEMORY IN HYPERTRIGLYCERIDEMIC RATS

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Introduction: Metabolic syndrome (MetS) is a known risk factor for cognitive decline. There is growing interest in using natural compounds to treat various diseases. We previously showed that, in an animal model of MetS, hypertriglyceridemic (HTG) rats fed a high-fat-fructose diet (HFFD) and treated with rutin exhibited improved learning performance in the Morris water maze compared with untreated rats [1].

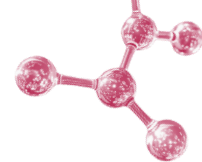
Aims: In the present study, we evaluated the effects of ferulic acid (FA), a potent phenolic antioxidant, on locomotor activity and recognition memory in HTG rats fed either a standard diet (SD) or HFFD.

Methods: The open field (OF) test was used to assess spontaneous locomotor activity and anxiety-like behavior, and the novel object recognition (NOR) test was used to evaluate recognition memory. Young male HTG rats (n = 32; 4–5 weeks old) were fed either SD or HFFD for 5 weeks and treated with FA provided in pellets (approximately 70 mg/kg body weight).

Results and Discussion: Contrary to our hypothesis, HFFD-fed rats showed a significantly higher discrimination ratio and greater preference for the zone containing the novel object in the NOR test compared with SD-fed rats, suggesting that HFFD did not impair recognition memory under the present experimental conditions. Fewer entries into the familiar-object zone accompanied the increase in the discrimination ratio, while exploration of the novel-object zone remained unchanged. Additionally, HFFD alone increased the exploration ratio compared with SD, indicating altered exploratory behavior toward novel stimuli. The absence of significant differences in OF parameters suggests that these changes were not related to altered locomotor activity. Treatment with FA did not affect NOR discrimination performance or OF parameters. In conclusion, our findings suggest that a five-week HFFD altered novelty-related exploratory behavior without producing measurable impairment in recognition memory, and FA did not significantly affect behavioral performance in young HTG rats.

Reference: [1] Micháliková et al. *Saudi Pharm J.*, 2019, 27: 1196-1202.

ACKNOWLEDGMENT: The work was supported by the project VEGA 2/0018/23.



ATORVASTATIN'S IMPACT ON AUTOLOGOUS BONE MARROW CELL THERAPY AND CARDIAC REMODELLING

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Introduction: Atorvastatin exhibits potent pleiotropic properties that modulate the PI3K/Akt and IGF/Akt signalling pathways, which are essential for enhancing stem cell survival and guiding tissue adaptation within hostile, ischemic environments.

Aim: The objective of this study was to evaluate the effects of atorvastatin at the cellular and organismal levels by analysing its clinical efficacy in critical limb ischemia and in human cardiac fibroblasts.

Methods: The clinical study evaluated the impact of atorvastatin on six-month therapeutic efficacy, tissue oxygenation, and pain reduction after autologous bone marrow cell transplantation. The in vitro model utilised primary human cardiac fibroblasts treated with atorvastatin to evaluate cell viability, mesenchymal identity, and the relative expression of fibrosis-related transcription factors and microRNAs via immunofluorescence and qRT-PCR.

Results: Patients taking atorvastatin before bone marrow cell therapy had significantly higher concentrations of mononuclear cells in their transplant, leading to improved tissue oxygenation ($TcPO_2$) and reduced pain. In vitro analysis revealed that atorvastatin directly attenuates fibroblast activation by significantly downregulating the myofibroblast marker α -SMA and transcription factors GATA4/MEF2C, and anti-fibrotic microRNAs (miR-24, miR-26a, miR-133a).

Conclusion: Our findings demonstrate a direct link between laboratory and clinical outcomes, showing that the molecular pathways through which atorvastatin prevents pathological cellular remodelling in fibroblasts translate into tangible therapeutic benefits and pain relief for ischemic patients.

ACKNOWLEDGMENT: This work was supported by NFP401101C023, APVV 023-0557 and VEGA 1/0523/25.

Keywords: Atorvastatin; Autologous cell therapy; Critical limb ischemia; Human cardiac fibroblasts; MicroRNA; Pleiotropy

MIRTAZAPINE IN AN INNOVATIVE DOSAGE FORM AND ITS EFFECT ON THE METABOLISM OF LABORATORY RAT

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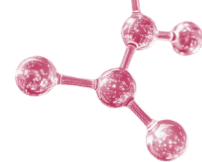
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Introduction: Mirtazapine is an effective and widely used antidepressant with typical side effects such as sedation or increased appetite leading to weight gain. Like many other psychopharmaceuticals, one of the challenges of therapy is adherence to treatment. One way to improve adherence is through the development of sustained-release formulations. They offer controlled drug release, stable therapeutic plasma levels, and significantly improved patient adherence. In preclinical setting, prolonged dosing interval can also minimize handling-induced stress, supporting 3Rs principles.

Aims: The aim of the study was to prepare mirtazapine-loaded PLGA microparticle delivery system for parenteral administration and evaluate pharmacokinetics, metabolic effects, and safety to determine impact of the drug delivery systems and mirtazapine in in vivo model.

Methods: Drug-containing microparticles were prepared by the o/w solvent evaporation method using PLGA polymer. The experiment was conducted on male Sprague-Dawley laboratory rats. The test groups received intramuscular injections of a prepared mirtazapine formulation at a dose of 10 mg/kg/day for 2, 4, or 6 weeks. Body weight and food intake were monitored regularly. At the end of the experiment, serum samples were collected for the analysis of biochemical parameters (lipid profile, glucose) and the determination of adipokine levels (leptin, resistin, adiponectin) using the ELISA method.

Results and Discussion: We observed significant alterations in lipid and glucose levels and statistically nonsignificant modifications in adipokine levels during the 6-week treatment period. This occurred without significant changes in body weight, fat mass, or food intake. The newly developed sustained-release formulation of mirtazapine represents a promising direction; however, our results also underscore the need to monitor metabolic parameters even in individuals without visible weight gain.



AMS GUIDE: A NON-COMMERCIAL POINT-OF-CARE PLATFORM SUPPORTING ANTIMICROBIAL STEWARDSHIP

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Introduction: Antimicrobial prescribing in hospital and intensive care settings requires clinicians to integrate local guidelines, antimicrobial drug information, renal dose adjustment, therapeutic drug monitoring, microbiological procedures, local epidemiology, and stewardship principles. Although these resources are clinically valuable, they are often dispersed across documents, information systems, and professional sources, limiting their immediate usability at the point of care. AMS Guide was developed as a non-commercial, locally adaptable digital platform intended to translate fragmented antimicrobial recommendations into structured bedside decision support.

Aims: The aim was to develop and pilot implement AMS Guide as a modular mobile and web-based point-of-care tool supporting antimicrobial stewardship, and to describe its technical-clinical architecture, governance principles, safety model, and early platform-level use.

Methods: AMS Guide was developed in a tertiary hospital environment with input from physicians and clinical pharmacists. The platform integrates diagnostic stewardship, empirical antimicrobial therapy, antimicrobial drug information, kidney function-based dosing, therapeutic drug monitoring, de-escalation, treatment duration, antifungal stewardship, and access to local epidemiological data. It was implemented as a web application and Android application package without integration into the hospital information system and without processing patient data. Usage was evaluated using anonymized, aggregated Firebase Analytics data covering a 60-day period from 1 April to 30 May 2026. Web and Android data were analyzed separately.

Results and Discussion: AMS Guide was successfully implemented as a low-barrier digital platform accessible via web and mobile interfaces. During the 60-day observation period, the web version recorded 4186 screen/page views and 582 initiated sessions, whereas the Android application package recorded 1817 screen views and 169 initiated sessions. The web version represented the primary channel of early platform-level use. Views per initiated session were 7.2 for the web version and 10.8 for the Android application package, suggesting active navigation across multiple screens during individual sessions. Core antibacterial support modules accounted for approximately half of all views on both platforms. Engagement-time metrics were consistent with brief, targeted use, with median average engagement time per session of 36.1 s for the web version and 61.6 s for the Android application package. These findings support interpretation of AMS Guide as an on-demand point-of-care decision-support resource rather than a continuously used electronic prescribing system. Further evaluation should assess usability, workflow integration, and effects on antimicrobial care process indicators.

ACKNOWLEDGMENT: This work was supported by the Specific University Research Grant of the Faculty of Medicine, Masaryk University, grant number MUNI/A/1815/2025, and by University Hospital Brno through the Ministry of Health of the Czech Republic – RVO (FNBr, 65269705).

TOXIC PSYCHOSIS IN CLINICAL PRACTICE: EPIDEMIOLOGY AND PHARMACOTHERAPEUTIC MANAGEMENT

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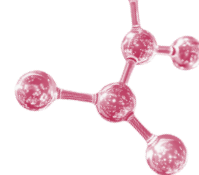
Introduction: Toxic psychosis, also called substance-induced psychosis, represents severe psychiatric conditions triggered by psychoactive substance use. Management is challenging and often requires rapid pharmacological intervention.

Aims: To characterize the epidemiology, clinical presentation, and pharmacotherapeutic management of patients admitted with substance-induced psychosis in routine clinical practice.

Methods: A retrospective observational study included patients hospitalized for ICD-10 diagnoses due to psychoactive substance use: F1x.5 Psychotic disorder and F1x.7 Residual and late-onset psychotic disorder at the Department of Psychiatry, University Hospital Brno, between 2020 and 2025. Demographic characteristics, causative substances, psychiatric comorbidities, hospitalization parameters, pharmacotherapy and adverse effects, and treatment modifications were analyzed in a subcohort of admissions from 2023 to 2025.

Results and Discussion: In 86 patients across 96 hospitalizations, males represented 71% of the cohort, with a median age of 25.5 years. High psychiatric comorbidity and heredity were present. Psychosis related to use of cannabinoids was the most common diagnosis, followed by psychosis associated with polysubstance use, predominantly involving methamphetamine. The median hospitalization duration was 16 days. Initial treatment most frequently consisted of a combination of an atypical antipsychotic and a benzodiazepine; treatment modification was indicated in the majority of cases. At discharge, antipsychotic monotherapy became the leading strategy, while benzodiazepine use markedly declined. Risperidone was the most common discharge antipsychotic. Adverse drug reactions occurred in 32% hospitalizations. Relapse was noted in ten admissions.

Toxic psychosis, most frequently associated with cannabinoids, requires acute management commonly combining antipsychotic–benzodiazepine therapy, whereas long-term stabilization favors atypical antipsychotic monotherapy. The increasing incidence parallels the growing prevalence and potency of recreational drugs. Close integration of psychiatric care and addiction services is essential to optimize outcomes and reduce the risk of relapse and progression to chronic psychotic disorders.



NEUROPLASTIC EFFECTS OF TRYPTAMINE ALKALOIDS FROM PSILOCYBE SPP. IN PRIMARY NEURONAL CULTURES

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Introduction: Psychedelics are promising therapeutic agents because of their rapid effects on brain plasticity. While psilocybin has been extensively studied, little is known about related tryptamine alkaloids naturally occurring in *Psilocybe* mushrooms and their potential neuroplastic effects.

Aims: To evaluate the acute effects of selected tryptamine alkaloids, alone and in combination with the monoamine oxidase inhibitor harmine, on molecular markers of neuronal activity and synaptic plasticity in primary neuronal cultures.

Methods: Primary cortical neurons isolated from embryonic rats were cultured for 21 days in vitro and exposed for 1 hour to 10 μ M psilocybin, psilocin, baeocystin, norbaeocystin, norpsilocin or aeruginascin, with or without harmine pretreatment. Gene expression (ARC, BDNF, PSD-95, Syn1, Syn2), protein expression (PSD-95, synaptophysin, gephyrin, BDNF) and synaptic organization were evaluated using qPCR, Western blot and immunocytochemistry.

Results and Discussion: One-hour exposure did not increase neuroplasticity markers in any experimental approach. Baeocystin and norbaeocystin significantly reduced synaptophysin protein levels, while qPCR indicated a trend toward decreased expression of activity-dependent and synaptic markers. Immunocytochemistry revealed significant changes in PSD-95 puncta density between treatment groups. Overall, the findings suggest that acute exposure induces transient suppression rather than activation of neuroplastic processes, indicating that longer exposure periods may be required to detect plasticity-related effects.

ACKNOWLEDGMENT: This work was supported by the Ministry of Education, Youth and Sports of the Czech Republic (project From Magic to Medicines Using Psychoactive Mushrooms, LUAIZ24146) and by the Ministry of the Interior of the Czech Republic (project VK01010212).

PHARMACOKINETICS, SYSTEMIC TOXICITY, AND ACUTE BEHAVIORAL EFFECTS OF PHENETHYLAMINE DERIVATIVE 25E-NBOH IN RATS

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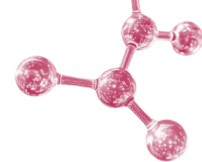
Introduction: 25E-NBOH is an ultrapotent and highly efficacious agonist of serotonin 5-HT_{2A} and 5-HT_{2C} receptors. Originally synthesized for research purposes, it may emerge on the illicit drug market as an alternative to traditional psychedelics, similarly to related N-benzyl phenethylamine derivatives. However, information regarding its systemic toxicity and acute behavioral effects remains limited. The present study therefore investigated the acute toxicity and behavioral effects of subcutaneously administered 25E-NBOH in Wistar rats.

Methods: Systemic toxicity of 25E-NBOH was evaluated using the acute toxicity test according to OECD Guideline 423. Locomotor activity and psychomimetic-like behavioral effects were assessed using the Open Field Test following subcutaneous administration of 25E-NBOH at 0.2, 1, and 5 mg/kg, with testing initiated 15 or 60 min after administration. Sensorimotor gating and psychotomimetic-like effects were evaluated using prepulse inhibition of the acoustic startle response (PPI ASR) at the same doses and time onsets. Data were subjected to statistical analysis.

Results: According to the OECD 423 acute toxicity procedure, 25E-NBOH was classified as GHS acute toxicity Category 4, with a predicted LD₅₀ of 1000 mg/kg. In the Open Field Test, subcutaneous 25E-NBOH decreased locomotor activity at 1 and 5 mg/kg and altered its spatial distribution across all tested doses. In the PPI ASR test, a significant effect of treatment was observed ($F(3,69) = 12.222$, $p < 0.001$), whereas neither onset ($F(1,69) = 1.016$, $p = 0.317$) nor the treatment $\times$ onset interaction ($F(3,69) = 1.138$, $p = 0.342$) was significant. All 25E-NBOH-treated groups exhibited significantly reduced prepulse inhibition compared with controls (Tukey post hoc test; maximum $p = 0.040$).

Conclusion: 25E-NBOH produced measurable acute behavioral effects following subcutaneous administration in rats, characterized by reduced locomotor activity, altered spatial distribution, and disruption of sensorimotor gating. Together with its classification as GHS acute toxicity Category 4, these findings provide preclinical evidence regarding the acute behavioral and systemic toxicity profile of this potent serotonergic psychedelic.

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IDENTIFICATION OF A NOVEL INHIBITOR OF SULFUR METABOLISM IN COLORECTAL CANCER CELLS BY HIGH-THROUGHPUT SCREENING

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Introduction: Colorectal cancer (CRC) remains one of the most prevalent malignancies worldwide and is associated with particularly high incidence rates in Slovakia. Increasing evidence implicates cystathionine- β -synthase (CBS), a key enzyme of sulfur metabolism, in supporting colorectal tumor growth and metabolic adaptation.

Aims: This study aimed to identify novel CBS inhibitors from a drug-like compound library and to characterize the most promising hit with respect to its potency, mechanism of action, selectivity, and activity in human colorectal cancer cells (HCT116).

Methods: A fluorescence-based high-throughput screening assay was used to evaluate the Express-Pick Library (SelleckChem, 3010 drug-like compounds) for inhibitors of CBS activity. Primary hits were validated using two orthogonal absorbance-based enzymatic assays. The lead compound, WAY-230765, was further investigated for inhibitory potency, direct interaction with CBS, influence on pyridoxal-5'-phosphate (PLP) binding, selectivity against other PLP-dependent enzymes, and its biological activity in HCT116 cells.

Results and Discussion: WAY-230765 had a lower potency ($IC_{50} = 18.20 \mu M$) than the reference inhibitor AOAA ($IC_{50} = 5.62 \mu M$), but did not act via the CBS cofactor PLP (pyridoxal-5'-phosphate). WAY-230765 also did not inhibit other PLP-dependent enzymes. Gradual thermal denaturation of CBS suggested target engagement by WAY-230765. Unlike AOAA, WAY-230765 inhibited hydrogen sulfide production by HCT116 cells.

Conclusion: This study identifies WAY-230765 as a novel, selective inhibitor of CBS with a cofactor-independent mechanism of action. Its ability to suppress sulfur metabolism in colorectal cancer cells highlights its potential as a promising lead compound for the development of targeted therapies against CRC.

ACKNOWLEDGMENT: This work was supported by APVV-23-0178 and VEGA 1/0619/24.

MOLECULAR PROFILE OF CARDIAC METABOLIC REMODELING IN PULMONARY ARTERIAL HYPERTENSION: TRANSCRIPTIONAL ANALYSIS OF GLUCOSE TRANSPORTERS

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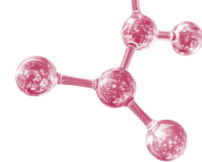
Introduction: Pulmonary arterial hypertension (PAH) is a severe, incurable disease with high mortality leading to vascular remodelling and right ventricular (RV) failure. Many PAH patients concurrently present with type 2 diabetes (T2DM). Thus, although cardiac metabolic reprogramming has come to the forefront, the transcriptional changes of glucose transporters in this context remain poorly characterised.

Aims: Our study aimed to evaluate the temporal mRNA expression of the insulin receptor (Insr), glucose transporters (GLUT1-4, SGLT1-2), and Hgf (marker of myocardial damage) in RV and left ventricle (LV) during monocrotaline-induced PAH progression.

Methods: PAH was induced in rats with monocrotaline (MCT, 60 mg/kg, s.c.). Samples were collected after 1, 2, and 4 weeks (1w, 2w, 4w) and at the stage of advanced clinical worsening (ptMCT). The mRNA expression of Insr, Slc2a1-4 (GLUT1-4), Slc5a1-2 (SGLT1-2), and Hgf was determined using RT-qPCR.

Results and Discussion: Evaluating these time-dependent changes revealed unaltered Insr mRNA expression but a profound biventricular downregulation of Slc2a4 (GLUT4) at 4w and ptMCT, independent of localized injury severity (Hgf increased significantly in the RV, but not in the LV). Sharing common features with T2DM-like insulin resistance, stable Insr expression point toward a post-receptor defect. These transcriptional alterations were absent during the early phases (1w,2w), demonstrating that metabolic reprogramming is a late-stage phenomenon tightly bound to clinical decompensation. To compensate for loss of Slc2a4 expression, Slc2a1 (GLUT1) mRNA increased biventricularly, may reflect a generalised shift to insulin-independent fetal transporters. Conversely, Slc2a3 (GLUT3) upregulation was RV-exclusive, aligning with more severe localised tissue injury under pressure overload. Regarding cotransporters, Slc5a2 (SGLT2) was undetectable biventricularly, while Slc5a1 (SGLT1) mRNA remained near the detection threshold only in the RV.

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MOLECULAR ANALYSIS OF IBUPROFEN EFFECTS ON SURVIVAL AND COX-1/2 PATHWAYS IN HUMAN CARDIAC FIBROBLASTS IN VITRO

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Introduction: Ibuprofen (IBU), a non-steroidal anti-inflammatory drug, is among the frequently used analgesics, including in patients with cardiovascular diseases. Inflammatory stress in these patients contributes to dysregulation of human cardiac fibroblasts (HCFs), whose pathological activation promotes myocardial remodeling, fibrosis, and progression of heart failure. Despite its widespread clinical use, the molecular effects of ibuprofen on HCFs and the regulation of COX signaling remain insufficiently elucidated.

Aims: (1) To assess how ibuprofen modulates COX-1 and COX-2 expression in HCFs under basal conditions and under TNF- α -induced inflammatory stress. (2) To evaluate the effect of ibuprofen on HCF viability and apoptosis under acute inflammatory stress.

Methods: Primary HCFs (p6, PromoCell) were treated with TNF- α (10 ng/mL) and IBU (150/300 μ M, 24–48 h). Cell viability (MTT), apoptosis (Annexin V/PI flow cytometry), and COX-1/2 protein expression (Western blot, GAPDH normalization) were evaluated.

Results and Discussion: TNF- α significantly induced COX-2 expression in HCFs (1.92-fold, $p < 0.05$), thereby confirming the functional validity of the experimental inflammatory stress model. Ibuprofen markedly suppressed COX-2 expression under both basal and inflammatory conditions, with the high dose nearly completely eliminating TNF- α -induced COX-2 expression (IBU2 + TNF- $\alpha \approx 0$, $p < 0.001$). The observed changes in COX-2 expression suggest that the effect of ibuprofen may not be limited to inhibition of COX enzymatic activity alone; however, the precise mechanism requires further investigation. High-dose ibuprofen reduced HCF viability (~75%) and synergistically increased apoptosis under inflammatory stress conditions ($p < 0.001$). The unexpected upregulation of COX-1 following TNF- α stimulation suggests that COX-1 expression may be more dynamic under inflammatory conditions than is traditionally assumed. As a possible mechanistic explanation for this effect, we propose post-transcriptional regulation or a compensatory cellular response to disrupted prostanoid homeostasis. Further experimental studies are required to confirm these hypotheses.

ACKNOWLEDGMENT: This work was supported by grants APVV-23-0557 and VEGA 1/0523/25.

OPTIMIZATION OF BREAST CANCER CELL LINE IN VITRO MODELS FOR ASSESSING ALTERATIONS IN PD-L1 LEVELS

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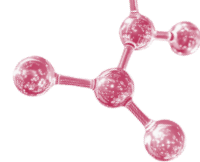
Introduction: Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway represent a breakthrough in oncology. However, therapeutic resistance remains a critical challenge. Targeting PD-L1 expression in cancer cell lines represents a promising approach for studying potential improvements in the outcomes of immune checkpoint immunotherapy. To screen for new compounds that affect PD-L1 levels, reliable in vitro models with stable constitutive and inducible expression are required.

Aims: This study aimed to establish and optimize models using breast cancer cell lines with different levels of PD-L1 expression to screen small-molecule compounds for their ability to modulate PD-L1 expression.

Methods: Two human breast cancer cell lines, MDA-MB-231 (constitutive PD-L1 expression) and MCF-7 (IFN- γ -inducible PD-L1 expression), were utilized. The assay conditions were optimized using a reference small-molecule inhibitor as a positive control. Subsequently, both models were used to screen a panel of small-molecule compounds for their effects on PD-L1 levels.

Results and Discussion: Methodological optimization confirmed high constitutive expression of PD-L1 in MDA-MB-231 cells and reproducible induction of PD-L1 by IFN- γ in the MCF-7 model. Further, a reproducible positive control for PD-L1 downregulation was successfully established. This enabled verification of the entire in vitro screening model across selected cell lines during the evaluation of small-molecule candidates that alter PD-L1 levels while maintaining acceptable cell viability.

ACKNOWLEDGMENT: This work was supported by the project NW26-03-00542.



VLIV GENDER-AFFIRMING TERAPIE NA FARMAKOKINETIKU A FARMAKODYNAMIKU LÉČIV: IMPLIKACE PRO SLEDOVÁNÍ POHLAVÍ A GENDERU V KLINICKÝCH STUDIÍCH

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Gender-affirming hormonální terapie (GAHT) je spojena s fyziologickými změnami, které mohou ovlivnit farmakokinetiku a farmakodynamiku léčiv. Změny tělesného složení indukované GAHT mohou vést i ke zkreslení renálních funkcí odhadovaných pomocí běžně používaných rovnic. Transgender osoby kromě toho vykazují odlišnou prevalenci některých onemocnění oproti cisgender populaci. Přesto zůstává transgender populace ve výzkumu opomíjena a údaje o genderové identitě nejsou v klinických studiích systematicky sledovány. Poster shrnuje dostupné poznatky o vlivu GAHT na farmakokinetiku a farmakodynamiku léčiv a zdůrazňuje význam sledování biologického pohlaví a genderové identity v klinických studiích.

PODĚKOVÁNÍ: Podpořeno ze státního rozpočtu prostřednictvím MŠMT projektem VVI CZECRIN (LM2023049) a projektem ERASMUS+ SENSITISE (2023-1-IE02-KA220HED-000159532).

ZMĚNY FARMAKOKINETIKY MITOTANU V OBRAZE JEHO TDM

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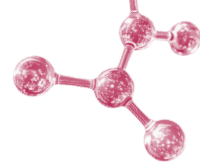
Úvod: Po více než 50 let zůstává mitotan základním léčivem v adjuvanční a paliativní terapii adenokortikálního karcinomu. Současná doporučení indikují monitoring plazmatických hladin s cílem dosažení plazmatické koncentrace mezi 14-20 mg/l.

Cíle: Zachytit změny farmakokinetiky mitotanu na úrovni monitoringu jeho plazmatických koncentrací v jednotlivých kazuistických případech a pokusit se tyto změny interpretovat.

Metody: V kazuistických případech tří pacientů jsme sledovali výsledky monitoringu jeho plazmatických hladin v závislosti na dávce a v průběhu času s cílem dosažení terapeutického rozmezí. Soustředili jsme se na neočekávané výkyvy plazmatických hladin a pokusili se je analyzovat se zřetelem na možné změny farmakokinetiky na všech úrovních (absorpce, distribuce, metabolismus, eliminace).

Výsledky a závěry: Farmakokinetika mitotanu vykazuje velkou variabilitu. Některé její změny lze vysvětlit interakcí na úrovni P-glykoproteínu či cytochromového systému P450, jiné vlivem změn absorpce léčiva, část změn má komplexní charakter a do budoucna vyžaduje další zkoumání.

Literatura: Cazaubon Y, Talineau Y, Feliu C, Konecki C, Russello J, Mathieu O, et al. Population pharmacokinetics modelling and simulation of mitotane in patients with adrenocortical carcinoma: an individualized dose regimen to target all patients at three months? *Pharmaceutics*. 2019;11(11):566.



PŘEKONÁVÁNÍ BARIÉR LÉČBY KLOZAPINEM: ZKUŠENOSTI Z AMERICKÉ KLINICKÉ PRAXE A JEJICH MOŽNÉ VYUŽITÍ V ČESKÉ REPUBLICE

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Úvod: Klozapin je nejúčinnější léčbou farmakorezistentní schizofrenie, přesto zůstává celosvětově nedostatečně využíván. Mezi hlavní bariéry jeho širší preskripce patří obavy z nežádoucích účinků, pravidelná hematologická monitorace a organizační náročnost léčby. Přestože české i americké doporučené postupy vycházejí z obdobných vědeckých důkazů, jejich implementace do klinické praxe se v některých oblastech liší.

Cíl: Představit vybrané přístupy americké klinické praxe, které mohou přispět ke snížení bariér léčby klozapinem, a diskutovat jejich možné využití v českém zdravotnictví.

Metodika: Byla provedena komparativní analýza českých a amerických doporučených postupů a odborné literatury zaměřené na léčbu klozapinem. Přehled je doplněn o poznatky získané během odborné stáže autorky na Maryland Psychiatric Research Center (Baltimore, USA).

Výsledky a diskuze: Doporučené postupy v České republice i USA se v základních principech léčby významně neliší. Rozdíly spočívají především v organizaci péče a implementaci podpůrných nástrojů. Mezi přístupy využívané v USA patří telementoringový program CHAMPION Project ECHO®, zaměřený na podporu preskribujících lékařů, zvyšování jejich znalostí a kompetencí v léčbě klozapinem a podporu jeho širšího využívání, multidisciplinární spolupráce a point-of-care monitorace absolutního počtu neutrofilů pomocí zařízení Athelas Home, které umožňuje rychlé stanovení ANC z kapilární krve přímo v ambulanci. Tyto přístupy mohou podpořit širší využívání klozapinu v klinické praxi a snížit související praktické bariéry.

Závěr: Vedle samotných doporučených postupů je pro širší využívání klozapinu zásadní také jejich efektivní implementace. Organizační podpora, vzdělávání a moderní technologie mohou přispět ke snížení bariér léčby a být inspirací pro další rozvoj péče v České republice.

UPREGULATION OF EPITHELIAL-MESENCHYMAL TRANSITION MARKERS SNAIL AND SLUG IN EPICARDIAL ADIPOSE TISSUE OF HEART FAILURE PATIENTS

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Introduction: Epicardial adipose tissue (EAT) is a metabolically active organ secreting numerous bioactive molecules. Given its direct contact with the myocardium, EAT is proposed to significantly influence cardiac remodelling and heart failure progression through complex paracrine effects.

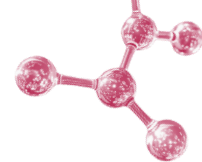
Aims: To compare the expression profiles of genes and proteins involved in cardiac development, hypertrophy, and inflammation between EAT and the left ventricular (LV) myocardium in end-stage heart failure, and to identify relevant clinical correlations.

Methods: Paired EAT and LV tissue samples were collected from 37 patients (7 women, 30 men; age 49±9 years) with end-stage heart failure (NYHAIII-IV) undergoing heart transplantation. Gene and protein expressions were analysed using qRT-PCR and Western blot.

Results and Discussion: Most analysed genes linked to heart development and remodelling (e.g., CALN, NFAT3, PDGFB, ET-1, IGF-1) were significantly upregulated in EAT compared to the LV. Notably, regulators of epithelial-mesenchymal transition, SNAIL and SLUG, were dramatically overexpressed in EAT (SLUG by 18.5-fold, while SNAIL was undetectable in the LV). TGF-β1 mRNA and inflammatory/protective proteins (NF-KB p105, CAV-1, Bcl2) were also expressed at higher levels in EAT. Conversely, VEGFA and adiponectin expressions were significantly lower in EAT. Connexin 43 was detectable exclusively in the LV. Furthermore, strong correlations were found among specific cardiac hypertrophy genes across tissues, as well as between EAT SLUG expression and central venous pressure.

Conclusion: These results demonstrate that EAT is a highly active endocrine tissue with a distinct molecular environment. This highlights its crucial role in driving the pathophysiology and remodelling processes of end-stage heart failure through paracrine signalling.

ACKNOWLEDGMENT: This work was supported by NFP401101 C 023, APVV-23-0557, VEGA 1/0523/25.



THE GUT MICROBIOME AS A TARGET OF PHARMACOLOGICAL INTERVENTION IN MENTAL HEALTH

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Introduction: The gut microbiome is increasingly recognized as a key regulator of brain function through the gut–brain axis, and dysbiosis has been implicated in depression. Despite growing interest in psychobiotics as adjunctive therapy, clinical evidence remains heterogeneous. This study systematically evaluated the efficacy of psychobiotic supplementation in reducing depressive symptoms.

Aims: The aim of this study was to evaluate the efficacy of psychobiotic supplementation in depression through a systematic review and meta-analysis.

Methods: A systematic review and meta-analysis were conducted according to PRISMA guidelines. Seven randomized, double-blind, placebo-controlled trials (2016–2024) were included. The primary outcome was the change in depressive symptom severity, and pooled effect sizes were calculated using a random-effects model. Heterogeneity was assessed using the I^2 statistic.

Results and Discussion: Psychobiotic supplementation significantly reduced depressive symptoms compared with placebo (Hedges' $g = 0.40$; 95% CI 0.20–0.60; $I^2 = 30\%$). The observed effects may be mediated by modulation of inflammation and the gut–brain axis.

Conclusion: Psychobiotic supplementation represents a promising adjunctive strategy for alleviating depressive symptoms, although further high-quality clinical studies are required.

ACKNOWLEDGMENT: The authors gratefully acknowledge the supervision and valuable guidance of doc. PharmDr. Andrea Gažová, Ph.D.

QUANTIFICATION OF ANTIBIOTIC CEFEPIME BY LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY METHOD

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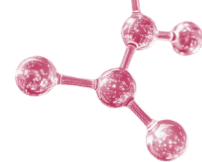
Introduction: Cefepime is a cephalosporin used in clinical practice against Gram-positive and Gram-negative bacteria in critically ill and in immunocompromised patients. Cefepime demonstrates time-dependent bactericidal activity. Its efficacy is defined by the time for which the unbound concentration is maintained above the minimum inhibitory concentration of bacteria. Patients with sepsis have increased interstitial fluid volumes due to capillary leak syndrome, which can lead to an increased volume of distribution. They exhibit often increased renal blood flow and glomerular filtration, leading to increased clearance of cefepime. Administration of large doses of cefepime is associated with dose-dependent toxicity particularly neurotoxicity, mainly in patients with renal dysfunction and a trough concentration $c_{min} > 20$ mg/L. It is necessary to individualize cefepime dosing in order to achieve effective concentrations (4-5x MIC over 70-100% of the dosing interval), to limit selection of resistant bacteria, and avoid toxicity. Therapeutic drug monitoring represents a valuable tool for optimizing cefepime concentrations in patients and improving clinical outcome.

Aims: In order to facilitate TDM of cefepime, a new bioanalytical method based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) was developed and validated.

Methods: Sample preparation included simple protein precipitation of plasma samples using a mixture of methanol and acetonitrile (1:1) enriched with the internal standard cefepime-d₃. Cefepime and cefepime-d₃ were separated on YMC-Triart PFP column using isocratic elution of mobile phase consisted of 10mM ammonium formate buffer and methanol with 0.1% formic acid. Analytes were monitored using tandem mass-spectrometry equipped with an electrospray ion source and adjusted in positive multiple-reaction-monitoring mode: m/z 481>396 (cefepime) and 484>396 (cefepime-d₃).

Results and Discussion: Validation experiments confirmed that the performance of new method was suitable for TDM of cefepime. The limit of detection was 0,01 mg/L. The range of applicability and linearity was from 0.17 mg/L (LOQ) to 174 mg/L (ULOQ). Accuracy and precision were acceptable. The accuracy reached values from 91.85 % to 100.09% of the recovery, and precision ranged from 0.83% to 6.36% of coefficient variation. No interference was observed (haemoglobin, bilirubin, lipides). A benefit of presented method is that it covers with appropriate multiple-reaction-monitoring in one run other antibiotics such as meropenem, ceftazidime, piperacillin and linezolid.

ACKNOWLEDGMENT: This work was supported by the programme Cooperatio, research area ONCO.



NOVEL COMPOUNDS THAT MODULATE PD-L1 EXPRESSION IN CANCER CELL LINES

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Introduction: PD-L1 represents a well-established target in cancer immunotherapy. Despite this, the clinical efficacy of anti-PD-L1 therapies remains constrained by incomplete patient responses and the emergence of therapeutic resistance. Therefore, identifying novel compounds capable of regulating PD-L1 expression and elucidating the signalling pathways governing its expression in cancer cells is essential.

Aims: The aim of this study was to assess whether salicylanilide derivatives and related compounds inhibiting STAT3 signalling could modulate PD-L1 expression in selected cancer cell lines. The study also investigated whether treatment of cancer cell lines with the tested compounds altered the cytotoxic activity of CD3⁺/CD8⁺ T cells.

Methods: Preliminary assessment of the antiproliferative activity of the tested compounds in selected cancer cell lines was performed using the WST-1 assay. Membrane PD-L1 expression was assessed by flow cytometry. Western blot analysis was performed to evaluate levels of proteins involved in the STAT3 signalling pathway. In addition, a co-culture model comprising selected cancer cell lines and activated CD3⁺ T cells within PBMCs was used to assess changes in T-cell cytotoxic activity following treatment with the tested compounds.

Results and Discussion: The tested substances decreased PD-L1 levels in cancer cell lines, and this effect was associated with inhibition of STAT3 phosphorylation. In addition, they modulated the cytotoxic activity of CD3⁺/CD8⁺ T cells within PBMCs.

ACKNOWLEDGMENT: This work was supported by the projects NW26-03-00542 and MUNI/A/1488/2024.

CHALLENGING VORICONAZOLE TITRATION DUE TO CONCOMITANT METAMIZOLE ADMINISTRATION: PITFALLS OF ENZYMATIC INDUCTION AND THE ROLE OF TDM IN MULTIDISCIPLINARY PRACTICE

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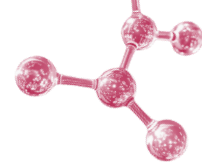
Introduction: Voriconazole exhibits non-linear pharmacokinetics with a narrow therapeutic index, complicating dose optimization in critically ill patients. Recent evidence highlights the frequently overlooked interaction potential of metamizole (dipyrone). As a potent inducer of cytochrome P450 enzymes, specifically CYP3A4 and CYP2C19, metamizole can substantially reduce voriconazole exposure by up to 70%, predisposing patients severe therapeutic failure during antifungal treatment.

Aims: This report aims to present a case of a critically ill patient in whom a profound drug interaction between metamizole and voriconazole resulted in subtherapeutic voriconazole exposure, and to underscore the critical role of a multidisciplinary approach in managing complex pharmacokinetic interactions.

Methods: Serum voriconazole concentrations were determined using a validated bioanalytical method based on liquid chromatography-tandem mass spectrometry. Sample preparation involved liquid-liquid extraction with voriconazole-d3 as the internal standard. Pharmacokinetic data analysis, exposure prediction, and dosage regimen optimization were performed using the MWPharm pharmacokinetic software. Real-time therapeutic drug monitoring (TDM) was conducted with close, interdisciplinary collaboration to guide empirical and targeted dose adjustments.

Results and discussion: A 55-year-old multimorbid female patient receiving extensive polypharmacy (22 concurrent medications) was admitted to the cardiac intensive care unit following cardiac arrest secondary to massive pulmonary embolism. Her clinical course was complicated by invasive pulmonary aspergillosis confirmed via bronchoalveolar lavage. Despite standard voriconazole dosing, including an appropriate loading dose, TDM revealed near-zero trough concentrations (0.07 mg/L; target range 1.00–5.50 mg/L). Concurrent metamizole therapy (1 g every 8 hours) was identified as the underlying cause. Due to persistent enzymatic induction following metamizole discontinuation, the voriconazole dose was escalated to 400 mg every 8 hours intravenously (more than double the standard dose). Upon gradual resolution of enzyme induction, therapeutic, trough concentrations stabilized within the therapeutic range, allowing the progressive dose tapering and eventual transition to an oral maintenance regimen of 200 mg every 12 hours.

Conclusion: Metamizole poses a severe, yet frequently neglected risk for voriconazole treatment failure due to potent CYP450 induction. This case illustrates that managing the safe titration and subsequent de-escalation of a drug with non-linear pharmacokinetics requires proactive TDM and close multidisciplinary collaboration among clinical pharmacists, attending physicians and clinical biochemists.



INTOXIKACE PARACETAMOLEM. ANALÝZA PUBLIKOVANÝCH KAZUISTIK A NÁRODNÍCH TOXIKOLOGICKÝCH DAT (2018 – 2023)

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Úvod: Paracetamol je široce používané analgetikum a antipyretikum, jeho snadná dostupnost jej zároveň činí častým léčivem zneužívaným k úmyslnému předávkování. Rostoucí výskyt úmyslných otrav paracetamolem, zejména u dospívajících, představuje významný problém v otázce veřejného zdraví.

Cíle: Cílem naší studie bylo analyzovat publikované kazuistiky případů předávkování paracetamolem v letech 2018–2023, identifikovat rizikové skupiny a zhodnotit situaci v České republice ve sledovaných letech.

Metody: Byla provedena systematická přehledová studie publikovaných kazuistik (2018–2023) popisujících předávkování paracetamolem s využitím databází PubMed, Scopus, Web of Science a Cochrane Library. Současně byla provedena retrospektivní analýza telefonických dotazů z Toxikologického informačního střediska (TIS) v České republice za stejné období.

Výsledky a diskuze: Do analýzy bylo zařazeno 68 publikovaných kazuistik, přičemž udávané dávky se pohybovaly v rozmezí 6,5–250 g paracetamolu. Úmyslné předávkování bylo zaznamenáno v 50 případech (74 %), z toho u 11 dospívajících dívek (27 % úmyslných případů), přičemž v této podskupině nebyla hlášena žádná úmrtí. TIS zaznamenalo v letech 2018–2023 celkem 3 318 dotazů týkajících se expozice paracetamolu, z nichž ve 2 032 případech (61 %) se jednalo o úmyslné předávkování. Kombinace systematického přehledu kazuistik a analýzy národních toxikologických dat poskytuje ucelenější obraz epidemiologie intoxikací paracetamolem v České republice a doplňuje informace o jejich klinických charakteristikách a populačních souvislostech.

INFLAMMATORY AND METABOLOMIC CHANGES RELATED TO GENDER IN A GUINEA PIG MODEL OF ALLERGIC AIRWAY INFLAMMATION

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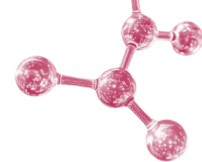
Introduction: Severity of bronchial asthma can be influenced by action of sex hormones; however, little is known about their effect on the metabolism.

Aims: This study aimed to evaluate metabolomic changes in relation to several inflammatory markers in guinea pigs with ovalbumin (OVA)-induced allergic airway inflammation.

Methods: Guinea pigs of both sexes underwent OVA-sensitisation, or served as naive controls. Total and differential white blood cell counts, wet-dry lung weight ratio (WDR), and total and differential cell counts in bronchoalveolar lavage fluid (BALF) were determined. Metabolomic analysis of plasma was performed by hydrogen-1 nuclear magnetic resonance spectroscopy.

Results and Discussion: OVA-sensitisation increased counts of leukocytes and eosinophils in blood and total cells and eosinophils in BALF in animals of both sexes, with obvious involvement of neutrophils in females. OVA-sensitisation significantly increased WDR, a marker of lung edema, only in females. Metabolomic analysis of plasma revealed significant changes in 3 metabolites in males but in 7 metabolites in females compared to controls. The between-gender comparison showed significant differences in some metabolites after 14 days or 21 days of OVA-sensitisation but also in healthy controls. The results indicate a contribution of gender to regulation of inflammation and metabolism in OVA-sensitised guinea pigs.

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DEXRAZOXANE ANALOGUES WITH IMPROVED SOLUBILITY AND PRODRUG POTENTIAL FOR ANTHRACYCLINE CARDIOPROTECTION

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Introduction: Anthracyclines are among the most effective and widely used chemotherapeutic agents, but their clinical use is limited by chronic cardiotoxicity, which may develop even several years after treatment. Dexrazoxane (DEX) is currently the only clinically approved cardioprotective agent against anthracycline-induced cardiotoxicity. Although its cardioprotective effect was initially attributed to iron chelation, it is now known to result from inhibition of topoisomerase II β (TOP2B).

Aims: This study aimed to develop a novel cardioprotective agent targeting TOP2B, a key mediator of anthracycline-induced cardiotoxicity, while avoiding interference with anthracycline efficacy.

Methods: TOP2 inhibition was evaluated by DNA decatenation assay. Cardioprotective effects were assessed in primary neonatal rat cardiomyocytes isolated in house from 1- to 3-day-old Wistar rats. Antiproliferative activity was examined in relevant leukemia cell lines. Cell viability was measured by MTT and LDH assays, and DNA double-strand breaks were assessed by H2AX western blotting. To confirm that the iron chelation activity of the studied compounds is not connected to their pharmacological activity in cardiomyocytes and/or cancer cells, iron chelation was compared for DEX and its new analogues and their hydrolysis products.

Results and Discussion: We found that the spatial arrangement of the ATPase domain of TOP2B allows hydroxymethyl extension of DEX, leading to the synthesis of hydroxymethyl DEX (HMDEX). The hydroxyl group increases the solubility of this analogue and provides a new site for prodrug formation. While both stereoisomers were prepared, despite their close structural similarity, only the erythro, not the threo form, showed potent TOP2B inhibition and protection against anthracycline-induced cardiotoxicity and cardiac DNA damage in NRCMs, without affecting daunorubicin's antileukemic activity. Neither stereoisomer exhibited intrinsic toxicity to NRCMs, even at higher concentrations. These results identify HMDEX as a promising new cardioprotective agent against anthracycline-induced cardiotoxicity. Early pilot data also support further development of HMDEX-derived prodrugs.

THE EFFECT OF CAFFEINE ON METABOLISM OF NUCLEOS(T)IDES IN PLACENTA: CHANGES IN GENE AND PROTEIN EXPRESSION, METABOLOMIC PROFILE AND EPIGENETIC REGULATION

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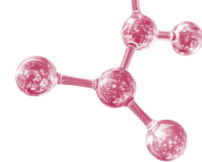
Introduction: Caffeine is a widely consumed purine alkaloid, present in coffee and various other food and beverages that acts primarily as an antagonist of adenosine receptors. Despite extensive evidence linking maternal caffeine intake to adverse pregnancy outcomes, the molecular mechanisms underlying its effects on placental biology are not fully understood.

Aims: Given caffeine's purine-based structure, this study aimed to investigate its effects on nucleos(t)ide metabolism and related molecular pathways at the levels of gene and protein expression, metabolomic profile and methylation status of selected loci.

Methods: Placental responses to caffeine were evaluated using in vitro and in vivo models. BeWo cells in cytotrophoblast and syncytiotrophoblast states were exposed to caffeine, while placentas were collected at gestational days 12, 15, and 20 from rats treated daily with caffeine from gestational day 1. Gene expression was assessed by RT-qPCR in both models, whereas protein expression, metabolomic profile, and DNA methylation were evaluated in the rat placentas using Western blotting, UHPLC/MS-based metabolomics, and targeted xGen Methyl-Seq.

Results and Discussion: Caffeine exposure did not significantly alter gene expression in BeWo cells, whereas rat placentas exhibited pronounced transcriptional changes, including genes related to placental growth and vascular development. These changes were accompanied by selected protein alterations, metabolomic shifts in the adenosine-inosine branch of purine metabolism and locus-specific DNA hypomethylation. These findings indicate that caffeine modulates placental adenosine signaling and nucleos(t)ide metabolism, potentially impairing placental adaptive capacity under physiological stress conditions and contributing to fetal programming.

ACKNOWLEDGMENT: The study was supported by GACR 22-17643S and GAUK 236523.



PERMETHRIN IMPAIRS INSULIN SECRETION AND ALTERS PROTEINS INVOLVED IN METABOLISM AND EXOCYTOSIS IN INS832/3 PANCREATIC BETA CELLS

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Introduction: Permethrin is one of the most widely used pyrethroid insecticides and has been associated with metabolic disorders, insulin resistance, and diabetes, yet its direct effects on pancreatic β -cells remain unknown.

Aims: The aim of this study was to investigate the effects of chronic exposure to permethrin on pancreatic β -cell function.

Methods: We exposed INS832/3 pancreatic β -cells to 1 and 10 μ M permethrin for one week to assess effects on protein expression employing ELISA and western blotting.

Results and Discussion: Chronic permethrin exposure significantly impaired both glucose- and KCl-stimulated insulin secretion while only modestly reducing intracellular insulin content. Mechanistically, permethrin altered the expression of proteins involved in glucose metabolism, energy sensing, lipid metabolism, and the exocytotic machinery, indicating broad disruption of β -cell homeostasis. Comparison with HepG2 hepatocytes further demonstrated tissue-specific responses to permethrin exposure. These findings provide the first evidence that chronic permethrin exposure directly impairs pancreatic β -cell function and support the potential contribution of this pyrethroid insecticide to the development of metabolic disorders and diabetes.

ACKNOWLEDGMENT: This work was supported by the Charles University Cooperatio METD and Cooperatio 31, and by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, ID Project No. LX22NPO5104) - Funded by the European Union - Next Generation EU.

PHARMACOLOGY PROBLEM-SOLVING: HUMANS VS. AI MODELS

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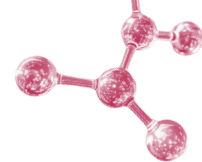
Introduction: Pharmacological knowledge is essential for safe and high-quality clinical decision-making in everyday practice. With the rapid implementation of artificial intelligence (AI) in healthcare, an important question arises whether its performance in pharmacology can match or even surpass that of healthcare professionals in this domain.

Aims: The aim of this study is to compare the level of pharmacological knowledge between human respondents and AI models using a standardized multiple-choice test. A secondary objective is to assess differences in test accuracy and time required to complete the test.

Methods: A total of 194 respondents, including physicians, pharmacists, medical students, and pharmacy students, were enrolled in the study. Pharmacological knowledge was evaluated using an anonymous online test comprising 15 single-best-answer questions, while overall score and completion time were recorded for each participant. The results of the human groups were compared with those of 8 AI models, which completed the test repeatedly under standardized conditions. Group differences in accuracy and completion time were assessed using the Kruskal-Wallis test.

Results and Discussion: Responses from 194 human participants and 8 AI models were analyzed. AI models achieved the highest mean score (97.7%) and the shortest test completion time (mean 14 s). Among human respondents, physicians reached the highest success rate (82%), followed by pharmacists (79%), medical students (74.4%), and pharmacy students (53.3%). Differences between groups were statistically significant in both test accuracy and completion time (Kruskal-Wallis, $p < 0.0001$). These findings indicate that AI tools can achieve very high accuracy and extremely rapid performance under standardized test conditions; however, such results reflect a controlled environment and cannot be directly extrapolated to complex real-world clinical decision-making. AI may therefore serve as a supportive educational and consultative tool rather than a replacement for professional clinical judgment.

ACKNOWLEDGMENT: This work was supported by IGA_LF_2025_009 and IGA_LF_2026_006.



EXPERIENCE WITH PIPERACILLIN/TAZOBACTAM MONITORING AT UNIVERSITY HOSPITAL OLOMOUC

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Introduction: Piperacillin/tazobactam (PPT) is a broad-spectrum antibiotic with time-dependent bactericidal activity, correlating with the time free plasma concentrations exceed the minimum inhibitory concentration (% fT > MIC). Due to high pharmacokinetic variability in critically ill patients, therapeutic drug monitoring (TDM) is highly recommended.

Aims: To evaluate whether standard dosing (4.5 g q8h via 30-minute infusion) achieves target pharmacokinetic/pharmacodynamic (PK/PD) endpoints in Intensive Care Unit (ICU) patients, and to assess the clinical utility of TDM.

Methods: This retrospective observational study evaluated ICU patients. Administered dose, dosing interval, and renal function were recorded. Steady-state TDM-determined piperacillin plasma concentrations were analyzed, and calculated free fractions were compared against MIC values to assess PK/PD target attainment (100% fT > MIC). Statistical analysis evaluated the relationship between creatinine clearance (CrCl) and drug concentrations.

Results and Discussion: Steady-state concentrations were evaluated in 16 ICU patients. No patient reached toxic concentrations (>160 mg/l). A moderate negative correlation was confirmed between CrCl and piperacillin concentrations ($R = -0.6$; $p = 0.024$). However, renal function accounts for only 30% of the concentration variability ($R^2 = 0.30$), highlighting highly unpredictable pharmacokinetics in the critically ill. In patients with $CrCl > 45$ ml/min, standard intermittent dosing (4.5 g q8h) may fail to achieve therapeutic targets. To ensure adequate drug exposure, alternative strategies – such as reducing the dosing interval (q6h), implementing prolonged 3-hour infusions, and administering a loading dose – should be considered and guided by routine TDM.

ACKNOWLEDGMENT: This work was supported by the internal grant agency IGA_LF_2026_006.

VZTAH GENOTYPU CYP2C19 K ENZYMOVÉ AKTIVITĚ STANOVENÉ IN VITRO V LIDSKÝCH JATERNÍCH MIKROSOMECH

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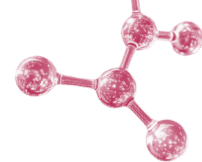
Úvod: Cytochrom P450 2C19 (CYP2C19) je významný enzym podílející se na metabolismu řady klinicky významných léčiv, přičemž jeho aktivita vykazuje značnou interindividuální variabilitu v důsledku genetického polymorfismu.

Cíle: Tato práce se zabývala posouzením vztahu mezi genotypem CYP2C19 a jeho enzymovou aktivitou stanovenou in vitro v lidských jaterních mikrosomech s odlišnými genotypy tohoto enzymu (CYP2C19*1/*1, CYP2C19*1/*2, CYP2C19*2/*2).

Metody: Rychlost metabolické přeměny v jednotlivých biologických vzorcích byla hodnocena na základě tvorby 5-hydroxyomeprazolu za optimalizovaných inkubačních podmínek. Stanovení bylo provedeno metodou vysokoúčinné kapalinové chromatografie s hmotnostní detekcí (LC-MS) s použitím omeprazolu jako modelového substrátu a lansoprazolu jako vnitřního standardu. Analyty byly separovány na koloně s reverzní fází C18 a detekovány v režimu monitorování vybraných reakcí (MRM) na základě poměru hmotnosti a náboje (m/z).

Výsledky a Diskuse: Nejvyšší enzymová aktivita byla překvapivě zjištěna u jaterních mikrosomů s genotypem CYP2C19*1/*2, zatímco nižší aktivita byla pozorována u vzorků s genotypy CYP2C19*1/*1 a CYP2C19*2/*2. Výsledky ukazují, že vztah mezi genotypem a výsledným fenotypem nemusí být přímočarý. Tento nelineární trend naznačuje, že samotný genotyp nemusí plně odrážet výslednou enzymovou aktivitu.

PODĚKOVÁNÍ: Tato práce byla podpořena granty OP TAK DiPha (CZ.01.01.01/01/22_002/0000717), a také vnitřním grantem Univerzity Palackého v Olomouci IGA_LF_2026_006.



METABOLIC SYNDROME PHENOTYPES DRIVE DISTINCT EXPRESSION PROFILES OF PHASE I AND II DRUG-METABOLISING ENZYMES

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Introduction: Metabolic syndrome (MetS) is one of the most prominent risk factors associated with elevated likelihood of cardiovascular diseases and type 2 diabetes mellitus (T2DM) development. MetS patients often require polypharmacotherapy. The pathophysiological components of MetS disrupt the regulation and function of enzymes involved in the drug metabolism, thereby increasing the potential for adverse drug interactions. Structures involved in drug metabolism include phase I enzymes, primarily the cytochrome P450 (CYP), alongside phase II conjugating enzymes, such as UDP-glycosyltransferases (UGT) and Sulfotransferases (SULT).

Aims: The work was divided into 3 parts. Firstly, we compared the gene expression of selected phase I and phase II drug-metabolising enzymes in the liver and small intestine of rat models representing different MetS phenotypes. Secondly, we performed a relative quantification of CYP protein within hepatic microsomes of the rat MetS models. Thirdly, we compared the catalytic activities of selected CYP enzymes in mentioned hepatic microsomes.

Methods: The study utilised non-obese MetS models bred from the Wistar strain. The experimental groups comprised 5 to 7 animals (n=5-7). The investigated phenotypes included the Hereditary Hypertriglyceridaemic (HHTg) rat, the Spontaneously Hypertensive Rat (SHR) and transgenic SHR-CRP rat.

Results and Discussion: The isolated factors defining distinct MetS phenotypes drove significant differences in the mRNA expression of biotransformation enzymes. These data correlate with previous studies, demonstrating, for instance, an upregulation of Cyp7a1.

Findings underscore that varying MetS phenotypes distinctively alter phase I and II enzyme profiles, providing a mechanistic foundation for future advanced trials focusing on drug-disease interactions.

ACKNOWLEDGMENTS: This work was supported by grants IGA_LF_2021_013, IGA_LF_2022_006, IGA_LF_2023_004, IGA_LF_2024_006, IGA_LF_2025_009, IGA_LF_2026_006, CZ-OPENSOURCE-LM2023052, EATRIS-CZ-LM2023053 and by the Ministry of Health of the Czech Republic as part of its programme to support conceptual development among research organisations IKEM, IN00023001.

EVALUATION OF THE ANTI-INFLAMMATORY ACTIVITY OF A PRENYLATED FLAVOLIGNAN IN A MODEL OF INDUCED PAW EDEMA IN LABORATORY MICE

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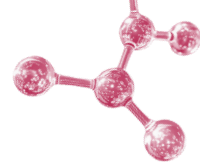
Introduction: In this study, synthetic prenylated flavonoid derivate structurally related to flavolignans from *Silybum marianum* was investigated. Flavolignans from milk thistle have demonstrated various biological activities, including antioxidant and anti-inflammatory effects, suggesting the potential biological relevance of this related compound.

Aims: The aim of this study was to evaluate, for the first time in vivo, the anti-inflammatory activity of novel prenylated flavonoid 8-prenyl 2,3-dihydrosilybinin.

Methods: The anti-inflammatory activity was evaluated using a carrageenan-induced plantar edema model in ICR mice. Forty male mice were randomly assigned into four groups receiving 8-prenyl 2,3-dihydrosilybinin in two doses 2 mg/kg and 4 mg/kg, indomethacin 5 mg/kg as reference and vehicle by oral probe. Edema was induced by intraplantar injection of 0.1 ml of 1% carrageenan and paw volume was measured plethysmometrically at 0, 30, 60, 120, 240 and 360 min.

Results and Discussion: The higher concentration of the compound (4 mg/kg) showed a more pronounced reduction of edema compared to the control group, particularly during the initial measurements. Although the differences between these groups decreased over time and did not reach statistical significance, the continuous reduction of edema indicates a potential anti-inflammatory effect. Higher concentrations of the compound may be considered for further evaluation. The plethysmometric results were complemented by histological evaluation.

ACKNOWLEDGMENT: Role of prenylation and glycosylation patterns in anti-inflammatory activity and metabolism of natural phenolic compounds (GA23-04655S).



HIGH-THROUGHPUT SCREENING VLIVU LEGO-LIPOFOSFONOXINŮ NA ENZYMOVOU AKTIVITU CYP3A4 a CYP2D6

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Úvod: LEGO-lipofosfonoxiny jsou novým typem antibiotik cílících na plazmatickou membránu bakterií. Významným aspektem v rámci preklinického hodnocení potenciálních terapeutik je stanovení jejich vlivu na enzymovou aktivitu mikrozomálního cytochromu P450 (CYP), který se podílí na metabolismu naprosté většiny léčiv.

Cíle: Analýza vlivu LEGO-lipofosfonoxinů (I76IK_219P1; I76IK_236P1; I76V1010P1; I76V845P1) na enzymovou aktivitu vybraných forem CYP.

Metody: Enzymová aktivita forem CYP3A4 a CYP2D6 v lidských jaterních mikrozomech byla stanovena za využití luminiscenčních metod P450-Glo™ dle protokolu výrobce (Promega Corporation, USA).

Výsledky a diskuze: V rámci screeningu byl zjištěn vliv testovaných LEGO-lipofosfonoxinů na enzymovou aktivitu CYP3A4 a CYP2D6. Výrazné snížení enzymové aktivity obou forem CYP bylo pozorováno především při vyšších koncentracích látek (150 a 300 $\mu\text{mol}\cdot\text{l}^{-1}$). Hodnota IC_{50} látky I76IK_219P1 byla stanovena na 30,82 $\mu\text{mol}\cdot\text{l}^{-1}$ (CYP3A4) a 79,99 $\mu\text{mol}\cdot\text{l}^{-1}$ (CYP2D6), látky I76IK_236P1 na 21,89 $\mu\text{mol}\cdot\text{l}^{-1}$ (CYP3A4) a 135,58 $\mu\text{mol}\cdot\text{l}^{-1}$ (CYP2D6), látky I76V845P1 na 136,54 $\mu\text{mol}\cdot\text{l}^{-1}$ (CYP3A4) a 288,72 $\mu\text{mol}\cdot\text{l}^{-1}$ (CYP2D6) a látky I76V1010P1 na 66,88 $\mu\text{mol}\cdot\text{l}^{-1}$ (CYP3A4). V případě I76V1010P1 nebyla pozorována inhibice CYP2D6, a proto hodnotu IC_{50} nebylo možné stanovit. Lékové interakce na úrovni metabolismu mohou ovlivňovat koncentrace léčiv v plazmě, čímž se zvyšuje riziko vzniku nežádoucích účinků či selhání terapie, a proto je nutné se těmito interakcemi dále zabývat.

PODĚKOVÁNÍ: Tato práce byla podpořena IGA_LF_2025_009 a IGA_LF_2026_006.

PHARMACOKINETICS, SYSTEMIC TOXICITY AND ACUTE BEHAVIOURAL EFFECTS OF NBOME/NBOH PSYCHEDELIC DERIVATIVES IN RATS

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Introduction: NBOMe and NBOH compounds are potent 5-HT_{2A} receptor agonists structurally related to classical psychedelics, but their use has been associated with severe intoxications and fatalities. Despite their increasing occurrence as novel psychoactive substances, comparative preclinical data on their pharmacokinetics, toxicity and acute behavioural effects remain limited. We therefore compared three serotonergic derivatives, 25CN-NBOMe, 2C-B-Fly-NBOMe and 25E-NBOH, in a series of rat studies.

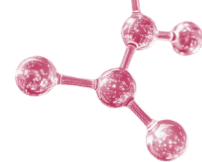
Methods: Adult male Wistar rats received acute subcutaneous administration of the investigated compounds at doses of 0.2, 1 and 5 mg/kg. Acute behavioural effects were assessed using the Open Field Test and the Prepulse Inhibition of Acoustic Startle Response at 15 and 60 min after administration. Pharmacokinetic profiles were characterised by LC-MS/MS analysis of serum and brain concentrations. Acute systemic toxicity was evaluated according to OECD Guideline 423 for 25CN-NBOMe and 25E-NBOH.

Results: All three compounds showed high brain penetration and sustained central nervous system exposure, with 25E-NBOH reaching the highest brain concentrations. Acute administration reduced locomotor activity in all three compounds: dose-dependently for 25CN-NBOMe and 2C-B-Fly-NBOMe, and at 1 and 5 mg/kg for 25E-NBOH, which additionally altered the spatial distribution of movement at all tested doses. Acoustic startle response was attenuated by all three compounds, whereas the effect on prepulse inhibition differed markedly: 25CN-NBOMe disrupted PPI only at 5 mg/kg at the 15 min onset, 2C-B-Fly-NBOMe produced no significant treatment effect on PPI despite strong ASR attenuation, and 25E-NBOH disrupted PPI across all tested doses and both onsets. Acute systemic toxicity also differed between the compounds: 25CN-NBOMe was classified as GHS acute toxicity Category 3, with an estimated LD₅₀ of approximately 200 mg/kg, whereas 25E-NBOH was classified as Category 4, with a predicted LD₅₀ of 1000 mg/kg. Significant hypothermia, rather than the expected hyperthermia, was observed after 25CN-NBOMe in individually housed animals.

Conclusions: Despite their structural similarity to classical psychedelics, NBOMe/NBOH derivatives display pronounced acute behavioural effects in rats. Their high CNS penetration, sustained brain exposure and inhibitory effects on motor and sensorimotor function highlight important safety concerns associated with these potent 5-HT_{2A} receptor agonists. The compounds nevertheless differed considerably in their disruption of sensorimotor gating and in acute systemic toxicity, demonstrating that relatively small structural modifications can substantially influence their pharmacokinetic, toxicological and behavioural profiles.

Keywords: NBOMe; NBOH; novel psychoactive substances; 5-HT_{2A} receptor; pharmacokinetics; prepulse inhibition; acute toxicity

ACKNOWLEDGEMENTS: This work was supported Ministry of the Interior of the Czech Republic (project VK01010212), Czech Science Foundation (project 23-07578K), Long-term conceptual development of research organization (RVO 00023752), Charles University research program Cooperatio-Neurosciences and private funds obtained via PSYRES, Psychedelic Research Foundation (<https://psyresfoundation.eu>).



ODPOVĚDNÉ NAKLÁDÁNÍ S LÉČIVY V ČESKÉ POPULACI: VĚK JAKO VÝZNAMNÝ FAKTOR BEZPEČNÉHO CHOVÁNÍ

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Úvod: Bezpečnost farmakoterapie závisí nejen na správném užívání léčiv, ale také na způsobu zacházení s nimi vč. jejich likvidace. Některé potenciálně rizikové postupy přetrvávají navzdory dostupnosti informací o bezpečném užívání léčiv.

Cíle: Zhodnotit vybrané aspekty bezpečného zacházení s léčivy v obecné populaci a identifikovat věkové rozdíly v odpovědném a rizikovém chování.

Metody: Průřezová dotazníková studie zahrnula 654 respondentů ve věku ≥ 15 let, rozdělených do skupin < 25 let ($n = 320$) a ≥ 25 let ($n = 334$). Hodnoceno bylo čtení příbalové informace, odevzdávání prošlých či nespotřebovaných léčiv do lékárny a konzultace problémů souvisejících s léčivy se zdravotnickým pracovníkem. Celková míra odpovědného chování byla exploratorně hodnocena pomocí indexu Percentage of Maximum Possible (POMP).

Výsledky a diskuse: Příbalovou informaci před užitím léčiva četlo 74,8 % respondentů bez rozdílu mezi věkovými skupinami (75,6 % vs. 74,0 %; $p = 0,687$). Prošlá či nespotřebovaná léčiva odevzdávalo do lékárny pouze 41,9 % respondentů < 25 let oproti 72,2 % respondentů ≥ 25 let ($p < 0,001$). Mezi respondenty se zkušeností s problémem souvisejícím s léčivem jej konzultovalo se zdravotnickým pracovníkem 84,5 % respondentů < 25 let vs. 75,5 % ≥ 25 let ($p = 0,064$). POMP index byl významně nižší u mladších respondentů (61,9 % vs. 73,4 %; $p < 0,001$). Úmyslné užití léčiva po uplynutí doby jeho použitelnosti uvedlo 51,5 % respondentů; tento postup současně uvedlo 51,9 % respondentů klasifikovaných jako vysoce či středně odpovědní podle POMP indexu. Výsledky poukazují na významné věkové rozdíly v bezpečném zacházení s léčivy a na nesoulad mezi deklarovanou odpovědností a některými formami rizikového chování.

LILY POISONING IN A CAT – A CASE STUDY

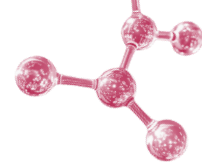
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Introduction: Poisoning by toxic plants is relatively common in animals. Lilies and daylilies are among the most dangerous plants specifically for cats. Their ingestion in cats (contrary to other animal species) is associated with the development of acute kidney injury and is frequently fatal. The time window for administering adequate therapy is very narrow, and once the renal tubular damage has developed, the prognosis of poisoning is poor.

Aims: This contribution aims to remind toxicologists, veterinarians, and the general public of the course of lily poisoning through a case that occurred in 2025. In this cat, poisoning developed after repeated consumption of water from a vase containing lilies, a route of exposure that has not yet been described in the literature.

Results and Discussion: The cat in this case was presented to the clinic several days after repeatedly drinking water from a vase containing lilies, and many hours after the onset of clinical signs. Typical clinical signs of lily poisoning include gastrointestinal symptoms, with vomiting also observed in our case. Specific symptoms of early kidney damage, such as polydipsia and polyuria, were not described by the owner. In contrast, signs of advanced renal damage, including oliguria, lethargy, depression, ataxia, and signs of probable pain, including vocalization, were reported in this case. Serum biochemical analysis revealed marked azotaemia, consistent with lily poisoning and other nephrotoxic insults. Gastrointestinal decontamination was not performed because of the prolonged interval between exposure and presentation to the clinic. Fluid therapy was initiated to reduce azotaemia and preserve kidney function. However, severe kidney damage rendered treatment ineffective, and urine production did not recover. Haemodialysis is not routinely available for veterinary patients in the Czech Republic; therefore, the cat was ultimately euthanized. Minimizing the risk of developing poisoning therefore mainly involves preventive measures and avoiding contact between cats and lilies.



THE IMPORTANCE OF INHALED ADMINISTRATION OF ANTIFIBROTIC DRUGS

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Introduction: To date, only two oral drugs have been approved for idiopathic pulmonary fibrosis treatment. No inhaled drugs providing effective local treatment are currently available.

Aims: The aim was to evaluate in vivo antifibrotic effects of selected drugs administered by nebulization in rats with bleomycin-induced fibrosis (BIF). Liraglutide and dexketoprofen were chosen based on previously described in vitro antifibrotic activity.

Methods: Rats were randomized in 3 groups: A/ treatment group (rats with BIF nebulized with study medication), B/ placebo group (rats with BIF nebulized with saline), and C/ control group (healthy rats nebulized with saline). Bleomycin was administered intratracheally during a short general anesthesia. The study medication or saline was administered once daily by nebulization using InExpose system for a month. Blood and BAL fluid were collected for antifibrotic markers concentration measurement by ELISA. Particular lung lobes were preserved for histology assessment, collagen quantification, and PCR evaluation of selected gene expression.

Results and Discussion: Liraglutide significantly reduced the expression of Fibronectin 1 (FN1) in comparison with placebo ($p = 0.0345$). FN1, typically upregulated in fibrotic diseases, represents a crucial fibrosis driver that promotes fibroblast proliferation, myofibroblast differentiation, and collagen deposition. Lower FN1 expression in rats treated with liraglutide indicates its potential antifibrotic effect. A similar, but not statistically significant, trend of overexpressed genes such as TGFB1, PDGFR-A, PDGFR-B, and COL1A1 was also observed in the placebo group. In the dexketoprofen study, a comparable trend of overexpressed FN1, TGFB1, and COL1A1 in the placebo group was found. Further analyses are currently ongoing.

ACKNOWLEDGMENT: This work was produced with the financial support of the European Union and the Ministry of Education, Youth and Sports, under the Jan Amos Komenský Operational Programme, project Returns at CU (Reg. No. CZ.02.01.01/00/24_037/0013839).

INTERAKCE NOVÝCH POTENCIÁLNÍCH ANTIBIOTIK - LIPOFOSFONOXINŮ S LIDSKÝM JATERNÍM CYP2A6 IN VITRO

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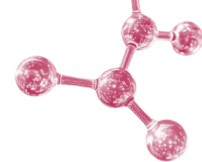
Úvod: Jednou z možných cest v boji proti stále se zvyšující antibiotické rezistenci bakterií je výzkum a zavedení nových tříd antibiotik, (lipofosfonoxinů), které vykazují potenciál v léčbě infekcí způsobených rezistentními mikroorganismy.

Cíl studie: Stanovení potenciálního inhibičního vlivu lipofosfonoxinů na enzymovou aktivitu lidského jaterního CYP2A6 in vitro.

Metodika: Byl sledován vliv nových potenciálních antibiotických látek lipofosfonoxinů na enzymovou aktivitu lidského jaterního CYP2A6. Testované látky byly inkubovány s mikrosomální směsí ve vzrůstající koncentraci (0-100 μM) ve dvou různých časech inkubace při 37 °C (3 min, resp. 30 min). Rovněž byly provedeny experimenty pro výpočet inhibiční konstanty K_i , tedy při čtyřech různých koncentracích specifického substrátu. Pro stanovení enzymové aktivity mikrosomálního CYP2A6 byl použit specifický substrát kumarin. Jeho metabolit 7-hydroxykumarin byl detekován pomocí HPLC s fluorescenční detekcí (excitace 338 nm, emise 458 nm).

Výsledky a diskuze: Inhibiční vliv testovaných látek na enzymovou aktivitu CYP2A6 byl pozorován až u vyšších koncentrací látek v reakční směsi, přičemž hodnoty IC_{50} se pohybovaly řádově v desítkách μM . Kinetická analýza interakce látky kódově označené LEGO-2 naznačuje možnou parciálně akompetitivní inhibici ($K_i = 27,66 \pm 5 \mu\text{M}$). Zatímco látka LEGO-4 pravděpodobně vykazuje netypický alosterický mechanismus inhibice enzymové aktivity CYP2A6. Tradiční linearizační výnosy (Lineweaver-Burkův, Dixonův) vykazovaly u této látky výraznou nelinearitu. Výsledky nelineární regrese za použití tříparametrické Hillovy rovnice ukazují, že studovaná látka LEGO-4 působí jako parciální alosterický smíšený inhibitor, který nemění primární afinitu k substrátu, ale inhibuje přeměnu tohoto substrátu na metabolit, současně tento process doprovází skoková ultra-senzitivita CYP.

PODĚKOVÁNÍ: Autoři děkují za finanční podporu IGA UPOL 2025_009 a IGA UPOL 2026_006.



IMPROVEMENT OF SUB-THERAPEUTIC METHOTREXATE BY CROCIN IN COMBINATION THERAPY IN AN ANIMAL MODEL OF ADJUVANT ARTHRITIS

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Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by synovial inflammation and progressive joint destruction. Pro-inflammatory mediators such as interleukin-1 β (IL-1 β), interleukin-17 (IL-17), and monocyte chemoattractant protein-1 (MCP-1) play a significant role in RA progression. Methotrexate (MTX) is the mainstay in RA therapy, but its efficacy may be limited by suboptimal responses and adverse effects. Crocin, the bioactive constituent of *Crocus sativus* L., has anti-inflammatory properties.

Aims: We investigated the effects of crocin alone and with subtherapeutic MTX in experimental adjuvant arthritis, with focus on HPV, IL-1 β , IL-17, and MCP-1 levels.

Methods: Adjuvant arthritis was induced in male Lewis rats. Animals were divided into five groups: HC, AA, AA+MTX, AA+CR, and AA+CR+MTX. MTX was given orally at 0.3 mg/kg twice weekly, while crocin was administered orally at 50 mg/kg daily. Hind paw volume (HPV) was measured as an index of disease severity. Plasma IL-1 β , IL-17, and MCP-1 levels were determined by ELISA on days 14 and 28.

Results and Discussion: Untreated arthritic animals showed significant increases in HPV and inflammatory mediators compared to healthy controls. MTX alone was only moderately effective. Crocin treatment, especially in combination with MTX, attenuated arthritis severity and suppressed pro-inflammatory mediators. Combination therapy significantly reduced HPV, MCP-1 and IL-17 compared to untreated arthritic animals and MTX monotherapy. Crocin-treated groups also showed lower IL-1 β concentrations. These findings suggest that crocin may enhance the therapeutic effect of low-dose MTX in experimental arthritis.

ACKNOWLEDGMENT: This study was supported with the project VEGA no.2/0126/23, VEGA no.2/20091/23, VEGA no.2/0079/24, FaF/26/2026, FaF 28/2026, and APP0714.

ENDOKRINNĚ DISRUPTIVNÍ POTENCIÁL SMĚSÍ ENVIRONMENTÁLNÍCH KONTAMINANTŮ VE VNITŘNÍM PROSTŘEDÍ

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Úvod: Endokrinní disrupce představuje významné zdravotní riziko spojené s expozicí chemickým látkám schopným narušovat hormonální signalizaci. Endokrinní disruptory (EDCs) mohou ovlivňovat endokrinní systém prostřednictvím řady mechanismů, včetně agonistických či antagonistických interakcí s hormonálními receptory nebo narušení syntézy, metabolismu, transportu či účinku hormonů. Zvláště citlivým obdobím je raný vývoj organismu, kdy může expozice těmto látkám vést k trvalým změnám reprodukčního, nervového, imunitního i dalších orgánových systémů.

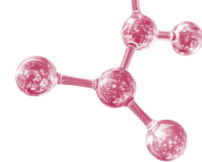
Expozice endokrinním disruptorům (EDCs) pochází z řady zdrojů a zahrnuje široké spektrum látek uvolňovaných z různých materiálů i složek životního prostředí. Pro hodnocení celkového potenciálu chemických směsí vyvolávat endokrinní disrupci jsou velmi vhodné in vitro biotesty zaměřené na klíčové mechanismy jejich působení.

Významné zdravotní riziko může představovat expozice polutantům ve vnitřním prostředí budov, kde lidé tráví až 90 % svého času a kde mohou koncentrace některých škodlivin převyšovat úroveň ve venkovním prostředí. Zvláště zranitelnou skupinou jsou malé děti (≤ 5 let), a to vzhledem k probíhajícímu vývoji organismu i vyšší expozici způsobené častým pohybem po podlaze a opakovaným kontaktem rukou s ústy.

Metody: V této studii byl proto odebrán usazený domácí prach z domácností s malými dětmi v osmi evropských zemích (Česko, Estonsko, Itálie, Nizozemsko, Portugalsko, Slovinsko, Švédsko a Anglie), ze kterého byly připraveny organické extrakty. Endokrinně disruptivní potenciál těchto komplexních směsí byl následně hodnocen pomocí souboru in vitro biotestů založených na strategii využívající koncept drah škodlivého účinku (Adverse Outcome Pathways, AOP).

Výsledky a diskuze: Výsledky ukázaly, že směsi chemických látek přítomné v domácím prachu vykazují napříč evropskými zeměmi různou míru biologické aktivity i odlišné mechanismy endokrinního působení. Nejčastěji byla zaznamenána antiestrogenní aktivita a účinky spojené s aktivací arylhydrokarbonového receptoru. Ve všech vzorcích analyzované podskupiny bylo navíc zjištěno významné narušení transportu tyroidních hormonů.

PODĚKOVÁNÍ: Projekt byl financován z programu Evropské komise v rámci programu Horizon Europe, HADEA, výzkum a inovace (INQUIRE - 101057499).



UNVEILING THE THERAPEUTIC POTENTIAL OF TOPICALLY APPLIED L-(+)-ERGOTHIONEINE IN THE PERIWOUND AREA

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Introduction: L-(+)-Ergothioneine (EGT), a naturally occurring thione–thiol antioxidant transported by the blood protein OCTN1, possesses strong cytoprotective and anti-inflammatory properties.

Aim: This study investigated whether topical application of EGT to the periwound skin could enhance wound repair.

Method: Full-thickness excisional wounds were created on the dorsum of Wistar rats, which were divided to three groups: the untreated control group and two groups treated with EGT-loaded gauze applied to the periwound area at doses of 130 or 650 µg/cm².

Results: Both EGT-treated groups exhibited faster wound closure than the untreated controls. Even EGT applied at the lower dose (130 µg/cm²) had the therapeutic efficacy 87 % over a 15-day period. The healing kinetics was also evaluated using Logistic and Weibull models. According to the Logistic model, wound healing reached approx. 70% in the control group compared with 93% in the group treated by EGT at the higher dose (650 µg/cm²) by day 15. These findings demonstrated that periwound topical application of EGT significantly promoted wound healing, highlighting its potential as a transdermally active antioxidant and a promising therapeutic approach for advanced wound management [1].

Reference: [1] Šoltés L., Jardine A.M., Biró C., Švík K., Mach M., Valachová K. Unveiling and benefits of topically applied L-(+)-ergothioneine in periwound region. *Int. J. Mol. Sci.* 2026, 27(14), 6102. <https://doi.org/10.3390/ijms27146102>.

ACKNOWLEDGMENT: The study was supported by the VEGA grant 2/0008/23.

PLASMA MIR-29A AND MIR-29B EXPRESSION ACROSS CHRONIC DISEASES: EXPLORING THEIR ROLE IN EXTRACELLULAR MATRIX REMODELING

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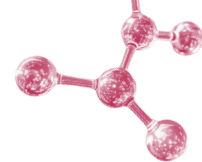
Introduction: Chronic diseases share common molecular mechanisms involving chronic inflammation, dysregulated tissue repair and extracellular matrix (ECM) remodeling. The miR-29 family is a major post-transcriptional regulator of ECM homeostasis and an emerging therapeutic target in fibrosis-associated pathways. However, the biological significance of circulating miR-29a and miR-29b remains incompletely understood. Rather than representing direct biomarkers of tissue fibrosis, circulating miR-29a and miR-29b may reflect systemic processes associated with ECM remodeling.

Aims: To compare expression the relative plasma of miR-29a and miR-29b in patients with chronic kidney disease, rheumatoid arthritis, sarcopenia, Parkinson's disease and multiple sclerosis, and to explore their association with common mechanisms of extracellular matrix remodeling.

Methods: Peripheral plasma samples were obtained from patients recruited at specialized clinical departments. Total RNA was isolated from plasma, and the relative expression of miR-29a and miR-29b was determined by reverse transcription quantitative real-time PCR (RT-qPCR).

Results and Discussion: The study investigates whether circulating miR-29a and miR-29b exhibit disease-specific or shared expression profiles across clinically distinct chronic diseases. The findings will be interpreted in the context of extracellular matrix remodeling rather than tissue-specific fibrosis. This approach may contribute to a better understanding of circulating miRNAs as minimally invasive biomarkers with potential utility for monitoring chronic disease progression and supporting the development of future pharmacological strategies targeting ECM remodeling.

ACKNOWLEDGMENT: This work was supported by APVV-23-0557, VEGA 1/0523/25, StemCell Pharmacol 401101C02.



SENSITIZATION TESTING OF MEDICAL DEVICES USING IN VIVO AND IN VITRO METHODS

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Introduction: Sensitization is an obligatory prerequisite of biocompatibility assessment of medical devices. The recently amended standard ISO 10993-10:2021 allows only in vivo test methods on animals or humans, but includes also a list of non-animal methods, validated for neat chemicals, which might be used after verification of applicability for complex mixtures as medical devices or their extracts.

Aims: Our pilot study aimed to compare results of regulatory testing of 10 real life medical devices by Local Lymph Node Assay (OECD TG 442A), performed in compliance with the ARRIVE guidelines, with results of a battery of assays covering all three key events of the Sensitization Adverse Outcome Pathway (DPRA, OECD TG 442C; LuSens, OECD TG 442D; h-CLAT, OECD 442E), conducted according to GCCP guidelines.

Methods: The samples were extracted or diluted in saline solution, DMSO and/or culture medium. The 4 positive samples in the in vivo test were correctly classified by the battery of non-animal tests using "the 2 of 3" principle of the Defined Approaches for Skin Sensitisation (OECD TG 497).

Results and Discussion: One sample (rubber glove) was negative in vivo and positive in vitro, showing the high sensitivity of the in vitro methods to latex and similar compounds. The presented results confirm the feasibility of non-animal methods for skin sensitization of medical devices and provide information on the optimization of these methods in accordance with the current European Commission initiative to define a Roadmap to phase out animal testing in the EU.

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MARINE MERODITERPENOIDS AS NOVEL POTENTIAL INHIBITORS OF PLATELET AGGREGATION

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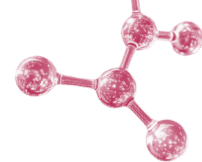
Introduction: Platelets are small, anucleated cells that play a crucial role in hemostasis and thrombosis. Excessive platelet activation contributes to the onset and development of thrombotic cardiovascular diseases. Since current antiplatelet pharmacotherapy present relevant side effects, increased attention is being paid to natural bioactive compounds. Marine products, such as algae represent an interesting source of pharmacologically active substances which is, however, largely unexplored. Meroditerpenoids isolated from the brown alga *Cystoseira usneoides* have previously been reported to exhibit potent antioxidant and anti-inflammatory properties.

Aims: To evaluate the effect of three meroditerpenoids (PH1, PH2, PH4) isolated from marine alga *Cystoseira usneoides* on platelet aggregation and to determine the effects on calcium homeostasis as a potential mechanism of their antiplatelet activity.

Methods: Impedance aggregometry was used to measure the platelet aggregation. Whole blood was collected into heparinized tubes from generally healthy volunteers of both sexes. Platelet aggregation was induced using various agonists: arachidonic acid (AA), adenosine diphosphate (ADP), platelet-activating factor (PAF), U-46619, and collagen. Intracellular calcium levels were measured in platelet suspension using a fluorescence spectrophotometer.

Results and Discussion: All three meroditerpenoids inhibited platelet aggregation induced by five different agonists. Tested compounds prevented calcium release but did not inhibit calcium entry. The obtained results indicate that meroditerpenoids isolated from *Cystoseira usneoides* may serve as promising lead compounds for the development of novel antiplatelet agents.

ACKNOWLEDGMENT: This work was supported by the program PRIMUS, Charles University (project No. PRIMUS/25/MED/001)



PRENATAL VALPROIC ACID EXPOSURE REDUCES HEPATIC CYTOCHROME P450 METABOLIC CAPACITY IN ADULT RAT OFFSPRING

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Introduction: Prenatal exposure to valproic acid (VPA) is a well-established teratogenic model in both humans and rodents. Disruption of neural tube development induces long-lasting behavioural abnormalities in offspring, including impaired communication and social interaction, increased anxiety, and repetitive behaviours, which resemble the core features of autism spectrum disorder (ASD). In rodents, the ASD model is commonly induced by a single administration of VPA on gestational day (GD) 12.5.

Aims: This study investigated whether prenatal exposure to VPA affects the metabolic activity of hepatic cytochrome P450 (CYP) enzymes in adult offspring.

Methods: Liver samples were collected from adult male and female Sprague–Dawley rats prenatally exposed to a single dose of VPA (500 mg/kg) or saline on GD 12.5. Liver microsomes were prepared and characterized by determining total protein and total CYP content. The metabolic activities of CYP1A2, CYP2C6, CYP2D, and CYP3A were assessed as the rate of conversion of selective probe substrates in the presence of an NADPH-generating system. Specific (per mg microsomal protein), molecular (per nmol total CYP), and tissue (per g liver tissue) metabolic activities were calculated.

Results and Discussion: Prenatal VPA exposure significantly reduced the total protein content of isolated liver microsomes. No significant changes were observed in the specific or molecular metabolic activities of the CYP enzymes studied. In contrast, tissue metabolic activity, reflecting the overall hepatic metabolic capacity, was significantly decreased for CYP1A2, CYP2C6, and CYP2D. These findings suggest that the effects of prenatal VPA exposure extend beyond the central nervous system and may also alter hepatic drug-metabolizing capacity. Although the underlying mechanisms were not investigated in the present pilot study, they warrant further investigation.

ACKNOWLEDGMENT: This work was supported by the Ministry of Health of the Czech Republic, grant no. NW25J-07-00046.

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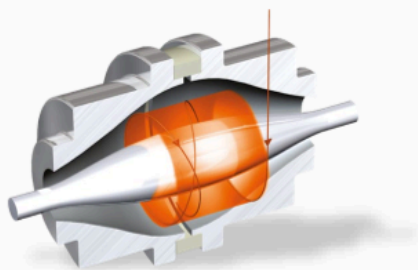
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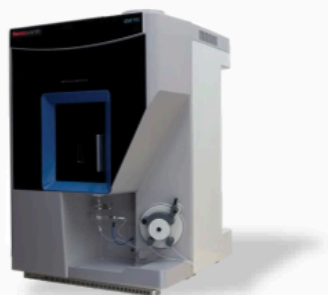
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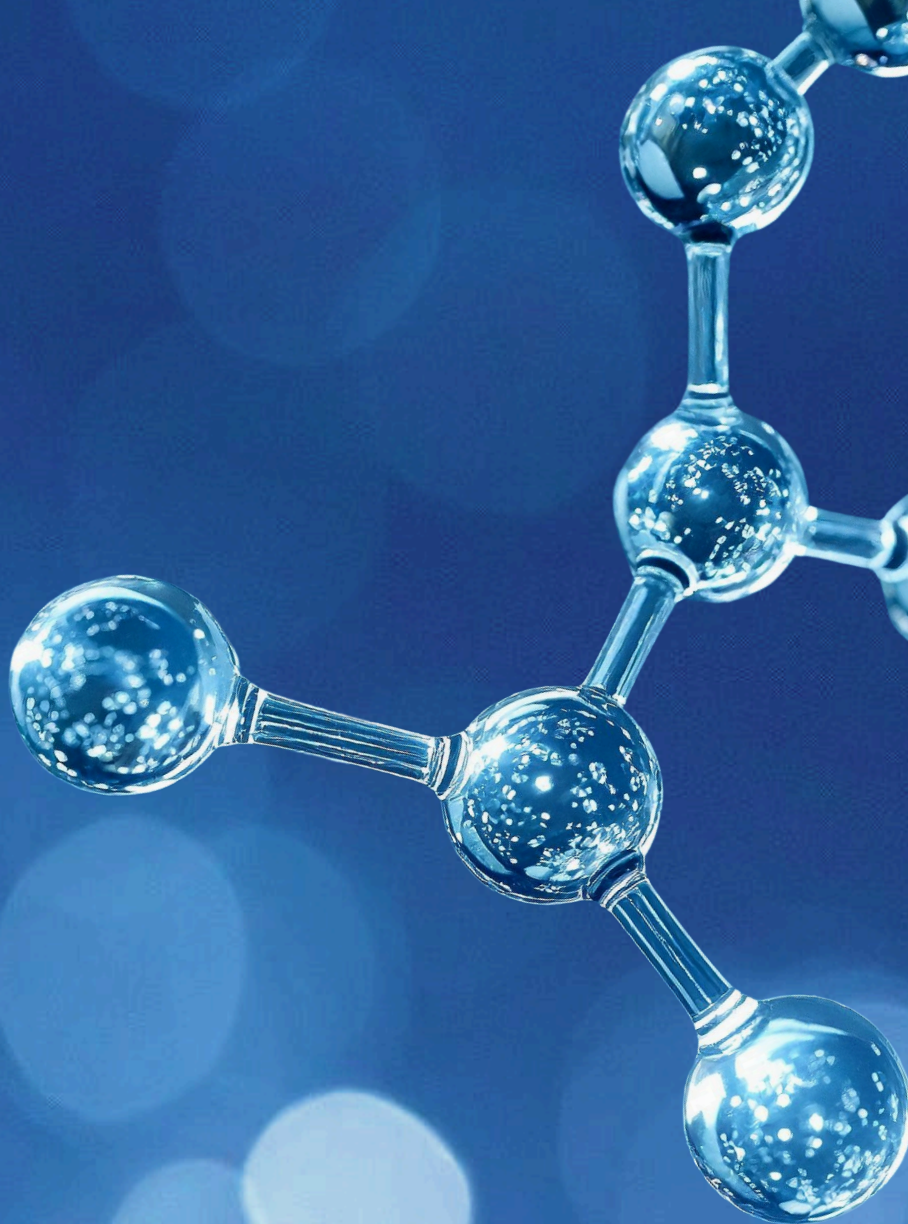
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