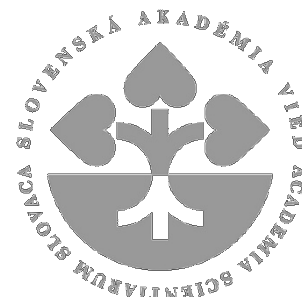


Institute of Experimental Pharmacology and Toxicology



Slovak Academy of Sciences

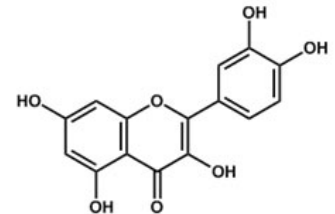
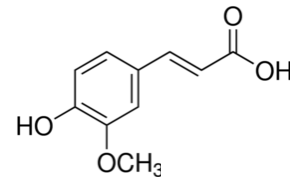


Assessment Period 2012-2015

November 24, 2016

Scientific foci

- **Pharmacological interventions of chronic „life-style” diseases**
- Inflammatory processes, reactive oxygen species (ROS) mediated pathologies, metabolic disorders, developmental aspects of chronic diseases
- Original synthetic substances
- Natural substances
- Known substances with new indications
- Animal models of human diseases
- Complex pharmacological research
- New molecules and therapeutic approaches





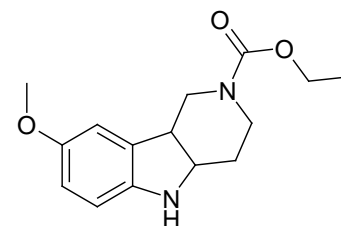
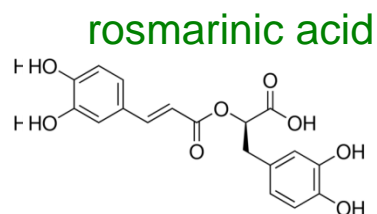
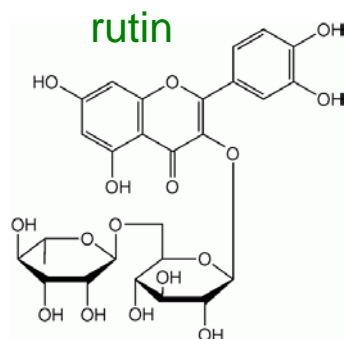
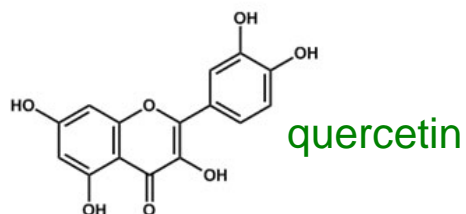
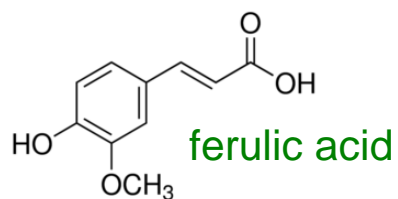
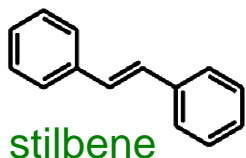
Department of Toxicology and Laboratory Animals Breeding at Dobra Voda

- Commercial toxicity studies in compliance with Good Laboratory Practice (GLP)
- Production of hyperimmune sera
- Breeding of small laboratory animals and production of feed diets

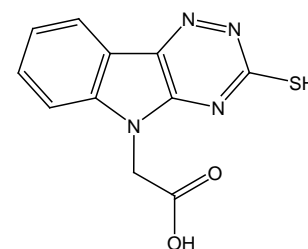


R&D activities

Compounds



SMe1EC2 –
selected from 84
derivatives

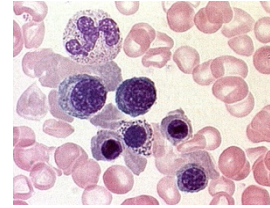


Cemtirestat - aldose
reductase inhibitor



Diseases/pathologies

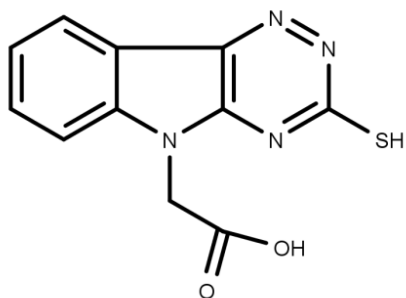
- Diabetes mellitus
- Rheumathoid arthritis
- Developmental disorders
- Neurodegenaration
- Neuroinflammation



Target systems

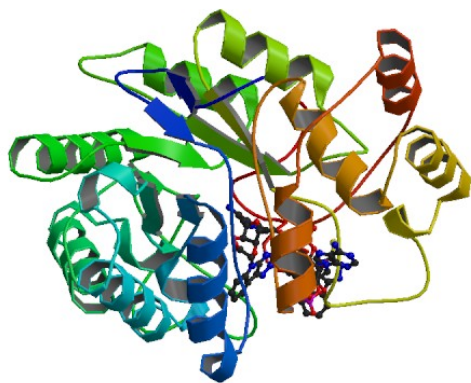
- Serine proteases
- Aldose reductase
- SERCA
- Hyaluronan
- Human neutrophils
- Endothelium
- Developing organism

Cemtirestat - a novel compound for the treatment and prevention of diabetic complications



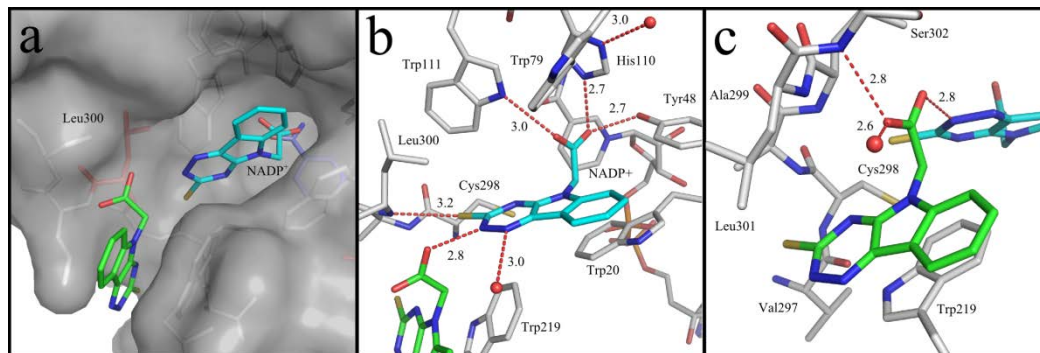
Inhibition of key enzymes

human aldose reductase	$IC_{50} = 0.057 \pm 0.002 \mu\text{M}$
rat aldose reductase	$IC_{50} = 0.097 \pm 0.019 \mu\text{M}$
rat aldehyde reductase	$IC_{50} = 40.55 \pm 2.05 \mu\text{M}$



pdb code

4QX4

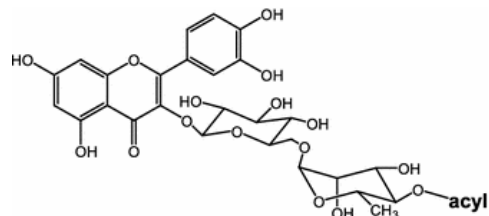


Efficient inhibition and high selectivity

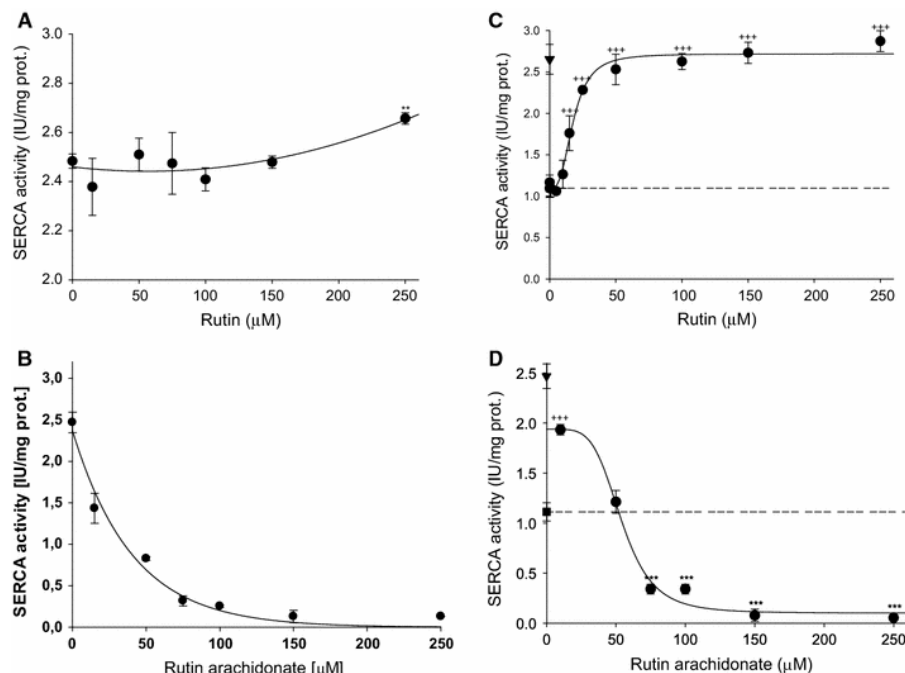
Patent: WO 2015/057175 A1.

M. Stefek et al. J Med Chem. 58(6):2649-57 (2015)

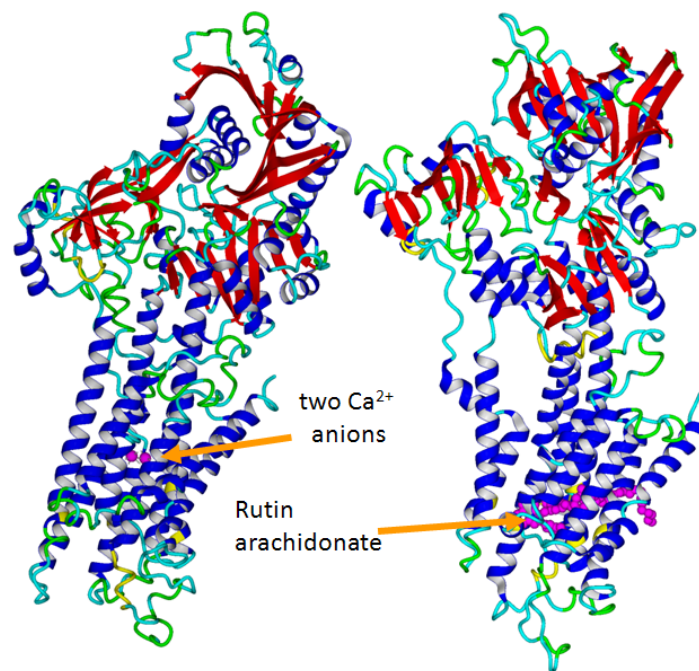
Rutin affects calcium homeostasis through SERCA protection and modulation



Rutin arachidonate is able to inhibit SERCA1 with $IC_{50} = 23 \pm 6.5 \mu M$
 Rutin and its derivatives protect SERCA1 against oxidative injury



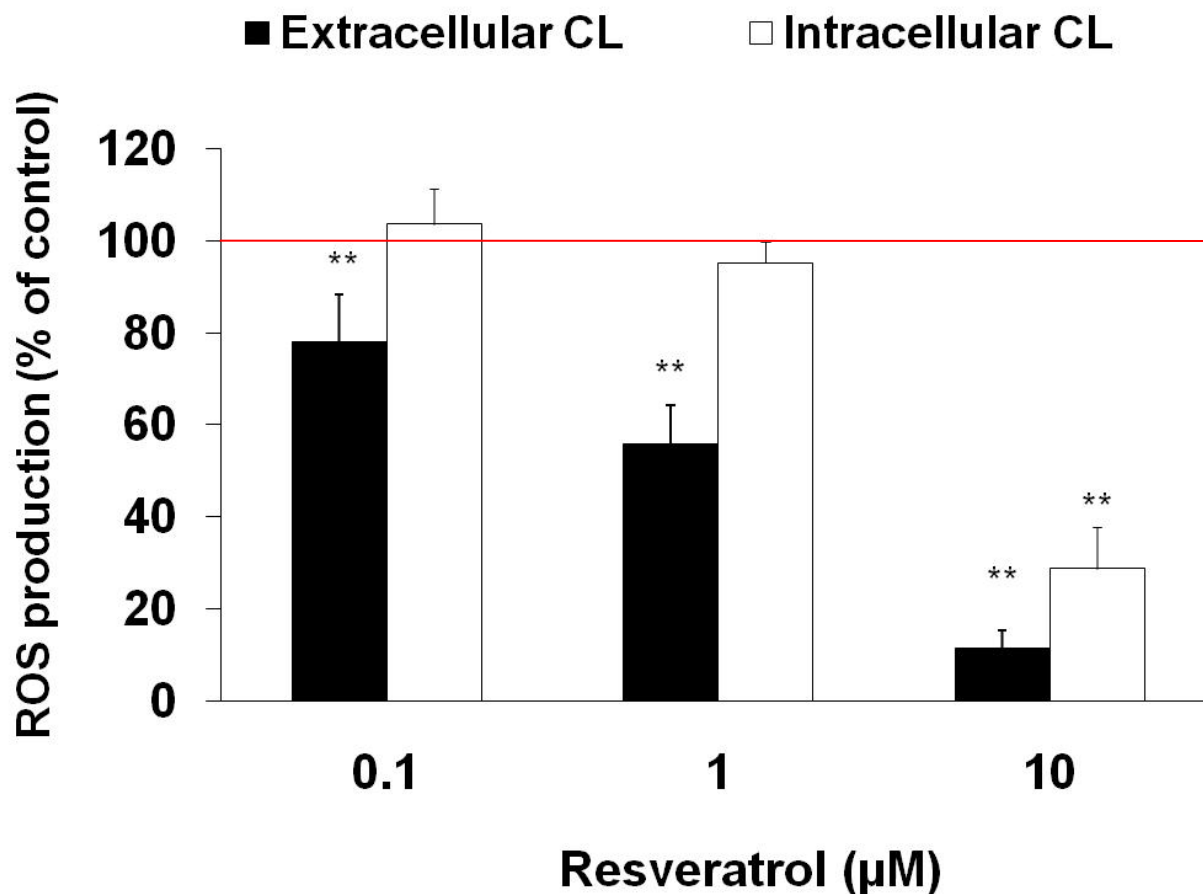
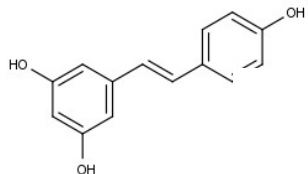
(SERCA1) activity after treatment with: **A** rutin and **B** rutin arachidonate (in the absence of $ONOO^-$), **C** rutin and **D** rutin arachidonate (in the presence of $ONOO^-$).



Position of rutin arachidonate in SERCA1
 (docking and optimization)

VISKUPICOVA J., STROSOVA MK., ZIZKOVA P., MAJEKOVA M., HORAKOVA L. *Mol Cell Biochem*, 2015 Apr; 402(1):51-62.

Resveratrol inhibits extra- and intra-cellular formation of ROS in human neutrophils



NOSÁL, Radomír - DRÁBIKOVÁ, Katarína - JANČINOVÁ, Viera - PEREČKO, Tomáš - AMBROŽOVÁ, Gabriela - ČÍŽ, Milan - LOJEK, Antonín - PEKAROVÁ, Michaela - ŠMIDRKAL, Jan - HARMATHA, Juraj. Oxidative medicine and cellular longevity, 2014, vol. 2014, article ID 706269, 9 p.

Novel quercetin derivative reduces inflammation in microglia

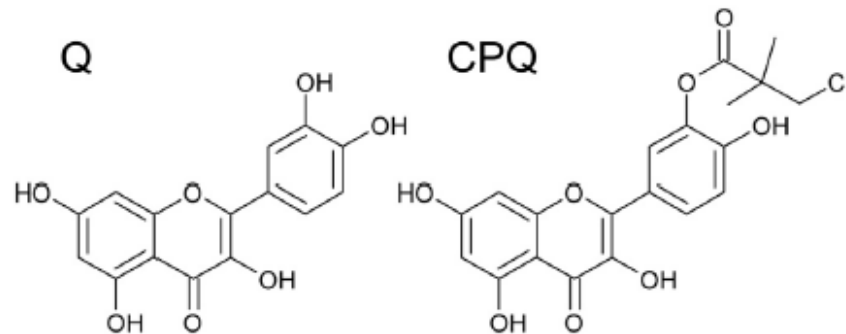
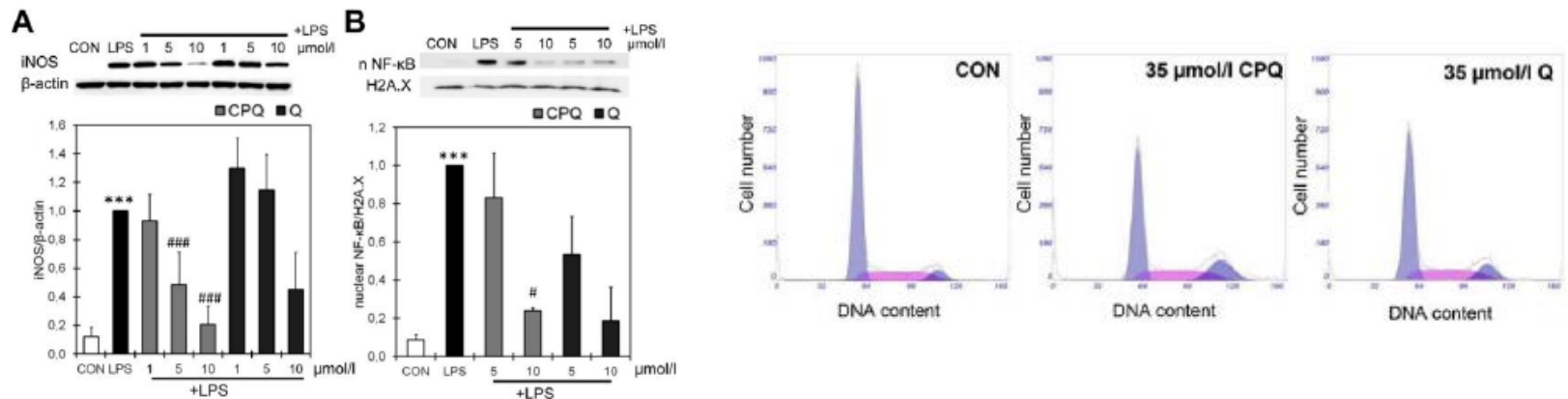
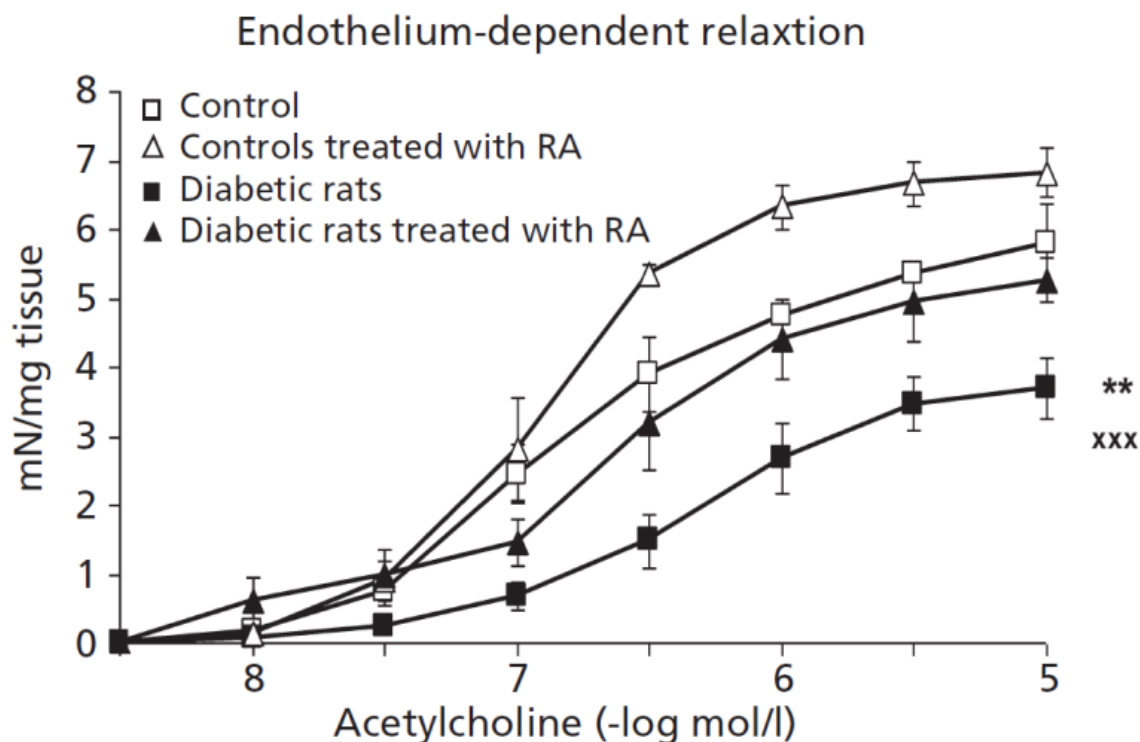
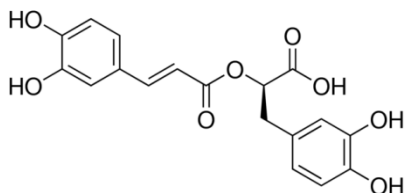


Fig. 1. Structures of the compounds tested, CPQ – 3'-O-(3-chloropivaloyl) quercetin, Q – quercetin.

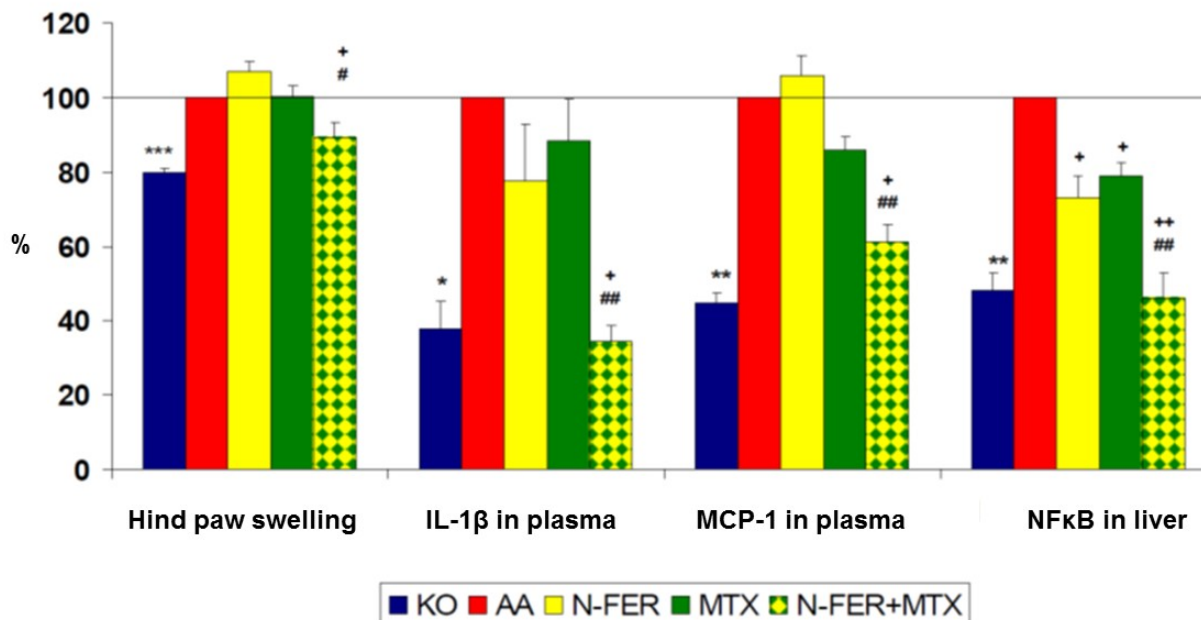
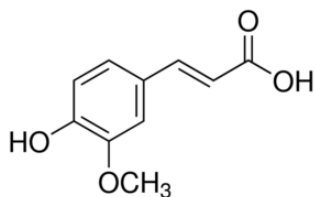


Rosmarinic acid protects endothelium in the diabetic rats

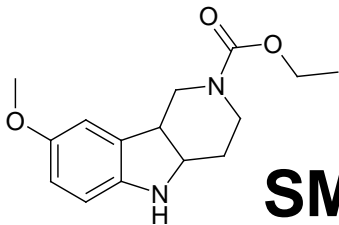


SOTNÍKOVÁ, Ružena - OKRUHLICOVÁ, Ľudmila - VLKOVIČOVÁ, Jana - NAVAROVÁ, Jana - GAJDÁČOVÁ, Beata - PIVÁČKOVÁ, Lenka - FIALOVÁ, Silvia - KŘENEK, Peter. *Journal of Pharmacy and Pharmacology*, 2013, vol. 65, no. 5, p. 713-723.

N-feruloylserotonin in combination with methotrexate ameliorates manifestations of adjuvant arthritis in rats

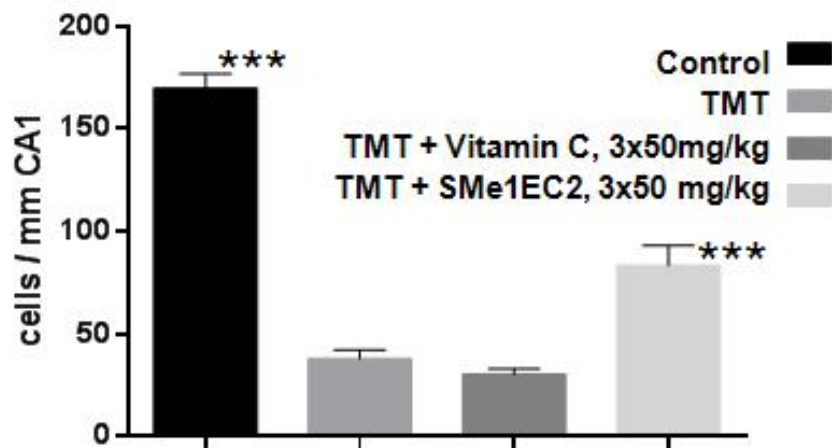


KUNCÍROVÁ, Viera - PONIŠT, Silvester - MIHALOVÁ, Danica - DRÁFI, František - NOSÁL', Radomír - ACQUAVIVA, Alessandra - GARDI, Concetta - HARMATHA, Juraj - HRADKOVÁ, Iveta - BAUEROVÁ, Katarína. *Fundamental & Clinical Pharmacology*, 2014, vol. 28, p. 616-626.



SMe1EC2 compound protects hippocampal CA1 area

CELLULARITY INDEX (CI)

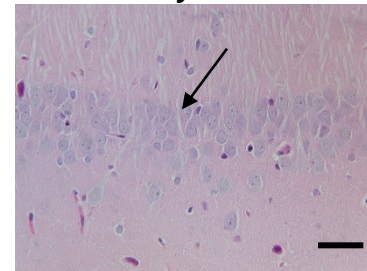


GÁSPÁROVÁ, Zdenka - STARÁ, Veronika - JANEGA, Pavol - NAVAROVÁ, Jana - SEDLÁČKOVÁ, Natália - MACH, Mojmír - UJHÁZY, Eduard. *Neuroendocrinology Letters*, 2014, vol. 35, no. 6, p. 454-462.

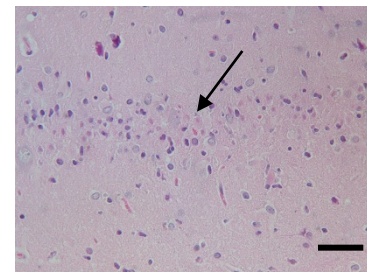
Day 31 after TMT
administration

Hematoxylin-Eosin

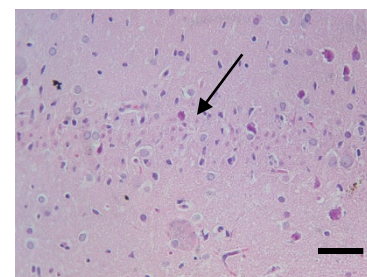
Control
100%



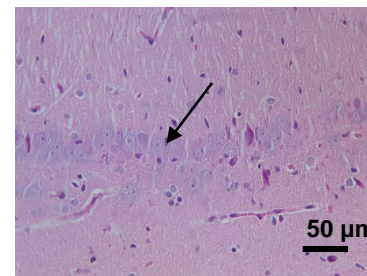
TMT
21%



TMT + Vitamin C
18%



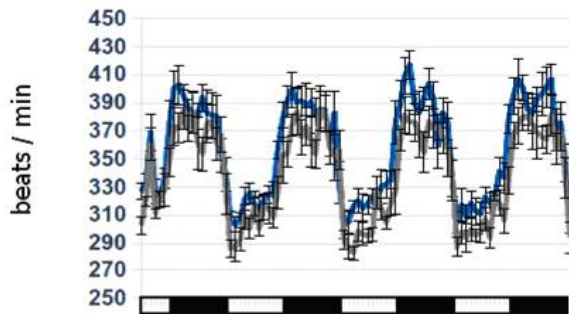
TMT + SMe1EC2
48%



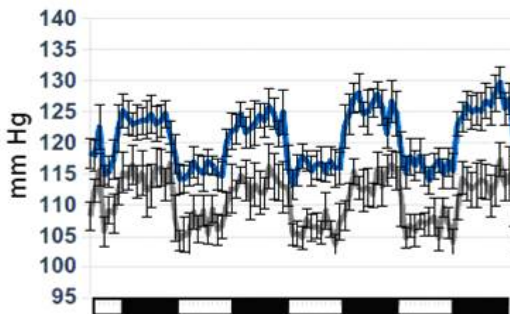
Prenatal hypoxia causes an increased blood and pulse pressure in adult rats

► Cardio telemetry

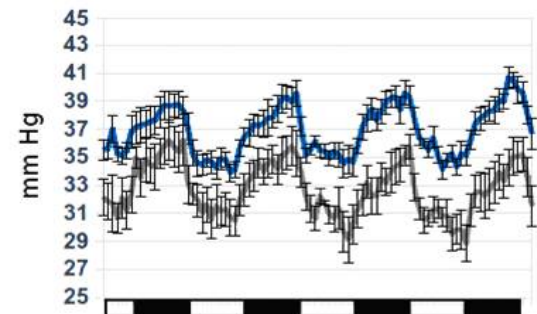
Heart rate



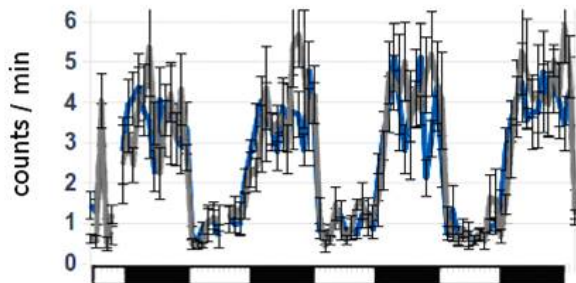
Systolic blood pressure



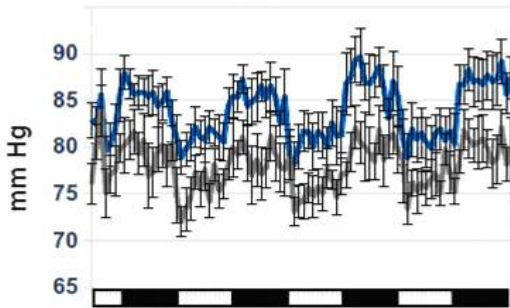
Pulse pressure



Locomotor activity



Diastolic blood pressure



— Control
— Prenatal hypoxia

Telemetry during weekend
10 days after cannulation

UJHÁZY, Eduard - DUBOVICKÝ, Michal - NAVAROVÁ, Jana - SEDLÁČKOVÁ, Natália - DANIHEL, Ľudovít - BRUCKNEROVÁ, Ingrid - MACH, Mojmír. *Food and chemical toxicology*, 2013, vol. 61, p. 233-239.

Research status of the Institute in the international and national contexts



International cooperation

- University College, London, **Great Britain**
- University of Saint Andrews, **Great Britain**
- Sapienza Universita, Roma, **Italy**
- University of Siena, Siena, **Italy**
- University of Turin, Turin, **Italy**
- Consiglio Nazionale delle Ricerche, **Italy**
- Friedrich Schiller University, Jena, **Germany**
- Spanish National Cancer Research Center, Madrid, **Spain**
- Institute of Neurosciences
Universitat Autònoma de Barcelona, Barcelona, **Spain**
- University of Athens, **Greece**
- Faculty of Medicine, Gazi University, Ankara, **Turkey**
- Middle East Technical University, Ankara, **Turkey**
- Research Center of Neurology, RAMS, Moscow, **Russia**
- Carol Davila University of Medicine and Pharmacy
Bucharest, **Romania**
- The Czech Academy of Sciences, **The Czech Republic**

National cooperation

- Institute of Heart Research **SAS**
- Institute of Molecular Physiology and Genetics **SAS**
- Institute of Normal and Pathological Physiology **SAS**
- Institute of Experimental Endocrinology BMC **SAS**
- Institute of Chemistry **SAS**
- Faculty of Pharmacy **CU**
- Jessenius Faculty of Medicine **CU**
- Faculty of Medicine **CU**
- Faculty of Natural Sciences **CU**
- Faculty of Chemical and Food Technology **STU**
- Faculty of Civil Engineering **STU**
- Advanced Technologies and New Materials Research Institute **STU**

EU Structural Funds

- Transfer of knowledge and technologies from research and development in toxicology on evaluation of environmental and health risk
- Evaluation of natural substances and their selection for prevention and treatment of lifestyle diseases
- Centre of excellence for glycomics (common core facility)
- University Science Park for Biomedicine Bratislava



International conferences

- International Interdisciplinary Toxicology Conferences TOXCON (Since 1996)
- Membership in EUROTOX and in Executive Committee of EUROTOX
- 2017 – EUROTOX 2017 Conference in Bratislava (Slovak Toxicology Society SETOX)



BRATISLAVA
SLOVAK NATIONAL THEATRE

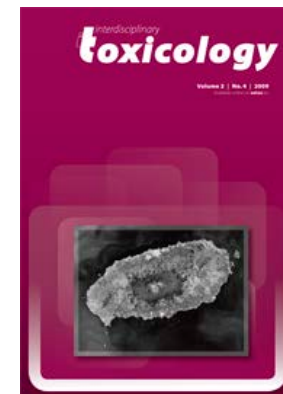
September 10–13, 2017

Journal edited / published

Interdisciplinary Toxicology

(Since 2008)

- The Institute has a leading role in the **development of toxicology in Slovakia**. Together with SETOX publishes an international open-access journal “Interdisciplinary Toxicology”, which is indexed in several well-known scientific databases (**PubMed, PubMed Central, Elsevier - SCOPUS, Medline, EBSCO, FSTA, DOAJ, Chemical Abstracts Service (CAS), etc.**)



EDITOR-IN-CHIEF

Michal Dubovický, Slovakia

EXECUTIVE EDITOR-IN-CHIEF

Mojmír Mach, Slovakia

EDITORIAL ADVISORY BOARD

Arturo R. Anadon, Spain

Radomír Nosál, Slovakia

Russel J. Reiter, USA

Christina Ruden, Sweden

Marie Stiborová, Czech Republic

Aristidis M. Tsatsakis, Greece

Martin F. Wilks, Switzerland

interdisciplinary
toxicology

OPEN  ACCESS



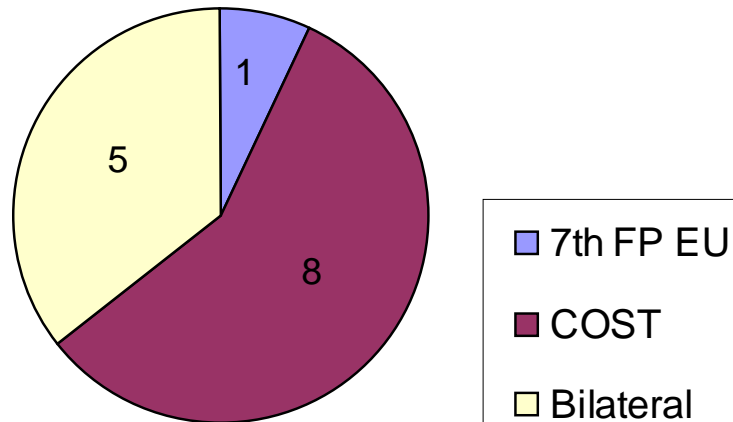
**DE GRUYTER
OPEN**

Projects structure, research grants and other funding resources

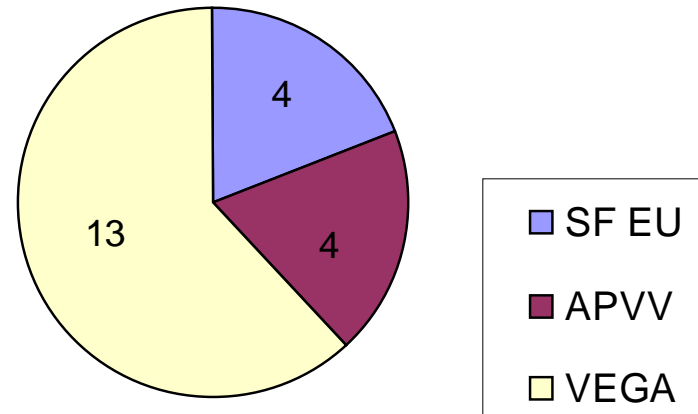


International and national project structure

International projects



National projects





Other funding resources

Contracts and research projects with commercial partners:

- Production of hyperimmune sera in rabbits
- Production of hyperimmune eggs in hens
- Verification of antiadhesive agents' efficacy in rats
- Production of laboratory animals and feed diets
- Repeated dose ocular tolerance testing – 28 days in rabbits
- Evaluation of skin irritability of fabric conditioner BUPI BABY and BUPI BABY AVIVAZ
- Prenatal developmental toxicity of the compound ATLEN.SK

PhD studies and educational activities



Education 2012 – 2015

- 1st grade = Bachelor study (Bc.) **(2, 0, 4, 4)**
- 2nd grade = Master study (Mgr., Dipl. Ing) **(17, 14, 9, 10)**
- 3rd grade = Doctoral study (PhD.) **(13, 16, 16, 14)**
- Supervisions of bachelor, diploma and PhD theses
- Lectures, courses and seminars

Lectures, courses, seminars

- **Design of biomolecules**, Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava
- **Doping control**, Faculty of Physical Education and Sport, Comenius University in Bratislava
- **Pharmacokinetics**, Faculty of Pharmacy, Comenius University in Bratislava
- **Selected chapters from pharmacology**, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava
- **Selected chapters from psychopharmacology, developmental neurotoxicology, behavioural pharmacology**, Faculty of Natural Sciences, Comenius University in Bratislava

Accredited programmes of PhD study

- **7.3.2 Pharmacology** – Jessenius Faculty of Medicine, Comenius University, Martin
- **4.1.22 Biochemistry** – Faculty of Chemical and Food Technology, Slovak Technical University, Bratislava
- **4.1.22 Biochemistry** – Faculty of Natural Sciences, Comenius University, Bratislava

Social impact

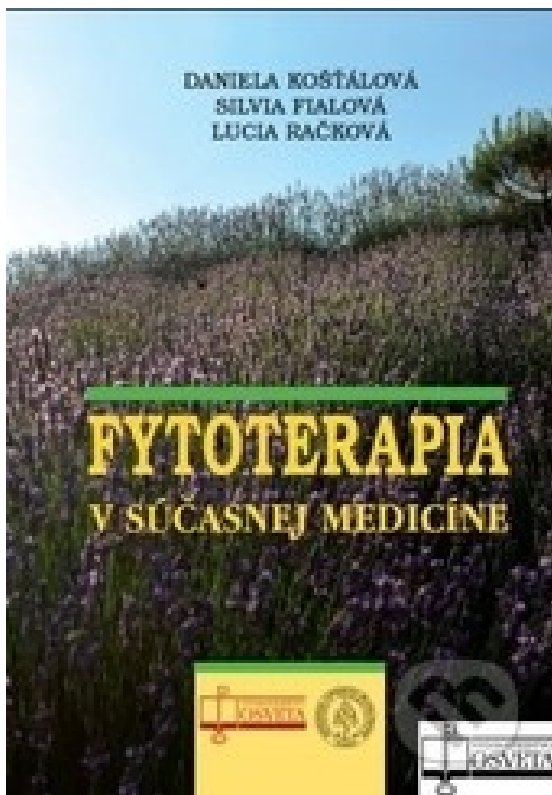


Social impact

- Education
- Patents
- Expertises
- Memberships in advisory bodies, training teams, commissions (VEGA, APVV, EUROTOX)
- Contract studies (toxicology, hyperimmune sera)
- Production of small laboratory animals and feed diets
- Popularization activities (DoD, Night of researches)
- Basic research in the drug development and new therapeutic approaches (from bench to bedside)



Important monographs



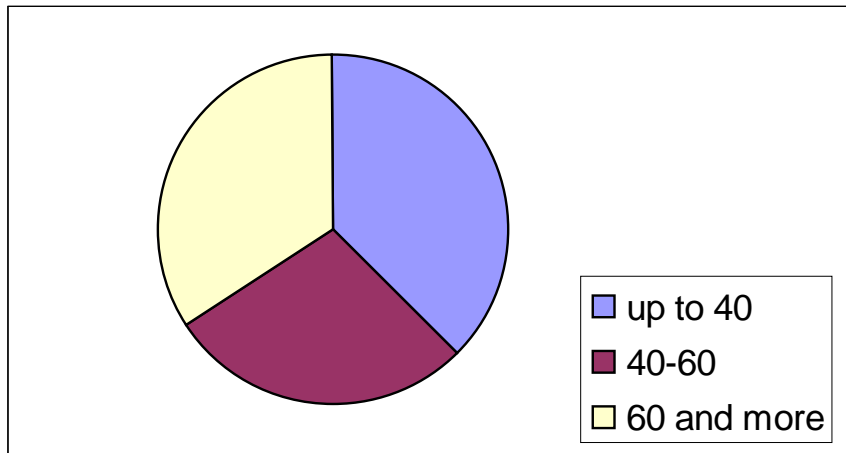
Premium for Scientific and Specialized Literature for year 2014 in the category of biological and medical sciences (awarded by Literary Fund)

Background and



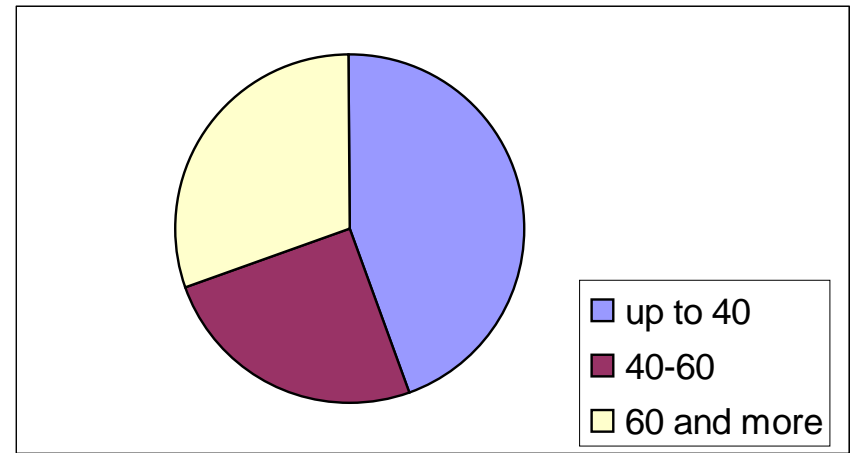
Age distribution of the research staff in 2015 and 2016

2015



Up to 40 = 12 workers (38 %)
40-60 = 9 workers (28 %)
60 and more = 11 workers,
more than 65 = 9, FTE = 6.8 (34 %)

2016



Up to 40 = 16 workers (44 %)
40-60 = 9 workers (26 %)
60 and more = 11 workers,
more than 65 = 9, FTE = 5.7 (30 %)

*„Science without youth is a tragedy. However,
science without old-age is a comedy“.*

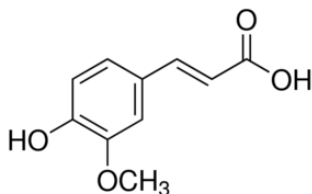


Research strategy and future development

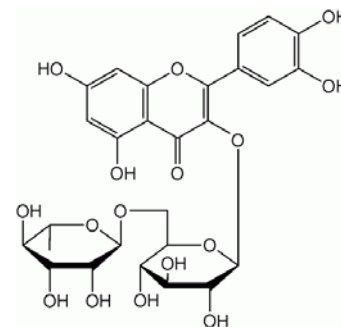


Research strategy 2016 - 2020

- **Natural and synthetic compounds and their derivatives in possible treatment of chronic diseases**

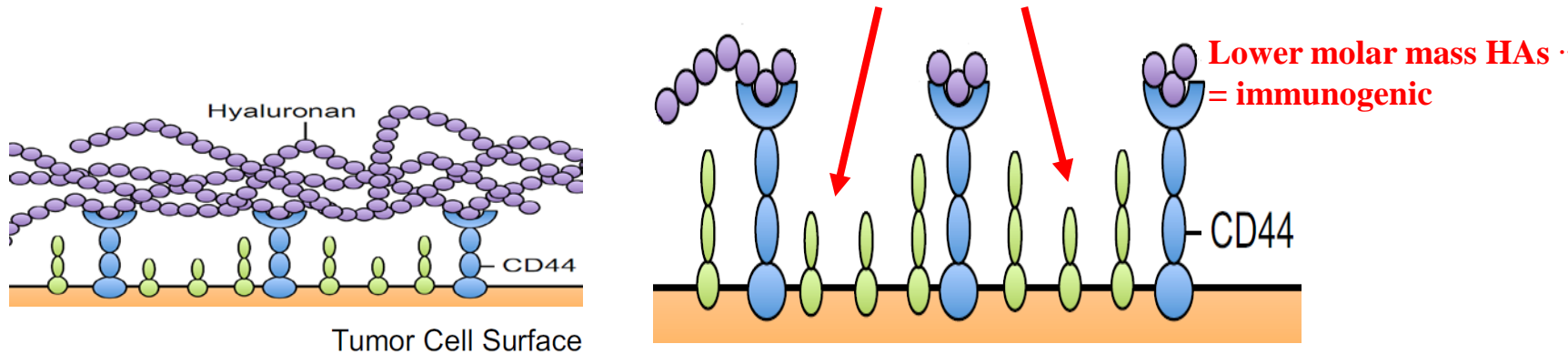


- Inflammatory processes (chronic inflammation)
- Pharmacology of chronic disease (role of ROS)
- Metabolic (and cognitive) syndrome
- Developmental studies



- **Intensive study of molecular mechanisms**

“Glycocalyx” - unmasking tumor cells



One of the current trends

“Unmasking” tumor cell(s)

➤ Degrading action of ROS !!! ... speculations of Šoltés et al.

{ transition metal ion e.g. Cu^{2+} + appropriate thiol } ... ascorbate i.v.

Results of our efforts in 2015 and 2016

- Movement to the new building
- Maintenance of the former building (animal facility and toxicology unit)
- 4 APVV projects
- 1 fellowship funded by the Schwartz Fund
- 2 middle-aged DrSc.
- Research stays of scientists (Egypt, Georgia, USA)
- Study stays of medical students (Spain, Poland)
- 4 young scientists employed
- Cooperation with the private sector (STUVITAL, BioMin)

Important strategy plans

- **Transformation** of the Slovak Academy of Sciences (individual Institutes) into Public Research Institutes
- Creation of a „***start up/spin off***“ (toxicology units at Dobra Voda and in Bratislava) = Center for toxicological research and education in toxicology (*EUROTOX*)
- Creation of **a common center for the research of life style diseases** together with the partner academical institutes (*Memorandum of Understanding*)
- Transfer from the budgetary to **contributory form of economy** from 2017

Thank you for attention