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from Fundamental Mechanisms to Biomedical  
Applications**

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## **Quiz Summary Romania**



## 1<sup>ST</sup> INTER-MEDICAL SCHOOL PHYSIOLOGY QUIZ

9<sup>th</sup> of May, 2018, Cluj-Napoca, Romania

Physiology Department of „Iuliu Hațieganu” University of Medicine and Pharmacy Cluj-Napoca, organized the *1<sup>st</sup> Romanian Edition of the Inter-Medical School Physiology Quiz*, a contest whose origins are attributed to Prof. Dr. Cheng Hwee Ming from the University of Malaya, Kuala Lumpur, Malaysia. The event took place on the 9th of May 2018 in „Iuliu Hațieganu” Auditorium and it brought together a number of 24 teams of medical students from several Romanian Medical Universities, thus comprising a total of 110 participants. We can highlight the fact that this event was also a premiere due to the involvement of English section medical students from Arad, Cluj-Napoca, Craiova and Oradea Medicine Universities.

The Quiz was named after the distinguished Romanian Physiologist, Professor Mircea Dorofteiu, remarkable scientist of Cluj-Napoca Physiology, perfect teacher, exceptional researcher, trainer for numerous student generations, and a real model for all of us.

Professor Cheng is a distinguished Physiologist, recognized in the whole world as a specialist in innovative approach to Physiology teaching and learning techniques. In Malaysia, this type of contest was organized for the first time in 2003, with 7 participant teams from Malaysia Universities. The enthusiasm of the students that participated to the competition, the contest impact on the Physiology teaching, but especially the implication and the unique vision of Professor Cheng, led to a progressive increase, year by year, of the interest for this quiz. The last edition of the Inter-Medical School Physiology Quiz in Malaysia, took place in Kuala Lumpur on 15<sup>th</sup>-16<sup>th</sup> of August 2018 and brought together 460 students from 24 countries, organized in 104 teams, with 120 physiology lecturers. Over the years, Professor Cheng was invited to participate in the coordination of this type of contest in different countries of Asia, but also in the United States and Australia.

Romania is the first country in Europe that organized this competition.

Professor Simona Clichici, Chief of Physiology Discipline, and Professor Adriana Filip organized the *1<sup>st</sup> Romanian Edition of the Inter-Medical School Physiology Quiz*, with the help of two dedicated students in physiology: Nicu Andronic and Anca Verdeș.

Professor Cheng honoured us with his presence and coordinated the entire competition.



The Romanian quiz was based on the original version with adaptation to the smaller number of participants we had. Our quiz had three rounds:

1. First round comprised 5 question sessions, each of them involving 4 - 5 competing teams
2. Second round comprised 3 question sessions, each involving 4 teams
3. The final round involved the winners of the previous round.

Professor Cheng asked the questions that were particularly focused on Respiration, Excretion, Cardiovascular

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System, Hormones and Neuronal Physiology. The teams had 30 seconds to give the answers. With the chronometer started and with the public in front of them, the students had to prove their ability to focus, to work together and to write the best response they had.



Our quiz was a real multicultural event and this fact was also visible in the winner teams.

Three teams from Cluj-Napoca Iuliu Hatieganu U.M.Ph. won the second and third prizes: two teams from the Romanian section and one team from the English section.



One team from Târgu Mureș University of Medicine and Pharmacy Hungarian section was awarded with the first prize and received the competition trophy.





The event was a great success, being dynamic and attractive for the competing students, the University staff and other colleagues who supported the teams and followed the contest evolution till its end.

One of the participants sent us his feelings and some remarks regarding the event: „The competition was very engaging and, most important, it put our brains to work. The questions were wisely chosen and I really liked the fact that if there was a misunderstanding regarding the answer, Professor explained it. Overall, I felt the competition as a great experience that helped me revise my physiology knowledge, understanding some physiological conditions even better now and, of course, making new friends. I am looking forward to the next edition!”

Professor Adriana Filip said that a great merit of this competition was the bringing together of the medical students from all over the country, students who spoke a common language of the science of physiology, and who demonstrated the great implications that physiology knowledge has in medical practice. They had the opportunity to share their knowledge and feelings regarding the medicine and the competition, and they had established long-lasting friendships.

We express our gratitude to Professor Cheng Hwee Ming for his encouragement, his organizational support and for giving us the opportunity to share our interest in Physiology.



We express our thanks to all the participants for their enthusiasm, interest and passion for physiology that made this milestone event possible!

Congratulations to the winners and we wish them to accomplish their dreams and expectations in their academic life!  
We invite you all to the next edition of this contest, in Cluj-Napoca, on 9<sup>th</sup> of May 2019!



## **Conferences**



## ACUTE AND SUBCHRONIC METHIONINE OVERLOAD INDUCE DIFFERENT CARDIOVASCULAR EFFECTS IN RATS: NON-HOMOCYSTEINE DEPENDENT MECHANISMS

**D DJURIC, Z MICOVIC, S KOSTIC, R OBRENOVIC, S STANKOVIC, D KRSTIC, T SOBOT, M LABUDOVIC BOROVIĆ, J JAKOVLJEVIĆ UZELAC, S MUTAVDZIN, T NIKOLIC, I SREJOVIĆ, V ZIVKOVIĆ, V JAKOVLJEVIĆ**

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Methionine is the precursor of homocysteine, a sulfur amino acid intermediate in the methylation and transsulfuration pathways; methionine-rich diets were used to induce hyperhomocysteinemia and cardiovascular pathology was often observed. Elevated plasma homocysteine (hyperhomocysteinemia) is associated with cardiovascular-, neural pathology and cancer. Whether homocysteine per se or a coincident metabolite causes this pathology is still an open question. It is noted that animals with genetic hyperhomocysteinemia have so far not displayed atheromatous lesions, but when methionine-rich diets are used to induce hyperhomocysteinemia, cardiovascular pathology is often observed. It is very important to realize that such studies have not distinguished the effects of excess dietary methionine from those of hyperhomocysteinemia. Recently we applied an interesting experimental approach in healthy rats, using three weeks of DL-methionine overload (i.p.) with obtained homocysteine values in normal range, and in order to distinguish the adverse effects of methionine vs. homocysteine. We also compared acute vs. subchronic effects of methionine application on different biochemical and haemostatic parameters in blood, plasma oxidative stress, cardiac acetylcholinesterase activity as well as cardiodynamic variables and coronary oxidative stress parameters in isolated rat heart. It has been hypothesized that a methionine overload can malfunction the cardiovascular system in a four ways: (1) by affecting oxidative stress; (2) by inflammatory manifestations; (3) by affection haemostatic variables; and (4) by cardiac tissue hemorrhage. Other sulfur amino acids interfere with this metabolism, i.e. L-cysteine (Cys) and N-acetyl-L-cysteine (NAC), and probably also affect cardiovascular system. Their effects are controversial due to their ability to act both as anti- and pro-oxidant.

This work was supported by the Ministry of Education, Science and Technological Development of Republic of Serbia, grant number 175043 and by the COST Action [CA16225 RS] "Realizing the therapeutic potential of novel cardioprotective therapies (EUCARDIOPROTECTION).

## NEW PERSPECTIVES ON THE MECHANISMS OF COMMUNICATION IN BIOLOGICAL SYSTEMS

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If Information generates and organizes matter at the deepest level of existence, communication between structural and functional identities is the fundamental condition of evolution, complexity and space-time continuity of the Universe.

Despite the difficulty in establishing a boundary between the living and non-living realms, the presentation attempts a holistic synthesis of the intrinsic and extrinsic mechanisms of communication of the human being and implications in medicine, biotechnology and artificial intelligence.

This work describes electromagnetic (bioelectric, magnetic, bio-photonics), chemical (molecular, supramolecular - genetic, epigenetic, exosomic), mental and computational communication.

## RECOMBINANT ALLERGENS FOR IMPROVING AMBROSIA ALLERGY DIAGNOSIS AND THERAPY

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GABRIELA TANASIE<sup>1,3</sup>, MONICA COTARCA<sup>1,3</sup>, LAURA MARUSCIAC<sup>1,3</sup>, PAUL TAMAS<sup>1,3</sup>,  
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**Introduction.** In Romania and other parts of Eastern Europe, common ragweed (*Ambrosia artemisiifolia*) has a strong impact on human health with a sensitization frequency of up to 50% among allergic individuals. Extract-based diagnosis and treatment may not be so accurate and effective due to varying allergen content. Therefore a precise diagnosis and effective therapy are needed. First requirement for the improvement of diagnosis and therapy of ragweed allergy is the expression of recombinant allergens followed by the characterization of these allergens.

The aim of the project is to express, purify and characterize ragweed allergens.

**Methods.** For the expression of the recombinant allergens two different expression system were used, *E. coli* cells and insect cell. Amb a 1, 3, 4, 5, 6 and 11 were expressed in insect cells and Amb a 8, 9, 10 and 12 were expressed in *E. coli*. All recombinant allergens were expressed as his-tagged proteins and purified via Ni NTA agarose. IgE reactivity allergens were determined in ELISA using sera from 90 ragweed allergic patients.

**Results.** So far, we managed to express Amb a 8, 9, 10 and 12 in *E. coli* and purified them to homogeneity. Similar procedure were done with Amb a 4, 6 and 11 in insect cells. ELISA experiments showed that 30% of the patients reacted with our recombinant Amb a 8 and 10% were reacting with Amb a 9 and 10.

**Conclusion.** The recombinant allergens expressed in this project were IgE reactive and therefore are suitable for component-resolved diagnosis.

**Keywords:** allergy, allergy diagnosis, ragweed, *Ambrosia artemisiifolia*, recombinant allergens

## ARTERIAL STIFFNESS AND HEMODYNAMICS

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**Introduction.** Arterial stiffness was shown to be a major non-modifiable risk factor for cardiovascular pathology. Ageing produces typical structural alterations in the large elastic arteries: deterioration of the elastic fibers, modified elastin/collagen proportion, extracellular matrix growth, and increased number and migration of the smooth muscle cells.

**Hemodynamic consequences to arterial stiffening.** The cushioning function of the large arteries is markedly impaired. Consequently, aortic systolic pressure rises while diastolic pressure is reduced. These alterations harm the coupling between cardiac and vascular function. Elevated systolic pressure exerts an increased afterload to the left ventricle with the ensuing augmented cardiac work. Incongruity arises between the increased cardiac oxygen demand and the reduced left ventricular coronary oxygen delivery consequent to the lowered aortic diastolic pressure. In addition to its deteriorating

effect on the cardiac function, arterial stiffness impairs target organ function due to the decreased protection of peripheral microcirculation from the higher pressure transmission.

**Pulse wave analysis.** The golden standard for arterial stiffness evaluation is measurement of carotid-femoral pulse wave velocity and/or pulse wave analysis. Numerous studies have shown that central (aortic) pressure is more relevant in the evaluation of cardiovascular risk than peripheral (brachial) pressure. Applanation tonometry is a modern non-invasive method for assessment of the central arterial pressure and several derivative indices. The most important parameters are the augmentation index, the amplification ratio and the time to return of the reflected pulse wave.

**Own research.** Sixty-four individuals subdivided in four groups were subjected to the active orthostatic test (OT): young males and females; middle aged males and females. Pulse wave analysis was applied (Sphygmocor, AtCor Medical) at the end of each experimental period. The compensatory hemodynamic response to OT in the middle aged groups was less efficient as evidenced by the lesser heart rate elevation and the greater aortic systolic and pulse pressure reduction as well as by the augmentation indices dynamics. We presumed the underlying mechanism was a reduced baroreflex sensitivity resulting from the arterial stiffening. Our study added new data concerning the age and gender related hemodynamic alterations and their implementation for cardiovascular risk evaluation.

## EFFECTS OF POLYPHENOLIC COMPOUNDS AND STATIN THERAPY IN EXPERIMENTAL METABOLIC SYNDROME

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**Introduction.** Current treatments for cardiovascular and obesity associated diseases, such as statin therapy, may be associated with considerable residual risk and several side effects. Products from food sources with polyphenolic compounds may represent promising agents in the treatment of cardiovascular and metabolic diseases with minimal side effects.

**Aim.** Thus, the goal of our study was to evaluate the effect of red wine polyphenolic compounds (RWPC), sesame oil (SO) and simvastatin treatment on plasma lipid profile and nitric oxide (NO) signaling pathway in heart and aorta in obese SHR-cp and Zucker rats.

**Methods.** Obese SHR-cp and Zucker rats were treated with RWPC, SO, simvastatin, or simvastatin together with CoQ. NOS activity was determined by measuring L-[3H]citrulline formation from L-[3H]arginine and expression of NOS isoforms, including phosphorylated eNOS, by Western blot. Oxidative load was measured by determination of conjugated diene level and TBARS.

**Results.** Treatment with RWPC decreased plasma glucose and triglyceride levels in both SHR-cp and obese Zucker rats. It decreased oxidative load in the heart and aorta. Moreover, RWPC increased eNOS expression which may significantly contribute to NOS activity enhancement in the same tissues. Finally, RWPC treatment slowed the blood pressure increase in obese SHR-cp rats. Similarly, SO treatment decreased oxidative load and increased NOS activity in both tissues studied. Simvastatin treatment was unable to further reduce the oxidative burden or increase NOS activity, except for the aorta in obese Zucker rats. Only simvastatin and CoQ co-treatment increased NOS activity in the aorta under the level already increased by SO treatment.

**Conclusion.** Red wine polyphenolic compounds may represent a good alternative treatment of different metabolic disorders, when standard therapy cannot be applied for various reasons.

**Acknowledgement.** Study was supported by APVV [No. APVV-14-0932] and VEGA [No. 2/0195/15, 2/0137/16, 2/0170/17, 2/0165/15].



## RAGWEED POLLEN ALLERGY –PATTERNS OF SENSITIZATION

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**Background.** Ragweed is an invasive species in Europe and worldwide, and its pollen has a high potential for eliciting allergic reactions, in late summer and fall. In Western Romania, ragweed allergy accounts for 40% of the monosensitized and 60% of the polysensitized patients. The main ragweed allergen is Amb a1, but other 11 potential allergenic fragments are also described.

**Method.** In order to evaluate the sensitization to ragweed, a number of 97 participants (study group = 84 sensitized to ambrosia pollen and control group = 13 sensitized to other allergens) were included in an observational cross-sectional study. The sensitization pattern was established by (1) clinical evaluation, (2) skin prick test (SPT) to a standard panel of 18 inhaled allergens, (3) serum specific IgE (sIgE) to 176 allergens detection by ImmunoCAP ISAC microarray (including Amb a1 for ragweed sensitization). A current symptoms score (CSS) was calculated and the subjects were asked to grade the allergy impact on quality of life from 1 (lowest) to 10 (highest).

**Results.** All 84 subjects with symptoms to ambrosia had positive SPT to ragweed pollen extract (RPE), but only 83% showed an increased ragweed Amb a1 sIgE, while in 17% Amb a1 sIgE was negative. Clinical manifestations of allergy included asthma (23 cases) and rhinoconjunctivitis (total of 87, including 84 ragweed allergy cases and 3 house dust mite allergy cases). A comprehensive correlation analysis revealed: (1) A weak correlation between the overall self-assessed impact of disease and CSS (Spearman's  $\rho = 0.25$ ,  $p = 0.0317$ ) and moderate correlation between the current self-assessed impact of disease and CSS ( $\rho = 0.584$ ,  $p < 0.0001$ ), (2) a weak correlation: severity, duration of allergy vs total SPT score ( $\rho = 0.25$ ,  $p = 0.0224$ ); (3) moderate correlation: Amb a1 sIgE level (ISAC class) vs total ISAC class sum ( $\rho = 0.510$ ,  $p < 0.0001$ ).

**Conclusion.** A significant part of the population react to ragweed pollen extract and have symptoms, but a part of them develop sIgE to other allergenic fragments than Amb a1, revealing that there is a need for better targeted tests towards a larger spectrum of allergen molecules.

**Acknowledgement:** Study done within INSPIRED Project (SMIS code 103663).

## FUNCTIONAL NEUROIMAGING. A REVIEW OF THE PRECLINICAL AND CLINICAL STATE OF THE ART

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Functional neuroimaging or visualization of brain action in activity is based on the contemporary possibilities offered by radiology and nuclear medicine. The basis of functional neuroimaging makes positron emission tomography (PET) of the brain and functional magnetic resonance (fMRI) of the brain. In the fMRI of the brain, the signal indicating the intensity of the brain activity is based on the ratio of oxy- and deoxyhemoglobin in them. Deoxygenated hemoglobin is paramagnetic while oxygenated hemoglobin is diamagnetic, and blood deoxygenation introduces a magnetic signal variation (BOLD signals). The BOLD signal is indirectly related to neuronal activation through the neurovascular coupling, PET of brain registers a quantity of captured fluorodeoxyglucose (FDG) marked by PET emitters whose entry into the cerebral cell corresponds to the total amount of glucose that these cells receive, indicating their metabolic activity. The drawback of PET is the use of radiation and a low spatial resolution, and it must be combined with a complementary imaging modality, such as MRI or CT, for better



spatial/anatomical imaging. In functional neuroimaging, we can include an optical imaging of the brain. Optical neuroimaging techniques are fast and provide excellent spatiotemporal resolution. With this technique, we can image blood flow variations at different scales: intrinsic optical imaging characterized by a submillimeter resolution, to a two-photon microscopy with a micrometer resolution. Calcium imaging can be applied to genetically modified animal models, showing firing/activations of a group of surface layers neurons, or neurons in some of the brain slices with a high spatiotemporal resolution for surface imaging. In that case, fluorescent molecules are used as calcium indicators as they respond to binding of  $\text{Ca}^{2+}$  ions by changing their fluorescence properties. Optical FNI/functional near-infrared spectroscopy, through the absorption of diffused near-infrared light at different wavelengths, can also be used to detect levels of oxygenating hemoglobin, but only in the surface layers of the brain, like in the neonatal skull. There are also data on the use of ultrasound in functional neuroimaging since the time and space of this visualization modality have already been achieved. Recently, a functional connectivity of various brain parts in real-time is often performed using functional neuroimaging.

## EARLY LIFE STRESS AND HEALTH: A PHYSIOLOGICAL PERSPECTIVE

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Stressful life events are associated with increased risk for both mental disorders and physical illness. In particular, traumatic events during childhood and adolescence have been related to lifelong negative effects on health. Studies in the last decades have tried to identify the underlying mechanisms through which early life stress can alter health in the long term. The prevailing explanation is that exposure to stressful events during development is associated with the disturbance of physiological responses to stress, resulting in increased wear and tear of the organs or allostatic load. Our research has focused on the disturbances of neuroendocrine and autonomic responses to stress, which characterizes adolescents and adults who have been exposed to trauma early in life. Recent results from our studies have indicated that blunted cortisol response and enhanced sympathetic reactivity to stress are linked to maladaptive behavioral and subjective characteristics such as distress intolerance, non-acceptance of emotions, and increased sensitivity to social rejection. We argue that this pattern of physiological and psychological disturbances contributes to allostatic load and may explain the health sequelae of early life stress.

## NEWLY-DESIGNED ALPHA TRICALCIUM PHOSPHATE CEMENT: BIOCOMPATIBILITY STUDY

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Nowadays successful regeneration of damaged bone tissue is a major problem of the reconstructive medicine and tissue engineering. Alpha-tricalcium phosphate ( $\alpha$ -TCP) is a biomaterial that is currently used in clinics for bone repair; however, to optimize and achieve better performances of  $\alpha$ -TCP we applied modified hydrothermal method for its synthesis. This newly developed  $\alpha$ -TCP has several important advantages over currently employed material, but its biocompatibility is unknown. The aim of the study was to assess its biocompatibility and inflammatory potential using in vitro and in vivo models. Experiments were carried out by the recommendations of international standards for testing biocompatibility ISO 10993. Upon subcutaneous implantation of  $\alpha$ -TCP (2. and 12. weeks) histopathological analysis compared the inflammatory

reaction of soft tissue in response to  $\alpha$ -TCP with the results of already widely used virtually non-toxic, non-immunogenic and almost chemically inert dental ceramic and HAP ceramic and showed that there were significant differences in the tissue-implant reactions based on the time of estimation, while there were no differences based on the type of ceramic materials. Additionally, we employed commercially available ELISA kits for in vitro evaluation of biohumoral parameters (IgG, IgM, IgA, IgE1, C3, C4, CRP, RF, haptoglobine) of blood to the presence of  $\alpha$ -TCP. Results of immunochemical blood parameters revealed that inflammatory potential of  $\alpha$ -TCP was not significantly different between the groups ( $p>0.05$ ) as compared to the negative control. In conclusion, newly developed  $\alpha$ -TCP does not have inflammatory potential, but, to fully assess its safety and biocompatibility many other biocompatibility tests need to be carefully performed.

**Keywords:** bone tissue regeneration, calcium phosphate cement, toxicity

## HOW DOES DANTROLENE INHIBIT THE RYANODINE RECEPTOR?

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Dantrolene is a ryanodine receptor (RyR) inhibitor, which is used to relax muscles in malignant hyperthermia syndrome. Although, dantrolene binds to the RyR protein, its mechanism of action is unknown, mainly because of the controversial data showing that dantrolene inhibited  $\text{Ca}^{2+}$ -release from intact fibers and sarcoplasmic reticulum (SR) vesicles, but failed to inhibit single ryanodine receptor (RyR) channel currents. Accordingly, we concluded that an important factor for dantrolene's action was lost during the purification procedure of RyR. Recently,  $\text{Mg}^{2+}$  was demonstrated to be the essential factor for dantrolene to inhibit  $\text{Ca}^{2+}$ - release in skinned muscle fibers. Unfortunately, single-channel analysis was not performed to support these results. Here, we wish to add this important information to the research. To this end, purified RyRs from rabbit skeletal muscle were incorporated into planar lipid bilayers and dantrolene's effect was tested in the presence of  $\text{Mg}^{2+}$  and ATP. We found that dantrolene decreased the open probability of the channels by  $36.6\pm 7\%$ . In addition, our  $\text{Ca}^{2+}$ -release experiments using SR vesicles demonstrated that the effect of dantrolene and  $\text{Mg}^{2+}$  was cooperative; and that ATP enhanced the inhibiting effect of the drug. Altogether, our data provide important complementary information that support the  $\text{Mg}^{2+}$ -dependent mechanism of dantrolene's action and suggest that dantrolene also requires ATP to inhibit RyR. We propose that RyR binds dantrolene only in a specific allosterically modified state.

## THE ROLE OF MELANIN CONCENTRATING HORMONE (MCH) IN THE PATHOMECHANISM OF CHILDHOOD OBESITY AND DIABETES MELLITUS

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**Introduction.** Our previous preclinical experiments proved that various tissues contains a great concentration of MCH and the diet induced release of MCH results in significantly increased plasma levels of the hormone. These findings have concluded that MCH is not only a neurotransmitter in the central nervous system but a gastrointestinal hormone that controls the food intake and plays an important role in digestion. It is presumed to have effects on some clinical conditions such as abnormal obesity or abnormal tenderness. The objective of our study was to evaluate the MCH as a possible prognostic biomarker in the development of obesity.

**Materials and methods.** The volunteers enrolled in the study were children between 6 and 18 years of age. The

inclusion criteria were the body-weight, body-fat and gender. In all cases, anamnesis and physical examination were performed. In addition, for each volunteer, MCH and insulin concentrations were determined from plasma samples using our own developed RIA method. All volunteers completed a questionnaire about their physical characteristics, daily activity, eating and sleeping habits.

**Results.** Our findings support the original hypothesis that high MCH concentrations correlates with a higher incidence of obesity in both male and female volunteers. Besides higher MCH plasma concentrations we observed a decrease in glucose tolerance, a higher prevalence of diabetes mellitus and in females a higher concentration of triglycerides.

**Conclusions.** We absolutely agree that biological processes are very complex, therefore the alteration in some key parameters (in this case the MCH) will not fully explain all problems related to juvenile obesity, but as a possible diagnostic parameter it may be useful at recognizing obesity. As our results suggested there is an important difference between genders. The adolescent female volunteers with increased MCH levels present a higher body mass index (BMI), higher glucose and triglyceride levels in comparison with their male counterparts. Our results suggest that MCH may serve as a diagnostic and prognostic biomarker of obesity.

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**Keywords:** juvenile obesity, diabetes mellitus, MCH, RIA

## LEGISLATION ON ANIMAL EXPERIMENTATION IN ROMANIA

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Experimenting on animals is a social and political issue in many EU countries. This issue is highly regulated to meet both animal rights defenders and scientific community opinion. Thus, Directive 63/2010 replacing the old Directive 609/1986 is a normative act that registers the smallest detail of the use of animals for scientific purposes. With the obligation of Member States to transpose the Directive by 01.01.2013, Romania transposes it by Law 43/2014. Quite unusual in the legislative framework to transpose a Directive by law (only in the case of the 5th Directive was it done), this fact shows the importance of the law on the protection of laboratory animals. The law has a substantial size; it has about 70 pages and is very complex. Since 2014, the law has changed twice, the last time in 2018 to meet the requirements of the European Union. Even so, Romania is still in the infringement procedure for failing to correctly apply the legislation, missing sanctions and the obligation to provide sanitary veterinary assistance in the animal facility. Following the adoption of Law 43/2014, the Order of the President of the Veterinary Authority 97/2015 adopted the order regulating the authorization of the breeders, suppliers and users of laboratory animals and authorizing the projects that use animals for scientific purposes and Order 106/2016 regulating the establishment of the National Committee for the protection of animals used for scientific or educational purposes. There are plenty of issues to be covered: training, statistical reporting, experiments on wildlife etc. Romania as a member country of the EU has the obligation to implement this legislation correctly and to apply it.

## PRINCIPLES OF IMMUNOTHERAPY IN HEMATOLOGIC MALIGNANCIES

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**Introduction.** The understanding of the interactions between immune system surveillance and tumor growth progressed exponentially in the last years. This has led to therapeutic advances in malignant hemopathies, as in other types of solid tumors.

Pathogenetic mechanisms and therapeutic approaches. The possible mechanisms to escape from immune surveillance are: loss or alterations of specific antigens, promotion of an immunotolerant microenvironment by manipulation of cytokines, upregulation the expression of immune checkpoint inhibitors and activation of oncogenic cell signaling pathways. A number of therapeutic approaches are being studied to stimulate the immune system and control malignancy. These approaches include cytokines, checkpoint inhibitors, manipulation of T cells, oncolytic viruses, etc.

Lenalidomide and pomalidomide, immunomodulatory drugs that have antitumor effect via destruction of Ikaros family protein that inhibit IL2 secretion have prolonged survival in multiple myeloma.

Nivolumab, a check point inhibitor has been approved for the treatment of relapsed and refractory Hodgkin Lymphoma.

Chimeric antigen receptor (CAR) T cells, genetically modified T cells, have been studied most extensively in hematologic malignancies and have shown remarkable success in B cell acute lymphoblastic leukemia (B-ALL) and other lymphoproliferative malignancies.

Bispecific antibodies and monoclonal antibodies have improved overall survival (OS) and disease free survival (DFS) in B cell lymphoproliferative diseases: Acute lymphoblastic Leukemia, Hodgkin and B-cell non Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Multiple Myeloma and also in myeloid malignancies: Acute Myeloid Leukemia.

**Conclusion.** In the last few decades immunotherapy has become an important part of treating some types of malignant hemopathies and other types of solid tumors.

**Keywords:** immune system, monoclonal antibodies, lymphoproliferative malignancies, myeloid malignancies

## IS PSORIASIS VULGARIS A SKIN DISEASE OR A MULTISYSTEM GENERALIZED DISEASE?

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Vulgar psoriasis does not take your life but it ruins it. Psoriasis vulgar is considered to be a chronic inflammation, the result of a persistent stimulation of (CD4+ and CD8+) T lymphocytes by immunogens of epidermal origin (AMP-antimicrobial peptides) and a condition that implies both innate and adaptive immunity. The new pathophysiological concept refers to a chronic inflammatory disease that is continuously emerging from the genetically modified skin under the action of environment factors and that expands throughout the entire body producing comorbidities. The hypothesis we issue here is that this chronic inflammation determining comorbidities is initiated in the skin. The evidence consists of the array of comorbidities associated with vulgar psoriasis: -psoriatic arthropathy in 30% of patients -depression (suicidal thoughts in 10 %) and alcohol addiction -obesity (49%), associated with diabetes mellitus, HBP, dyslipidemia -myocardial infarction, 7 times higher risk by the action of Th1 -increased mortality rate shorter life expectancy of approximately 5 years -higher incidence of T cell lymphoma (Gelfand, 2006). The new psoriasis concepts speak about the activation of the skin immune system, which produces cytokines/mediators proinflammatory that turn a disease, initially localized cutaneously

into a systemic one. The inflammation mediators develop angiogenesis, insulin resistance, adipogenesis and immune cell traffic in the skin and also in other human body organs. Thus, psoriasis becomes a generalized disease that has a cutaneous starting point.

## THE ROLE OF EXERCISE IN CARDIOVASCULAR HOMEOSTASIS: FROM BASIC SCIENCE TO APPLIED CLINICAL INVESTIGATIONS

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Exercise is probably the most used and the most powerful non-pharmacological tool that affects cardiovascular system in both health and disease. Our laboratory seeks to investigate the effects of exercise in wide range of experimental and clinical conditions, combining functional, biochemical and morphological aspects. This abstract represents summary of our recent findings in this field. Our basic studies are conducted on rats and focused on swimming and running models via using different training regimes from moderate to intensive or from aerobic to anaerobic. Research estimated cardiac response to moderate and strenuous swimming in rats have shown that 9 weeks of moderate exercise induced slight depression of coronary function, while 3 additional weeks of moderate training improved hearts function, but not to the extent that the strenuous training program did. The results of this study add evidence about beneficial effects of regular moderate exercise on heart. In the study dealing with the effects of chronic administration of nandrolone decanoate (ND) on redox status in exercised rats we found that impact of ND alone, or in combination with swimming in is mildly pro-oxidative. Later we have shown that high intensity interval training (HIIT) can increase ejection fraction and mitochondrial capability of the rat heart. Moreover HIIT induced better response and less fluctuation in cardiodynamic parameters after ischemia compare to endurance training (MIT). When comparing the influence of training and detraining on redox state of rats, we noticed beneficial cardiac adaptations after moderate exercise of sufficient duration, which may be partially lost during detraining period. Interestingly, positive antioxidative effects of training remained longer in males. We have also compared the effects of short- and medium-term swimming on the isolated heart of hypertensive rats and recorded that both types of exercise protocols did not change myocardial function in hypertensive conditions. In case of the running model, we have shown that both HIIT and MIT decreased blood pressure of hypertensive rats but MIT was connected with milder disturbance of pro-oxidant production and better antioxidant response. Our applied investigation mainly focused on the study of oxidative stress in different sports. In one study we investigated the effects of long-term engagement in sports (rowing, cycling and taekwondo) on oxidative stress parameters during progressive exercise test. Different basal nitrite and lipid peroxidation levels were found in sportsmen. However, progressive exercise does not influence basal nitrite and oxidative stress parameters level neither at maximal load, nor during the first 10 minutes of recovery in all sportsmen. Another study on male handball players showed that unaccustomed short intensive exercise may induce oxidative stress in trained athletes, while longer sport-specific activity may not. In research conducted on young male soccer players we noticed that six-month training programme could strengthen antioxidant defense systems and, except lipid peroxidation, does not promote oxidative stress. At the end, our recent work pointed out that chokeberry extract supplementation had positive effects on redox status and body composition in handball players during competition phase.

## CLINICAL AND HEMATOLOGICAL EVALUATION OF THE NUTRACEUTICAL EFFECTS OF 3 TYPES OF ECO-ZONAR (LACTOSERUM ZONAR WITH EXTRACT OF ZINGIBER OFFICINALE AND HONEY) ON HEALTHY WISTAR RATS

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**Introduction.** Nutraceutical products obtained from natural sources represent the subject of numerous researches worldwide. Given their bioactive properties, the whey based products received an ever growing attention from many biomedical fields.<sup>1,2,3</sup>. The aim of this research was to investigate clinical, hematological and biochemical effects of 3 types of bioactive products (Eco-Zonar) obtained from different quantities of lactoserum Zonar, extract of Zingiber officinale root and honey, in healthy Wistar rats.

**Materials and method.** The study was carried out on a number of 20 Wistar rats, healthy adult females, with a body weight varying from 140 to 260 g/animal. They were distributed into 4 groups of 5 animals each. The three types of Eco-Zonar were prepared by SC. Embryom SRL, Satu-Mare, based on the experience gathered in the field, and taking into consideration the literature data regarding the synergetic effects of lactoserum Zonar, enhanced with Zingiber officinale root extract and mixed flower honey. The groups 2, 3 and 4 were given a dose of 30 ml/animal x 3/day of the 3 types of Eco-Zonar, night time included, while the control group received water ad libitum. All groups received a quantity of 15 g standard granulated forage/animal/day. The animals were afterward evaluated daily on their intake of forage and Eco-Zonar and any side effects. Body weight and blood sugar have been measured every week. In the 2nd and 3rd weeks the blood (CBC) and plasma samples were taken for the determination of the plasma total proteins, albumins, globulins. The animals were not killed at the end of experiment because the study did not aim at a histological evaluation of the tissues.

**Results and discussions.** The quantity of Eco-Zonar used varied between 30 and 80 ml/ animal/day with daily variations, as well as from a group to another. We recorded an increasing weight in all groups (+44.85% from T0 to T4 in Group 4). Blood sugar levels highlighted increased values for G4 at T4 (135.5 mg/dl). No variations were recorded in regard to CBC between experimental groups. Protein count values showed lower average values for Group 2 (5.73 mg/L) and higher for Group 3 (7.10 mg/L) and Group 4 (7.16 mg/L).

**Conclusions.** The clinical, hematological and biochemical results obtained confirm the nutraceutical bioactive effects of the 3 types of Eco-Zonar investigated on healthy Wistar rats.

**Keywords:** lactoserum, Wistar rats, nutraceutical, clinical and hematology determinations

# **Oral Presentations**





## TOOTH PHYSIOLOGY – TERRA INCOGNITA

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Tooth physiology is the missing chain link in the education of dentists. Our knowledge on tooth physiology is limited to the processes taking place during the formation and mineralization of the hard dental tissues. However, even this knowledge is incomplete and rather conceptual. After the tooth's eruption, the latter is seen as nothing more than a dead tissue, its physiological processes being restricted within the boundaries of the pulp, where the formation of secondary and, if necessary, tertiary dentine, carries on. The dental enamel is utterly ignored by the experts in physiology under the pretext that there is no life where there are no cells. The dental enamel is a living tissue and its physiological processes are remotely coordinated by the odontoblasts - the only specific cells from the dental pulp. These cells not only build new layers of dentine, but they also coordinate the processes taking place within the supervised tissues (i.e. the enamel and dentine) with the help of the dental fluid. In order to better understand the tooth's physiology, we set ourselves the goal to analyze the physiological processes taking place within this organ, starting from its development and mineralization stage and finishing with the processes taking place after its eruption and definitive development of the root. The physiological processes from the pulp chamber influence those from the mineralized tissues, including the superficial ones. The state of the enamel can be assessed by using a simple acid resistance test. The acid resistance of the enamel is itself influenced by an array of factors, such as rhythmic, biological, pharmacological or even psychological factors. Most of the conditions affecting the tooth, including dental caries, are pre-programmed at the stage of tissue formation, being determined by their degree of mineralization. Thus, the disease is merely a confluence of circumstances. The active implication of competent medical professionals employing well-documented prophylactic techniques could and should eliminate or minimize its incidence. The prophylactic techniques, as well as the treatment of dental caries must be devised only after having studied the physiological processes of the tooth.

**Keywords:** tooth physiology, odontoblasts, dental fluid

## INFLUENCE OF SOUND ON THE REPRODUCIBILITY OF EXPERIMENTAL RESULTS ON ANIMALS

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One of the most important issues facing animal experimentation is low reproducibility and validation of preclinical test results. The lack of reproducibility is mainly due to the variability of the conditions in which the experiments are conducted and the influence of the environmental factors on the welfare of the laboratory animals. The welfare of laboratory animals has a great influence and is directly related to the success of animal experiments. Reducing or lacking welfare and its effect on animals affects the way that the results of the experiment are interpreted. In this presentation I will examine the influence of a less-considered environmental factor: sound. The effects of sound on the physiology and behavior of animals depend not only on the intensity, its frequency, but also by its duration and the vibration potential. Significant sounds at low intensity levels can have a considerable impact on the physiology and behavior of animals. Noise in animal houses and animal testing areas may be sufficient to act as a stressor. Noise activates sympathetic nervous system producing a response with physiological characteristics similar to those triggered by other sensory stimuli. Sounds have a great influence on the physiology of laboratory animals and their behavior, both auditory and non-auditory effects. Intense sound can cause hearing impairment, audiogenic seizures, gastrointestinal, immunological, reproductive disorders, can affect the nervous and cardiovascular system, the number of blood cells, food consumption, body weight and behavior. Exposure to loud noises cause effects at the cellular level in particular ultrastructural changes of the adrenal myocardium and adrenal

glands. These ultrastructural changes have been shown to primarily involve mitochondria and endoplasmic reticulum. DNA damage in the organs mentioned above has been associated with this strong exposure to noise. Sound may be involved in several scientific studies, not as a controlled experimental variable, but often unintentional and uncontrollable variable that can affect the environment, in some cases the results of research on animals that can interfere with welfare affecting animals and causing stress.

## BIODISTRIBUTION AND EFFECTS OF A HYBRID NATURAL-SYNTHETIC CAPSULAR PRODUCT

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**Introduction.** The medical efficiency of age-old natural compounds has been intensely demonstrated lately. Also, various applications of nanotechnology have been reported, including antimicrobial and antifungal concepts and designs. Combining of benefits provided by natural and synthetic components, respectively could induce an improved medical effect. Oral administration of such hybrid represents one of the most accessible administration pathways. However, knowledge on biodistribution, digestive and systemic effects are limited.

**Method and material.** Synthesis and characterization of a chitosan-based capsular product containing silver nanoparticles and allium ursinum natural extract was carried out. Material was tested on a murine (mouse) model, in oral administration. The experiment included 5 groups, corresponding to 4 different concentrations of material as well as a control group.

**Results.** Data reveals between-group differences regarding biodistribution and effects.

**Conclusions.** Synthetized material presents promising characteristics of biodistribution and future applications.

**Keywords:** capsules, silver nanoparticles, allium ursinum, oral administration, biodistribution

## AN ATTEMPT TO RE-DEFINE TRADITIONAL TEACHING METHODS IN PHYSIOLOGY

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The enormous volume of information, the rapid progress of science and the emergence of new discoveries which contradict previously learned facts force us to reconsider the way in which *physiology* is taught to medical students. This laborious process should reflect in the educational objectives and in the teaching methods. Which are the optimal teaching methods? The conclusions of numerous specific studies from the literature underline the superiority of the active teaching

methods, which facilitate the real involvement of the students in the educational process, as compared with the passive methods. However, the dichotomisation of attitudes limits the efficacy of the educational process. Frequently, an equality sign is placed between the 'classical' lecture and passivity, lack of motivation, low performance in students, on the one hand, and between 'modern' methods and activism, high efficiency, on the other. However, renouncing the classic lecture cannot be considered a possible solution. A better solution is to re-define and to adapt the traditional teaching methods to the present and long-term needs of the future physicians. An *update* of the teaching methods is as needed as that of the scientific data. The updating process requires a good knowledge of the teaching methods, with their positive and negative aspects. The solution is not to give up the 'lecture', but to reinvent and to adapt it, underlining the fact that the lecture is a only the fundamental structure of a specific discipline, a map constructed actively by the teacher and the students, as partners in a logic build-up of the informational content.

**Keywords:** physiology, teaching, lecture, active methods

## OXIDATIVE STRESS IN ENDOTHELIAL DYSFUNCTION IN EXPERIMENTAL ATHEROSCLEROSIS IN RABBITS

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**Introduction.** Endothelial dysfunction is involved in many diseases that affect the cardiovascular system. The aim of this study is to demonstrate the implication of the oxidative stress in endothelial dysfunction in experimental-induced atherosclerosis model in rabbits.

**Material and method.** The study included 24 adult male rabbits, California breed, divided into two groups: control and test (n = 12). The test group received daily a hypercholesterolic diet (2% cholesterol). The inflammation was checked by measuring in the serum of interleukin-1 (IL-1) and C-reactive protein (CRP), the oxidative stress was investigated through determination of lipid peroxides (bound malondialdehyde –MDA), and the anti-inflammatory mechanisms through adiponectin activity.

**Results and discussion.** The results identified the presence of the oxidative stress (MDA  $p < 0.001$ ) and of the inflammation (IL-1  $p < 0.05$ ; CRP  $p < 0.05$ ) associated to experimental atherosclerosis, in parallel with significant early decreases of adiponectin ( $p < 0.001$ ), conditions that affect the endothelial functions. The histopathological examinations revealed atherosclerosis modification in all layers of the vessel wall, especially in intima. Our results suggest that atherosclerosis, a chronic inflammatory process, generates oxidative stress and inflammation, changes responsible for the endothelial dysfunction.

**Conclusions.** This study implement the multivalent pathogenetic correlation among the oxidative stress, inflammation, lipid-protein metabolism alterations, immunity and haemostatic status, inter-conditioned in a pathogenetic vicious cycle that is auto-propagated, augmenting itself.

**Keywords:** oxidative stress, endothelial dysfunction, atherosclerosis, dyslipoproteinemia, malondialdehyde, interleukin-1, C-reactive protein, adiponectin

## INTERVENTION OF SPIRONOLACTONE IN THE OXIDATIVE AND INFLAMMATORY PROCESSES IN THE PERIOVARIAN ADIPOSE TISSUE OF THE PCOS-INDUCED RATS

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**Introduction.** Polycystic ovarian syndrome (PCOS) is a heterogeneous medical condition that occurs in up to 8% of the females of the reproductive age, being one of the factors that can lead to insulin resistance, type 2 diabetes mellitus, obesity and infertility. In these processes, a pro-inflammatory status can interfere with insulin signaling, stimulates the hyperplasia of androgen producing theca cells and promotes hyperandrogenism. Based on these data, the aim of the study is to evaluate the effect of Spironolactone on oxidative stress and inflammation in the peri-ovarian adipose tissue (POAT) of estradiol valerate (EV) induced PCOS.

**Materials and methods.** 30 female Wistar rats were distributed in PCOS group (n=20; one i.m. injection of 5 mg OV/0.5 ml sesame oil) and non-PCOS group (control; n=10; 0.5 ml sesame oil). After a month, ultrasound was performed to confirm the PCOS and oral glucose tolerance test (OGTT) was performed. Afterwards, the PCOS group was divided in a treated PCOS group with vehicle (0.5 ml sesame oil) and PCOS group treated with spironolactone (2 mg/0.5 ml sesame oil). After 30 days, OGTT was assessed and the periovarian adipose tissue (POAT) was collected for oxidative stress, DNA damage and inflammatory status evaluation.

**Results.** While malondialdehyde (MDA) levels increased in the POAT of PCOS group, the expression of phosphorylated nuclear transcription factor (pNF)-kB and  $\gamma$ -H2AX decreased in the same group in parallel with reduced superoxide dismutase (SOD) activity and a higher fasting glycemia. Spironolactone treatment decreased MDA levels and increased glutathione peroxidase (GPx) activity in the POAT compared to vehicle ( $p<0.05$ ) suggesting its antioxidant effect. Additionally, the expression of pNF-kB increased after spironolactone treatment, but no notable differences were observed in the  $\gamma$ -H2AX level. An increase of monocyte chemoattractant protein (MCP1) level was observed after the administration of spironolactone. Histopathological analysis revealed no significant differences between PCOS group and PCOS treated with spironolactone, while immunohistochemistry indicated a positive expression of MCP1 in both groups.

**Conclusions.** Our results showed Spironolactone treatment improved antioxidant capacity and had a pro-inflammatory effect in the POAT of PCOS rats, while not inducing DNA damage.

**Keywords:** polycystic ovary, Spironolactone, inflammation, oxidative stress

## THYMUS PLANT EXTRACT IMPROVES GLUCOSE LEVELS AND REDUCES OXIDATIVE STRESS IN EXPERIMENTAL DIABETES MELLITUS

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**Introduction.** Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high glucose levels and increased risks of associated complications, depression and anxiety. The aim of the study is to evaluate the comparative effects of two species of *Thymus Marshallianus* (TM), wild flora (TMW) and culture (TMC), on spatial cognition, ambulatory activity, oxidative stress parameters and transcription factors on an animal model with streptozotocine (STZ) induced DM.

**Materials and methods.** 36 Wistar rats ( $G=130\pm15g$ ) randomized in 4 groups (n=9) were used: group 1, without DM, received 0.5 ml carboxymethylcellulose (CMC); group 2, with DM, received 0.5 ml CMC and groups 3 and 4, with DM, were treated for 14 days with 200 mg/kg b.w. TMW respectively TMC. DM was induced with STZ (30 mg/kg b.w.). In day 15, the animal's behavior was evaluated using open field test (OFT) and elevated plus maze (EPM) and blood samples were collected for measurement of glycaemia and oxidative stress parameters. Hippocampus (HC) and frontal lobe

(FL) were taken for evaluation of oxidative stress and nuclear factor kappaB (NF-kB) levels, methyl CpG binding protein (MECP) 2 and histone deacetylase 4 (HDAC4) expressions and also for histopathological analysis.

**Results.** TMW and TMC administration reduced blood glucose levels, improved the overall mobility and increased 5 times the entrances and time spent in the open arms in EPM. In the FL the lipid peroxidation diminished and the antioxidant capacity was enhanced in parallel with increasing of HDAC expression after both extracts. NF-kB and HDAC levels increased in HC in animals with STZ+TMW and MECP 2 expression diminished. The hippocampus of STZ+CMC showed slight perineuronal edema and rarely intranuclear vacuolation, changes reduced by both TM extracts.

**Conclusion.** Our findings indicate that TM administration might represent a good option as an adjuvant therapy for diabetes.

**Keywords:** Thymus Marshallianus, diabetes, anxiety, oxidative stress

## ANTIOXIDATIVE AND ANTIDIABETIC EFFECTS OF THIAZOLIDINEDIONES IN STREPTOZOTOCIN-INDUCED DIABETES TYPE 1

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**Introduction.** Diabetes mellitus (DM) is an established risk factor for cardiovascular. Thiazolidinediones (TZD) represent a class of antidiabetic agents that exert their glucose-lowering effects by reducing insulin resistance, through stimulation of a type of nuclear receptor, called peroxisome proliferator-activated receptor- $\gamma$ . To study the effect of a synthetic TZD compound (TZDs) treatment on oxidative stress in streptozotocin (STZ)-induced diabetic rats. The outcome was compared to the effect of a natural antioxidant (quercetin) and to pioglitazones.

**Material and methods.** Type 1 DM was induced in Wistar rats by intraperitoneal administration of STZ (60 mg/kg). The control non-diabetic rats and diabetic rats were orally treated for 5 weeks with thiazolidinediones (TZDs) (30 mg/kg body weight/day), quercetin (30 mg/kg body weight/day) or pioglitazone (30 mg/kg body weight/day), respectively. Serum levels of malondialdehyde (MDA) and protein carbonyl (PC) groups, superoxide dismutase (SOD) and catalase (CAT) activity were assessed.

**Results and discussions.** TZDS administration reduced oxidative stress in diabetic rats compared to quercetin and pioglitazone.

**Conclusions.** The antioxidant and hypoglycemic effects of the TZDS in diabetes type 1 suggest its therapeutic properties for clinical treatments of DM.

**Keywords:** diabetes mellitus, oxidative stress, quercetin

## ANTI-INFLAMMATORY ACTIVITY OF SOME NOVEL PHYTOSYNTHESIZED FLAVONOID BIOCONJUGATED NOBLE METAL NANOPARTICLES

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**Introduction.** Recently, gold and silver nanoparticles, conjugated with biomolecules from various fruits, have been intensively explored and investigated for their biomedical applications such as diagnosis, drug and gene delivery, probes



for imaging or treatment of different diseases due to their antibacterial, antiviral, antiangiogenic, anti-diabetes or anti-inflammatory capacity. Nowadays, the phytomediated synthesis of noble metal nanoparticles gained an increased attention as a cost effective, safe, and free of toxic chemicals with undesired side effects synthetic procedure for nanoparticles used in the biomedical field. The aim of the present study was the phytomediated synthesis of bioconjugated AuNPs and AgNPs using Cornelian cherry fruits extract and the evaluation of their anti-inflammatory properties.

**Materials and methods.** The flavonoids from Cornelian cherry fruits extract were used in the green synthesis of noble metal nanoparticles, serving as reducing agents of silver ions from silver nitrate solution and gold ions from tetrachloroaurate solution and as capping and stabilizing agents of the obtained bioconjugated NPs. The synthesis was conducted at different pH values, different extract concentrations or in the presence of UV light, in order to obtain high biocompatible nanoparticles with promising anti-inflammatory effects. These effects were in vivo investigated on a carrageenan induced acute inflammation model in Wistar rats, by measuring cytokines levels in the paw tissue at 2, 24 and 48 hours after carrageenan induction of inflammation.

**Results.** The optimum conditions for the synthesis of the bioconjugated noble metal nanoparticles using phytocompounds isolated from Cornelian cherry fruits were determined. The obtained gold and silver NPs were characterized using different techniques (UV-Vis, TEM, XRD, FTIR, DLS). Treatment with silver and gold nanoparticles significantly decreased the pro-inflammatory cytokines level and increased the anti-inflammatory cytokines, after induced inflammation in Wistar rats.

**Conclusion.** A novel eco-friendly, rapid and low cost method for the phytosynthesis of gold and silver nanoparticles using the flavonoids from Cornelian cherry fruits extract was developed. Investigation of their anti-inflammatory activity indicated a great potential of these nanoparticles as therapeutic agents for treatment of inflammation.

**Keywords:** noble metal nanoparticles, anti-inflammatory activity, Cornelian cherry fruits

## ANTIPROLIFERATIVE AND ANTIOXIDANT EFFECTS OF POMACE EXTRACTS FROM FETEASCĂ NEAGRĂ AND PINOT NOIR CULTIVARS

ȘTEFANIA SILVIA BALEA, ALINA ELENA PÂRVU, NASTASIA POP, CRISTINA ADRIANA DEHELEAN, LAURIAN VLASE, MANUELA CAMELIA MIRZA, MARCEL PÂRVU

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**Introduction.** Natural products rich in phytochemicals with chemopreventive properties may be a promising alternative for prevention and controlling cancer development. Grape pomace (GP) is a source of natural antioxidants. Phytochemical analysis, antiproliferative and antioxidant properties of fresh and fermented pomace extracts obtained from *Vitis vinifera* L. red variety Fetească neagră and Pinot noir grown in Romania in 2015 from Mures county, Mica parish, part of Târnăvelor Plateau were investigated.

**Materials and methods.** GP extracts phenolic content was investigated by LC/MS analysis, trans- and cis-resveratrol were measured by LC-MS/MS. Alamar blue (AB) cellular viability assay was used to determine the in vitro viability of both cancer cell lines (A549 – human lung carcinoma, MDA-MB-231 – human breast adenocarcinoma B16A5 – murine melanoma 549) and healthy cells (HaCat – keratinocytes) after they were stimulated with GP extracts. The in vivo antioxidant effects of seven days pretreatment with GP extracts on the turpentine oil induced inflammation in rats was assessed by measuring serum total oxidative status, total antioxidant response, oxidative stress index, malondialdehyde, total thiols, 3-nitrotyrosine, nitrites and nitrates.

**Results.** Higher phenolic content was found in fermented GP extracts when compared to fresh GP extracts. AB assay indicated an inhibitory effect not only on cancer cells (B16A5, A549, MDA-MB-231), but also on normal cell line (HaCat). Pretreatment with GP extracts significantly improved oxidative stress parameters. Fresh GP extracts had better effects than fermented GP extract, and Fetească neagră GP extracts had a better antiproliferative and antioxidant activity than Pinot noir GP extracts.

**Conclusion.** Due to the important polyphenolic content Fetească neagră and Pinot noir GP extracts had a good antiproliferative activity and antioxidant effect.

**Keywords:** Fetească neagră, Pinot noir, grape pomace, phenolic compounds, antiproliferative, antioxidant

## CHARACTERIZATION AND BIOLOGICAL EFFECTS OF HYPERICUM EXTRACTS ON ANXIETY-LIKE BEHAVIOR, OXIDATIVE STRESS AND INFLAMMATION IN RATS

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**Introduction.** The aim of this study was to chemically analyze *Hypericum maculatum* (HM) and *Hypericum perforatum* (HP) dry extracts, and to evaluate their effects along with Quercetin (Q), on ambulatory activity, brain oxidative stress, inflammatory cytokines and GABA levels. Serum corticosterone levels, NFkB expressions and histopathological changes in hippocampus and frontal lobe in FG 7142 (FG) induced anxiety in rats were also investigated.

**Material and methods.** The chemical analyses of total hypericins were performed by spectrophotometric analysis and hypericin, hyperforin and polyphenols derivatives were quantified by chromatographic methods. The animals were divided in 6 groups: carboxymethylcellulose 2% (CMC); CMC + FG; Alprazolam (APZ) + FG; Q + FG; HM + FG; HP + FG. APZ (0.08 mg/kg b.w), Q (30 mg/Kg b.w), HM and HP (350 mg/ kg b.w) were orally administered for 21 days. FG (7.5 mg/kg b.w) was intraperitoneally (i.p.) injected in a single dose, 1 hour before the behavioral tests, Open Field Test (OFT) and Elevated Plus Maze (EPM).

**Results.** Q increased the GABA levels in frontal lobe and enhanced general locomotion and central exploration behavior in OFT and EPM. *Hypericum* Extracts (HpE) improved central locomotion in OFT. Q and HpE exerted anti-inflammatory and antioxidant effects, enhanced NFkB and pNFkB expressions in the in brain and reduced serum corticosterone levels.

**Conclusions.** Our findings suggest that natural compounds may improve anxiety-like behavior and offer brain protection by modulation of oxidative stress and inflammation.

**Keywords:** *hypericum maculatum*, *hypericum perforatum*, FG 7142, brain, oxidative stress, anxiety

## NEUROPROTECTIVE TREATMENTS IN EXPERIMENTAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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**Introduction.** Cerebral hypoxia and ischemia are major causes for neonatal mortality and neurological morbidity. Hypoxia and ischemia produce massive brain damage following a typical pattern which is defined by selective vulnerability of the brain regions and oxidative stress involvement.

**Aims.** The main objective of this study was to assess the possible protective effect of moderate hypothermia and some of the antioxidant substances in hypoxic-ischemic encephalopathy experimentally induced in newborn rats. The changes in terms of histology and apoptosis were determined in brain so as to assess the local damages induced by hypoxic ischemia and oxidative stress parameters were evaluated as well.

**Materials and methods.** The experiment was performed on 56 newborn Wistar rats pretreated with melatonin in a dose of 20 mg/kg/day for seven days and resveratrol in a dose of 20 mg/kg/day for seven days. At the end of this period the animals were exposed to hypobaric hypoxia (9% O<sub>2</sub> for 90 minutes) and ischemia (by clamping the right carotid artery). In order to test the effect of combined therapy of melatonin with hypothermia, several animals were exposed after hypoxic-ischemic injury to whole body hypothermia (with 4°C) for 3 h.

**Results.** In global hypoxic-ischemic encephalopathy melatonin, at a dose of 20 mg/kg/day as premedication offers neuroprotection by reducing the number of cells expressing apoptosis in CA1, CA2, CA3 and Dentate Gyrus of the hippocampus, thalamus and cerebral cortex under the conditions of conjugation with post-injury hypothermia. Protein carbonyl level was decreased, and antioxidant enzyme defense increased. Resveratrol, at a dose of 20 mg/kg/day as premedication was also protective only when conjugated with post-injury hypothermia. In terms of oxidative stress, antioxidant enzyme defense expressed by SOD and CAT was increased.

**Conclusion.** The results of this study prove that melatonin and resveratrol offers neuroprotection in hypoxic ischemic brain injuries, but the protection is conditioned in most of the brain regions by conjugation of the protective therapy with post-injury hypothermia treatment.

**Keywords:** hypoxia, apoptosis, hypothermia, oxidative stress, antioxidants

## REPORTING OF SEVERITY IN ANIMAL EXPERIMENTATION PROJECTS –A PRACTICAL APPROACH

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Nowadays, animals experiments are a tightly regulated activity, the scientist have the moral and legal obligation to reduce up to minimum the level the suffering of laboratory animals during the procedures. According to Directive 2010/63/EU and the national legislation, any projects performed on the laboratory animals are subject of authorization and reporting. A project is a programme of work with defined objectives involving one or more procedures; a procedure means any use of an animal which might cause a level of pain, suffering distress or lasting harm higher than introduction of a needle in accordance with the good veterinary practice. All procedures are classified as “non-recovery”, “mild”, “moderate” or “severe”. Justification for a procedure should take in consideration the importance of the objective, probability of achievement and the harm to the animals. Severity assessment include: prospective – provide opportunity to consider the appropriateness of design and to ensure the suffering is minimized, ongoing – evaluates if protocol remains within established limits, and retrospective – review of actual severity. The reduction of severity is a main goal of each experimental protocol. It is commonly done by proper housing conditions including environmental enrichment, handling and properly done procedures, using adequate anesthesia during surgery, and postsurgical pain control, close monitoring and fast intervention whenever needed, proper veterinary care, appropriate human end-points etc. Overall assessment of severity require an expertise in animal health, welfare and behavior, a good communication between personal involved in the project, and good communication between comities at local, national and European level.



## EXHALED NITRIC OXIDE IN THE MANAGEMENT OF ASTHMA

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**Introduction.** According to the definition of pathophysiology, asthma is a chronic inflammation of the airways. An update for inflammation monitoring is represented by the dosage of nitric oxide (NO) in the exhaled air. Also known as endothelial relaxant factor, is produced in the endothelial nitric oxide synthase cell. This NO-synthase is activated in inflammatory processes when macrophages are activated by proinflammatory cytokines. Thus, the dosing of nitric oxide in the expired air allows the assessment of the inflammation in the bronchial tree, the response to treatment, and predicts the exacerbations of the disease.

**Methods.** Considering the benefits offered by this simple and non-invasive investigation, we can correlate NO values with clinical aspects and paraclinical data (changes in FEV1-determined by spirometry). We will monitor the NO variability for one year and the response to the medication (Inhaled Corticosteroid or Leukotriene Inhibitors). A group of 40 asthmatic patients, over 18 years of age, was monitored. It is a transversal study of the review of medical records in Gherla pneumology ambulatory, during 2017-2018. Based on the GINA classification of asthma, patients were evaluated by spirometry and NO at 3- 6 months. Subsequently, they were divided into two groups depending on the medication: inhaled corticosteroid use and those using leukotriene antagonists.

**Conclusions.** Through the present study, we want to show that the determination of NO in the exhaled air allows the analysis of disease progression and the identification of an individualized therapy that reduces the chronic inflammation of the bronchial tree.

**Keywords:** nitric oxide, asthma, inflammatory processes, expired air

## THE DETRIMENTAL EFFECTS OF SILVER NANOPARTICLES FUNCTIONALIZED WITH CORNUS MAS L. EXTRACT ON THE RAT TESTICLE

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**Introduction.** Studies have demonstrated that biosynthesized silver nanoparticles (Ag NPs) administered orally to rats accumulate in a number of tissues and organs over time including the rat testicle. The detrimental effects continue to escalate long after the exposure period has ended and depend on the dose administered.

**Aims.** To assess morphological and ultrastructural changes in conjunction with changes in activity of matrix metalloproteinases (MMPs), oxidative stress and apoptosis induced by AgNPs functionalized with Cornus mas L. extract in the healthy rat testicle.

**Method and material.** 36 adult male Wistar rats (n=6), divided in 3 groups (control, d1, d2) were used in the study. Animals from each group received oral treatment for 45 days, as following: normal saline (control) and AgNPs at 2 different doses, d1 (0.8 mg/kg b.w.) and d2 (1.5 mg/kg b.w.). Rats were sacrificed at 7 and 15 days post-treatment and testicles were harvested and used for transmission electron microscopy (TEM) and histopathology analysis and for evaluation of the metal content. Tunel assay, NF-kB, pNF-kB, p53 and Bcl-2 assessment by western blot, the activity of MMP-2 and oxidative stress parameters (malondialdehyde, protein carbonyls, glutathione reduced /oxidized) were also evaluated.

**Results.** TEM revealed, after low dose of AgNPs, severe ultrastructural modifications of interstitial tissue and seminiferous epithelium including necrosis of Leydig cells, retraction and separation of Sertolli cells from spermatogonia and primary spermatocytes and Sertolli cell necrosis. At high dose almost all Sertolli and Leydig cells were destroyed and intense positive signal for apoptosis in interstitial space was observed. The lesions were time-dependent and were associated with increased activity of proMMP-2. NF- $\kappa$ B levels were slightly raised at 7 days in both AgNPs doses compared to the control group ( $p < 0.05$ ), but a dramatic decrease was shown at 15 days. The same pattern was observed for Bcl-2 protein only to a higher extent ( $p < 0.001$ ). An important decrease in p53 values was also observed at 15 days post-treatment ( $p < 0.001$ ) but none existent in the group sacrificed at 7 days ( $p > 0.05$ ) suggesting that AgNPs continue to inflict high cellular damage long after exposure has ended.

**Conclusion.** Oral administration of AgNPs induced severe dose and time-dependent cell apoptosis, increased MMP-2 activity leading to morphological and ultrastructural disruption of the testicular parenchyma.

## THE IMPACT OF CHRONIC IVABRADINE ADMINISTRATION ON TRANSESOPHAGEAL PACING-INDUCED ATRIAL FIBRILLATION

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**Introduction.** In vitro studies suggested that hyperpolarization-activated inward current (If) blockade could reduce atrial arrhythmogenicity. Contrarily, clinical trials reported an increased risk of atrial fibrillation (AF) in ivabradine-treated patients. We aimed to evaluate the impact of chronic If current blockade on AF inducibility in in vivo rats.

**Materials and method.** Adult male Wistar rats were divided into three groups: SHAM ( $n=7$ ), AF ( $n=15$ ), and IVA ( $n=15$ ). IVA rats received ivabradine (10 mg/kg) daily for three weeks. Transesophageal atrial burst pacing was applied for 10 days to the AF and IVA rats; for the SHAM group, the same protocol was mimicked, without applying electrical stimuli. First day and overall AF inducibility (i.e., number of stimulation cycles followed by AF/total number of applied stimulation cycles) and the duration of pacing-induced AF episodes were assessed.

**Results.** Baseline heart rate was significantly lower in IVA ( $216.3 \pm 5.3$  bpm) compared to both SHAM ( $234.4 \pm 6.3$  bpm,  $p=0.04$ ) and AF ( $232.6 \pm 5.1$  bpm,  $p=0.04$ ) rats. During the 10 days of stimulation, AF was induced in all IVA and AF rats, whereas no AF episodes were induced in the SHAM group. In the first day of the protocol, there was no significant difference in AF inducibility between the IVA and the AF groups (28.9% vs. 25.6%,  $p=0.49$ ). However, overall AF inducibility was significantly higher in IVA (RR=1.17, 95%CI 1.02-1.35;  $p=0.02$ ). No significant difference was recorded in the duration of 'non-sustained' ( $<300$  sec) AF episodes between the two groups ( $p>0.05$ ). However, there was a significantly higher proportion of 'persistent' ( $\geq 300$  sec) AF episodes in the AF group (RR=3.99, 95%CI 2.32-6.87;  $p<0.0001$ ).

**Conclusions.** The present study demonstrates that chronic ivabradine administration increases AF inducibility, but does not prolong the duration of AF in healthy rats. On the contrary, ivabradine administration was associated with lower rates of 'persistent' AF. These results suggest that long-term ivabradine treatment may favor AF occurrence, but not AF maintenance, at least in the absence of a significant structural arrhythmogenic substrate.

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## BISPHENOL A – EFFECTS ON HEMODYNAMIC AND AUTONOMIC PARAMETERS AND ON CARDIAC ARRHYTHMOGENESIS IN HEALTHY FEMALE RATS

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**Introduction.** Bisphenol A (BPA) is a ubiquitous, estrogen-mimicking, plasticizing agent used in the manufacturing of polycarbonate plastics and epoxy resins. In female rat hearts, acute high-dose BPA exposure was shown to promote the development of ventricular arrhythmias. We aimed to evaluate the effects of chronic BPA exposure in relevant doses on cardiac arrhythmogenesis and on hemodynamic and autonomic tone parameters in in vivo female rats.

**Methods.** Healthy female Wistar rats were randomized into two groups: Control (n=7) and BPA (n=6). Rats in the BPA group received BPA (50 µg/kg/day) in the drinking water for  $9 \pm 1$  consecutive weeks. Systolic blood pressure was measured in all rats. All animals were implanted with radiotelemetry ECG devices and a 72-h continuous ECG recording was performed. Atrial and ventricular arrhythmic events and heart rate variability (HRV) were assessed.

**Results.** There was no significant difference in systolic blood pressure or heart rate between the two groups (both  $p > 0.05$ ). The number of atrial and ventricular premature beats, as well as the number and duration of atrial tachyarrhythmia episodes were also similar between the Control and BPA rats (all  $p > 0.05$ ). There was also no significant difference between the two groups in any of the frequency- or time-domain HRV parameters (all  $p > 0.05$ ).

**Conclusions.** The present study demonstrates that chronic exposure to BPA in relevant doses does not affect hemodynamic and autonomic tone parameters and does not promote cardiac arrhythmogenesis in healthy adult female rats. However, these results do not exclude the presence of subtle, subclinical BPA-induced cardiovascular changes. Also, it remains to be established whether these results are also applicable in subjects with coexisting heart disease.

**Acknowledgments.** This work was supported by the University of Medicine and Pharmacy of Tîrgu Mureş (grant number 15609/9/29.12.2017).

**Keywords:** animal model, bisphenol A, cardiac arrhythmias, hemodynamic parameters

## CHRONIC IVABRADINE ADMINISTRATION PREVENTS EXAGGERATED HEART RATE LOWERING DURING ACUTE IN VIVO PARASYMPATHETIC STIMULATION

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**Introduction.** The effects of long-term ivabradine treatment on the heart rate (HR) and systolic blood pressure (SBP) may provide a more clear view on its effects on the autonomic nervous system. We aimed to assess the effects of chronic ivabradine treatment on SBP and HR, in vivo and in vitro, during acute parasympathetic stimulation.

**Materials and methods.** Wistar male rats were divided into two groups: Control (n=6) and IVA (n=7). IVA rats received ivabradine 10 mg/kg/day in the drinking water for three consecutive weeks. After isolation of the right vagus nerve, all rats underwent acute electrical stimulation of the intact and then of the distal end of the sectioned vagus nerve (2, 5, 10 and 20 Hz for 15 s with a free interval of 5 min; pulse duration 0.5 ms, 20 V/2 mA). HR and SBP were assessed at baseline and during each stimulation. At the end of the stimulation protocol, the right atrium was isolated and the spontaneous sinus node discharge rate was assessed in vitro at different carbamylcholine concentrations (10<sup>-9</sup> mol/L to 10<sup>-6</sup> mol/L).

**Results.** A significant, progressive decrease in SBP was observed in both groups (all  $p < 0.001$ ). Baseline HR was significantly lower in IVA ( $205 \pm 18$  bpm vs.  $240 \pm 26$  bpm,  $p = 0.03$ ). A significant, progressive decrease in HR was observed in the Control group during stimulation on both the intact and the sectioned vagus nerve (all  $p < 0.0001$ ), whereas this was not the case in IVA (both  $p > 0.05$ ). The electrophysiological study showed a progressive decrease in spontaneous sinus node

activity in both groups (both  $p < 0.05$ ).

**Conclusions.** Long-term ivabradine administration prevented HR lowering in response to acute in vivo vagal stimulation, but this was not the case when acetylcholine receptors were stimulated in vitro and there was no effect of ivabradine on the SBP response. These results suggest that ivabradine therapy may be useful in preventing excessive cardioinhibitory responses in patients with vagal hypersensitivity. This finding is probably related to an effect of ivabradine on ganglionic transmission and/or postganglionic cholinergic fibers.

**Keywords:** animal model, carbamylcholine, ivabradine, parasympathetic nervous system, vagus nerve stimulation

## EFFECTS OF CHRONIC IVABRADINE ADMINISTRATION ON VENTRICULAR ARRHYTHMOGENESIS IN *IN VIVO* RATS

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**Introduction.** Ivabradine is a selective If current blocker known for its beneficial effects in patients with ischemic heart disease and heart failure. We aimed to investigate the effects of chronic ivabradine administration on ventricular arrhythmogenesis in a rat model of transesophageal atrial burst pacing.

**Material and method.** Male Wistar rats were randomized into three groups: control (SHAM;  $n=7$ ) and electrically stimulated for two consecutive weeks in the presence (STIM-IVA;  $n=16$ ) and absence of ivabradine administration (STIM;  $n=16$ ). STIM-IVA rats received ivabradine (10 mg/kg) daily, starting three weeks prior to electrical stimulation and until the end of the study. All rats were implanted with radiotelemetry ECG devices and five consecutive 72-h ECG recordings were performed in each rat prior to stimulation, midway and at the end of the stimulation period, and one and two weeks after the stimulation period. The number of VPBs/24-h was assessed and compared between groups.

**Results.** Baseline heart rate was significantly lower in the STIM-IVA rats compared to both SHAM and STIM rats (both  $p \leq 0.0001$ ). There was no significant difference in the number of VPBs/24-h between STIM and SHAM rats, at any of the five time points (all  $p > 0.05$ ). Also, at three of the five time points there was no significant difference in the number of VPBs/24-h between the STIM-IVA and the SHAM and STIM rats (all  $p > 0.05$ ). However, immediately and one week after the end of the stimulation protocol, a significantly higher number of VPBs/24-h was recorded in the STIM-IVA compared to the SHAM and STIM rats (all  $p < 0.05$ ). There was no significant correlation between the heart rate and the ventricular arrhythmic burden in any of the three groups (all  $p > 0.05$ ).

**Conclusion.** In the absence of an arrhythmogenic trigger, ivabradine administration had no effect on ventricular arrhythmogenicity. However, ivabradine administration was associated with significantly higher ventricular arrhythmic burden immediately and one week after the end of transesophageal atrial burst pacing. The mechanism underlying this effect, which does not seem to be directly related to decreased heart rate, remains to be established.

**Acknowledgments.** This work was supported by a grant of the Romanian National Authority for Scientific Research and Innovation, CNCS-UEFISCDI (PN-II-RU-TE-2014-4-1544).

**Keywords:** animal model, bradycardia, ivabradine, ventricular arrhythmias

## MPMoIII AS CRITERIA FOR INTERHOSPITAL TRANSPORTATION OF POLYTRAUMA PATIENTS. A PILOT STUDY

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**Introduction.** Trauma remains an important problem in medicine. Interhospital transportation of polytrauma patients enrolls series of risks including death. There are no any objective criteria/scores for survival rate prognosis. In our study, we estimate the Mortality Probability Admission Model III (MPMoIII) score to predict polytrauma patients transport outcomes.

**Materials and methods.** Retrospective analysis of 39 patients transported from regional hospitals to Emergency Medicine Institute (Chisinau, Republic of Moldova) was performed. For each patient, were registered age, gender and outcome (survive/nonsurvive) after transportation in specialized trauma care center and was determined MPMoIII score. This score is the result of the MPMoII scale improvement considering the age, the type of admission, physiological parameters, the chronic diseases or acute disturbances, including cardio-respiratory resuscitation and mechanical ventilation, and various combinations of these factors. The results were adjusted for age and gender using multivariate analysis (logistic regression, conditional forward method).

**Results.** The model has the following characteristics: Omnibus Tests of Model Coefficients (Chi-square = 17.094,  $df=1$ ,  $p<0.001$ ); determination coefficient Nagelkerke R Square = 0.51 (51%); Hosmer and Lemeshow test - Chi-square = 3.388,  $df=7$ ,  $p=0.847$ ; sensibility 89.3%, specificity 63.6%, overall percentage 82.1% - the results after optimization when cut-off was increased up to 0.61 instead 0.5; the area under the ROC curve 0.878, 95% CI 95% 0.773 and 0.983. Coefficient B for each 5% of MPMoIII was equal to -0.890,  $df=1$ ,  $p=0.008$ , OR=0.411 CI 95% 0.214 and 0.789. Age and gender did not reached the significance and were eliminated from the model according to the selected procedure.

**Conclusions.** MPMoIII was demonstrated to be promising criteria/score for survival rate prognosis in order to predict polytrauma patients transport outcomes. It can be used in different models as either independent factor or one of factors in multivariate analysis. In our study, despite the low number of patients, it had acceptable mathematical characteristics, especially determination coefficient and sensibility. Evidently, is too early to recommend it for daily clinical practice before prove the „power” of MPMoIII in a prospective clinical research and validation of the obtained model. We expect that MPMoIII can be completed by an anatomical scale as NISS (New Injury Severity Score).

## FUNCTIONAL CHANGES OF THE RETINA IN DIABETIC PATIENTS

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**Introduction.** Diabetic retinopathy (DR) is classically described as a microangiopathy, affecting the pericytes and endothelial cells, but recent studies focused more on the neurodegenerative aspects. The aim of our study is to evaluate functional changes in patients with different stages of diabetic retinopathy.

**Material and method.** The prospective study included 44 diabetic patients divided into four groups depending on the stage of diabetic retinopathy (without retinopathy, non-proliferative DR, proliferative DR without laser treatment, proliferative DR with laser treatment) and 14 aged-matched controls. All of the participants underwent ophthalmologic examination and full-field electroretinogram (ERG). The ERGs were recorded at Ocularius Research Centre with Metrovision MonPackOne system, which has the same stimulus parameters, according to the International Society of Clinical Electrophysiology of Vision standard. The implicit times were analyzed for a and b waves in dark-adapted (DA) 0.01 ERG, dark-adapted (DA) 3 ERG, dark-adapted (DA) oscillatory potentials, light-adapted(LA) 3.0 ERG, and 30Hz



flicker ERG, and compared between all five groups, using the ANOVA test.

**Results.** The significantly delayed responses, between healthy subjects and diabetic patients without retinopathy were the DA oscillatory potentials ( $25.49 \pm 1.04$  ms versus  $26.13 \pm 0.96$  ms,  $p=0.027$ ), DA 3 b wave ( $42.89 \pm 2.18$  ms versus  $43.99 \pm 2.26$ ,  $p=0.01$ ) and LA 3 b wave ( $31.62 \pm 1.62$  ms versus  $32.72 \pm 1.36$  ms,  $p=0.01$ ). When comparing diabetic patients without DR and diabetic patients with non-proliferative DR only the DA 3 b wave ( $43.99 \pm 2.26$  versus  $44.52 \pm 2.50$ ,  $p=0.01$ ) was modified. Between diabetic patients with non-proliferative DR and with proliferative DR without laser treatment, only the DA 0.01 b wave was delayed ( $61.94 \pm 5.52$  ms versus  $66.39 \pm 8.12$  ms  $p=0.0001$ ). The delayed responses between diabetic patients with proliferative DR without laser treatment and with laser treatment were the LA 3 b wave ( $32.67 \pm 2.55$  vs  $36.15 \pm 2.99$ ,  $p=0.0007$ ), 30 Hz flicker a wave ( $19.00 \pm 3.43$  vs  $21.57 \pm 4.38$ ,  $p=0.017$ ) and b wave ( $32.43 \pm 4.08$  vs  $36.62 \pm 3.26$ ,  $p=0.0051$ ).

**Conclusion.** The findings from our study indicate that there are substantial electroretinographic changes in all stages of diabetic retinopathy and that full-field ERG is a useful tool in assessing retinal function in diabetic patients.

**Keywords:** full-field ERG, diabetes, diabetic retinopathy

## THROMBOPHILIA SCREENING IN PREGNANCY - IS IT USEFUL OR NOT?

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**Introduction.** Both vein and artery thrombosis with embolic complications is probably the most important cause of morbidity and mortality in developed countries. Thrombophilias can be inherited or acquired. Excessive coagulation activation or inhibition of anticoagulant mechanisms may cause a state of hypercoagulability with the occurrence of thrombosis. It is already known that pregnancy can affect the haemostatic system into a hypercoagulable state. Generally there is significant change to coagulation, with increased factor VII, VIII, X and von Willebrand factor activity and increases in fibrinogen. The screening for thrombophilia in pregnancy is not routinely recommended in the absence of venous thromboembolism.

**Material and method.** The aim of our study was to identify the prevalence of thrombophilias in a group of women with normal pregnancy outcomes.

**Results and discussions.** The most common inherited disorders during pregnancy were mutations in factor V Leiden, prothrombin gene, and methylenetetrahydrofolate reductase (MTHFR).

**Conclusions.** Currently, routine screening for thrombophilic defects is not recommended in women without previous pregnancy complications. However, prevention of complications such as recurrent miscarriage remains a major and topical health issue.

**Keywords:** thrombophilia, pregnancy, hypercoagulable state

## AN EXPERIMENTAL MODEL FOR ANGIOTENSIN II-INDUCED ARTERIAL HYPERTENSION

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**Introduction.** Arterial hypertension represents a global health issue and it continues to be an undiagnosed, untreated or ineffectively treated condition. High concentrations of Angiotensin II can be a risk factor for cardiovascular diseases due to the fact that it causes a rise of the arterial blood pressure and also because of its direct effect on the vascular endothelium, cardiac and renal tissues. The arterial hypertension has the heart, blood vessels and kidneys as target organs and if it remains uncontrolled, hypertension will create a chain of events that strengthen themselves through a feedback loop to maintain a high arterial blood pressure. This paper presents the findings of an experiment whose purpose was to demonstrate the Angiotensin II-induced arterial hypertension.

**Materials and methods.** The laboratory rat, a rat of the Wistar species, aged 12 weeks and weighing 250g was used to conduct this experiment. The rats were split into two different groups, each one containing 14 of them: the first group received Angiotensin II and the second one received physiological serum. The Angiotensin II was administrated subcutaneously at the rate of 300ng/Kgc/min for 14 days, using Alzet osmotic pumps (model 2001). The fluids ingested, the weight and the arterial tension were measured with the help of the tail-cuff method.

**Results.** After 14 days, a rise of arterial tension was observed in the group of mice that received Angiotensin II.

**Conclusion.** The development of these experiments might lead to new pathways in understanding and treating arterial hypertension.

**Keywords:** hypertension, Angiotensin II, pumps

## ISOPROTERENOL INDUCED MYOCARDIAL INFARCTION IN RATS: DOSE IDENTIFICATION

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**Introduction.** Myocardial infarction (MI) is the irreversible damage of myocardial tissue caused by prolonged ischemia followed by hypoxia. MI can be caused by an imbalance between the myocardial blood flow and the metabolic demand of the myocardium. Isoproterenol (ISO) is a synthetic catecholamine and  $\beta$ -adrenergic agonist that produces severe stress in the myocardium and induce MI if administered in supramaximal doses. The aim of this study was to identify the dose of ISO that induce ECG alterations, enzymatic reaction and histopathological changes characteristic of MI.

**Material and methods.** MI was induced to Wistar-Bratislava white rats, weighing between 250 and 300 grams. Three different subcutaneous doses of ISO (85 mg/kg, 100 mg/kg, and 150 mg/kg) were administrated twice, with the second dose at 24h after the initial. The ECGs was recorded and blood samples were collected for measurement of serum creatine kinase and creatine kinase-MB at 24h after the last dose of ISO. In the end, rats were sacrificed and their hearts were excised and prepared for histopathologic examination.

**Results.** ISO in all doses induced alterations in ECG patterns such as decreased heart rate, increased QT and QTc intervals. ST segment depression coupled with marked T wave inversion, which reflects ISO-induced infarct-like lesion, were observed at 100 mg/kg and 150 mg/kg. All doses of ISO increased the levels of creatine kinase and creatine kinase-MB with highest levels at the dose of 150 mg/kg. The ISO doses of 85 mg/kg and 100 mg/kg induce subepicardial MI at



histopathologic examination, while the dose of 150 mg/kg induced transmural MI.

**Conclusion.** ISO in doses of 100 mg/kg and 150 mg/kg is useful for induction of infarct-like lesion on ECG, increased levels of myocardial necrosis enzymes and morphological changes characteristic for MI.

**Keywords:** isoproterenol (ISO), rats, myocardial infarction (MI)

## THE ORGANIC GROWTH FACTORS ROLE AT THE ORAL CAVITY LEVEL

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**Introduction.** From a biological point of view, growth factors are always active and are essential for all types of wound healing. However, in the clinic, the most common question is: are they always active?

**Purpose.** To highlight the utility of using growth factors in the healing of several types of plaques.

**Material and method.** Studies performed on the basis of available literature on the use of PRF in regenerative bone surgery after extraction in dental alleles, as well as isolated use in perimplantation regeneration.

**Results and discussion.** The new A-PRF protocol, Fibrin Advanced Platelet Rich Fibrin, based on the concept of low speed centrifugation is the most powerful concept because it combines the fibrin network, platelet growth factors and white cell activity for a single purpose : Rapid and thorough vascularization. I-PRF works on the same concept: platelets, white cells, fibrinogen, and stem cells in liquid form produced without any additive or anticoagulant: clot after injection. The goal is to improve soft and hard tissue. Injectable PRF is used to make a sticky bone graft by inducing a complete bone graft coagulation and to increase blood intake.

**Conclusions.** The clinical interest in the use of PRF consists not only in the simplicity of protocol and morphological versatility, but also in the potential for accelerating the process of tissue healing together with its potential stimulus of neoangiogenesis, characteristic of biomaterials.

**Keywords:** A-PRF, I-PRF, wound healing, oral cavity

## STUDY OF PDT ANTIANGIOGENIC EFFECT IN MELANOMA-ENDOTHELIAL CELLS CO-CULTURES

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**Introduction.** Photodynamic therapy (PDT) recently showed some encouraging results as an adjuvant therapy for late stages of melanoma. However, the PDT antiangiogenic effect is not yet fully understood. The purpose of our study was to investigate the efficacy of a synthetic porphyrin, THOPP, as photosensitizer for PDT against co-cultures of melanoma cell lines: human lightly pigmented (WM35, M1-15) and mouse strongly pigmented (B16-F10) and endothelial cells (HUVEC).

**Material and methods.** Co-cultures were established then treated with PDT. Cell viability was determined by colorimetry through MTS assay. Cell death mechanism was assessed through flow cytometry following FITC/PI double staining, TNF-related apoptosis-inducing ligand (TRAIL) and caspase 3 (ELISA), MitoID for mitochondrial lesions and

Western Blot for the detection of YH2AX protein, a marker for dsDNA lesions. Inflammatory changes and neoangiogenesis activation were assessed through ELISA measurement of tumor necrosis factor (TNF- $\alpha$ ), vascular endothelial growth factor (VEGF), soluble intercellular adhesion molecule 1 (sICAM1). Data were analyzed by two-way ANOVA and paired Student TTEST, followed by Bonferroni post test using GraphPad and results were considered significant for  $p \leq 0.05$ .

**Results.** THOPP mediated PDT decreased cell viability. All co-cultures underwent cell death following PDT; however, the mechanism was different. In the case of human WM35 and M1-15, cell death occurred through both apoptosis and necrosis, while for B16-F10 the predominant mechanism was necrosis, as shown by FACS analysis and sustained by increased caspase 3 and TRAIL, decreased mitochondrial membrane potential and increased YH2AX. TNF- $\alpha$  was only increased in the case of M1-15 and sICAM1 was increased only in the case of WM35. VEGF was significantly decreased in all co-cultures.

**Conclusion.** PDT mediated by THOPP efficiently inhibited angiogenesis and induced melanoma cell killing.

**Keywords:** photodynamic therapy, melanoma, endothelial cells, angiogenesis

## RESEARCHES CONCERNING THE IMPACT OF THE SALIVARY SECRETION DYSFUNCTIONS IN THE ORO-MAXILLO-FACIAL AREAS

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**Introduction.** Saliva is the secretion product of the three pairs of large salivary glands (parotid, sublingual and submaxillar) and of the numerous small salivary glands that are disseminated in the oral mucosa. Saliva functions are numerous and extremely important: mechanical cleaning, antimicrobial activity, pH control, remineralization of dental tissues, lubrication of tissue surfaces, maintenance of oral mucosa integrity. Xerostomia represents the main symptom in several secretor dysfunctions, but also can be met as a stand-alone disease. The aim of the study was to remark the changes at the oral cavity level in patients with xerostomia and to detect the incurring factors.

**Material and methods.** The research was carried on two groups: a study group (39 xerostomia clinical cases, presented in the dental office, accusing functional disorders, aggravated by the decreased flow salivary) and a control group (46 clinically healthy patients). The patients were selected from the request assistance. The diagnosis of xerostomia was based on: anamnestic data, clinical oral tissue examination, salivary salivary flow measurement in resting and stimulating conditions.

**Results and discussions.** The clinical examination showed a characteristic oral symptomatology: dryness, cheilitis, pale/congestive oral mucosa, atrophied and partially no papilla tongue, with deep fissures and ulcerations and increasingly frequent carious lesions. Changes in salivary flow appeared more evident with aging, being influenced by polypathology encountered and / or its treatments.

**Conclusions.** Xerostomia represents a reality encountered in dental medicine practice with unfavorable effects on the oral tissues, and which can significantly affect the life quality. It is necessary for the dentist to know the factors involved in the occurrence of salivary dysfunction, the ways to prevent their occurrence, and in the case of the installation, the appropriate therapeutical approach in order to restore homeostasis at local and general level.

**Keywords:** saliva, salivary flow, oral modifications, xerostomia

## INFLUENCE OF CARDIOVASCULAR DISEASES ON SALIVARY PARAMETERS

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**Introduction.** Cardiovascular diseases are a major group of diseases with increased prevalence among the population. Antihypertensive drugs are incriminated as responsible for reducing salivary flow and harm to oral health. The purpose of this study was to evaluate the influence of cardiovascular disease and implicitly of cardiovascular medication on salivary parameters in patients with cardiovascular disease.

**Material and method.** The cross-sectional study was conducted on 30 patients, an average age of 60.47 years. Subjects completed a questionnaire with general data and were clinical examined. The Saliva-Check Buffer (GC) tests were used to determine salivary pH, salivary flow and buffer capacity. Statistical analysis was performed with SPSS 14.0.

**Results.** 50% of them had hypertension, treated with one type of antihypertensive drug, 73.3% using beta-blockers. 80% of subjects have a low salivary secretion, 53% have a reduced buffer capacity, 90% of subjects have a very low and low salivary pH. 86% of the subjects had dental caries and periodontal disease. Most of the subjects with monotherapy presented the lowest acidic pH cases. The saliva buffer capacity was lower for multi-therapy subjects.

**Conclusions.** Cardiovascular disease is accompanied by changes in oral cavity homeostasis. Prevalence of dental caries, periodontal disease and edentation presented elevated values among subjects with cardiovascular disease.

**Keywords:** cardiovascular diseases, salivary parameters, oral cavity

## MONOAMINE OXIDASES ARE SOURCES OF VASCULAR OXIDATIVE STRESS IN THE SETTING OF INFLAMMATION IN PATIENTS UNDERGOING ELECTIVE ABDOMINAL SURGERY

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Oxidative stress is a widely recognized pathomechanism underlying both endothelial dysfunction and vascular inflammation but the contribution of cellular sources of reactive oxygen species (ROS) remains partially elucidated. We have systematically reported the role of monoamine oxidases (MAOs), mitochondrial enzymes with 2 isoforms, A and B, responsible for the constant generation of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), to the pathogenesis of endothelial dysfunction in animal models with inflammation, hypertension and diabetes. The present study was purported to evaluate the contribution of MAO to the vascular impairment in patients with inflammation confirmed by high C-reactive-protein (CRP) level. To this aim, mesenteric arteries branches were isolated from patients undergoing elective abdominal surgery and used for studies of vascular reactivity in organ bath, ROS production (H<sub>2</sub>O<sub>2</sub>) via two methods, qRT-PCR and immune-histology (IH), respectively. We have demonstrated both by PCR and IH that the mesenteric arteries contain both MAO isoforms

located in the entire structure of the vascular wall. In the vascular preparations harvested from patients with increased CRP a significant upregulation of MAO expression and impairment of vascular reactivity together with high ROS production were found. Incubation of the vascular rings with MAOs inhibitors (clorgyline, selegiline, 10 microM, 30 min) was able to partially restore the vascular reactivity and mitigate ROS production. In conclusion, both MAO isoforms are present in mesenteric arteries branches, are overexpressed in the setting of inflammation, and contribute via H<sub>2</sub>O<sub>2</sub> generation to the endothelial dysfunction in humans.

**Acknowledgments.** Research supported by the university grant PIII-C5-PCFI-2017/2018-01.

**Keywords:** endothelial dysfunction, monoamine oxidases, human mesenteric arteries branches, inflammation

## EFFECTS OF ACUTE AND SUBACUTE HYPOBARIC HYPOXIA ON OXIDATIVE STRESS BIOMARKERS: A STUDY ON THE ALPS

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**Introduction.** High altitude is the natural laboratory to study human physiological response to hypoxic conditions. Acute hypoxia induces accumulation of reactive oxygen species (ROS), which is often associated with increases in oxidative damage to cellular compartments.

**Objective.** The aim of this study was to investigate changes of oxidative stress (OxS) biomarkers and the possible correlation with functional renal impairment in acute and subacute exposure to hypobaric hypoxia (HH). The study was based on the evaluation of Oxidative stress (OxS) biomarkers: ROS production rate, antioxidant capacity, oxidative damage biomarkers inflammatory response and functional renal impairment: Possible correlations between ROS production levels and the other parameters were also investigated.

**Methods.** Fourteen lowlanders were examined (3F, 11M; mean age 28±6 yr). Anthropometric, physiological parameters, and biological samples (venous blood and urine) were collected at baseline (122m), and during the sojourn at 3269m: 24h-48h-72h-1and 2weeks. ROS production was determined by means of an electron paramagnetic resonance (E-Scan EPR scanner, Bruker) method; it operates at the common X-Band microwave frequency (~ 9.8 GHz). OxS biomarkers (oxidative damage on lipids (8-isoPGF<sub>2</sub>α), proteins, (PC), and DNA (8-OHdG) were assessed by immune and/or enzymatic methods. Functional renal impairment (creatinine and neopterin) by HPLC and urine parameters by standard analyses.

**Results.** ROS production rate significantly increased (p<0.05) peaking at 24 h (~40%), according to a reduction of SO<sub>2</sub> (-12%), increase in heart rate, in oxidative markers concentration and in a functional renal impairment. Plasmatic or urine concentrations of lipids (8-iso), proteins (PC) and DNA damage were significantly increased after 24h of hypoxia exposure (range ~40-60%) and decrease in antioxidant capacity (-20%). After prolonged exposure (2 weeks) to HH, ROS and OxS biomarkers tend to return slowly to baseline levels.

**Conclusion.** The difficulty of adapting to hypobaric hypoxia during ascent to high altitude can result in hypoxemia and tissue oxidative stress. OxS biomarkers may reflect the time-related response to acute HH during the early phase of acclimatization.

**Keywords:** hypobaric hypoxia, oxidative stress, renal function, electron paramagnetic resonance

## CROSSTALK BETWEEN MONOAMINE OXIDASE AND VITAMIN D: NEW ROLES FOR OLD FRIENDS

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Obesity epidemic remains a public health crisis in both children and adults worldwide. The excess body weight has been systematically related to chronic comorbidities, such as diabetes mellitus, cardiovascular disease, and cancer. A huge body of evidence suggested the association between cardiometabolic disease and vitamin D deficiency-mediated oxidative stress. However, the sources of oxidative stress in the presence of a suboptimal vitamin D status are far from being elucidated. Monoamine oxidase (MAO) with two isoforms, A and B, are dehydrogenases located at the outer mitochondrial membrane that catalyze the electron transfer from biogenic amines to molecular oxygen in brain but also in cardiovascular system and adipose tissue, with the constant generation of hydrogen peroxide, ammonia and aldehydes as by-products. We here present experimental and clinical evidence that: i) an increase in MAO expression occurs in the setting of cardiac and metabolic diseases; ii) ex vivo administration of the active vitamin D alleviated both oxidative stress and endothelial dysfunction, mimicking the effect of MAO inhibitors; iii) the protective effects of vitamin D are, at least partly, related to a decrease in MAO expression. Elucidation of the signaling pathways underlying the beneficial effects of vitamin D it is well worth in view of its therapeutic potential in several non-communicable diseases associated with increased MAO activity.

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## INTERRELATIONS BETWEEN PULSE WAVE SPEED AND ECG – A POSSIBLE CUFFLESS MEASUREMENT METHOD FOR SYSTOLIC BLOOD PRESSURE?

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**Introduction.** Multiple studies showed that 24h monitoring of the blood pressure can be used to confirm the efficacy of the arterial hypertension treatment and the non-dipper status was associated in some studies with increased cardiovascular risk. Usually the ABPM monitoring is carried on with standard devices using inflatable cuffs. These devices have multiple drawbacks (mechanical stress on the muscles and arterial wall, sleep troubles during nighttime, etc). Our team developed a device able to measure the timing between pulse wave and ECG, correlated in some studies with systolic blood pressure values.

**Material and method.** Our study was carried on 52 healthy students from U.M.F Tîrgu-Mures, 31 boys and 21 girls. During a standard stress test (Bruce protocol), blood pressure, pulse and PTT (Pulse transit time) were measured every 2 minutes. Pearson test was used to analyze the correlation between blood pressure and pulse transit time.

**Results.** The coefficient of determination ( $R^2$ ) for SBP and PTT was 0.301. Correlation coefficient ( $r=-0.5486$ ,  $n=260$ ,  $p<0.0001$ ) is showing a strong negative correlation between SBP and PTT.

**Conclusions.** In healthy young adults, an increase of the systolic blood pressure is strongly correlated with a

decrease of PTT. This may be used to develop a new method for blood pressure measurements without using an inflatable cuff, avoiding many drawbacks of the actual methods. Moreover, this method offers beat to beat SBP measurements, allowing researchers to study short time blood pressure variations.

**Keywords:** ABPM, PWTT, blood pressure

## ASSESSMENT OF HYPERICUM PERFORATUM ANALGESIC AND ANTIOXIDANT EFFECTS IN AN EXPERIMENTAL MODEL OF OROFACIAL PAIN

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**Introduction.** Orofacial pain is a serious issue for many people worldwide, regardless of the cause. A growing body of evidence indicates that nociception involves a complex network that includes, among others, inflammation and oxi-nitrosative stress. Hypericum perforatum or St. John's wort (SJW) has been used for many years traditionally as herbal medication for wound healing, depression, and as antioxidant and anti-inflammatory agent. However, the only use of Hypericum perforatum that has been supported by clinical studies is as antidepressant in mild to medium depression. Our objective was to evaluate the analgesic effects of 2 different doses of SJW, in connection to its effects upon oxidative stress, in an experimental model.

**Material and methods.** 30 female Wistar rats were divided into 3 groups, as follows: controls (5 animals), SJW 150 mg/kg bw (5 animals) and SJW2 300 mg/kg bw (5 animals). SJW was administered by gavage, daily, for 3 weeks. At the end of the experiment, pain perception tests were conducted in each animal of the 3 groups. Analgesic effects were estimated in orofacial region (formalin test), as well as in hot plate test and paw pressure test. After pain measurements, blood samples were drawn and malonaldehyde (MDA) and nitric oxide (NO) levels, hydrogen donating ability (HDA) and reduced over oxidized glutathione (GSH/GSSG) ratio were measured in plasma. Mann-Whitney U and Student "t" were used for statistical calculations; a  $p < 0.05$  was considered significant.

**Results.** Both SJW doses reduced the area under the curve corresponding to inflammatory pain in formalin test ( $p < 0.001$ ) and increased the nociceptive threshold in paw pressure test ( $p < 0.01$ ). At the same time, both doses of SJW increased plasma levels of HDA ( $p < 0.01$ ), GSH/GSSG ratio ( $p < 0.001$ ) and MDA ( $p < 0.01$ ). A strong positive correlation between HDA and GSH/GSSG ration was recorded. No changes in plasma NO levels or hot plate latency times were seen.

**Conclusion.** SJW improves antioxidant plasma capacity and exerts an antinociceptive effect on inflammatory but not on neuropathic orofacial pain, in both dosages.



## EFFECTS OF *EQUISETUM ARVENSE* L. EXTRACT ON ENDOTHELIAL VASCULAR CELLS EXPOSED TO HYPEROSMOTIC STRESS

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**Introduction.** Research in the past few years had shown an increased interest in the medicinal plant extracts. The study of the cytotoxicity and antimicrobial activity of plant extracts is important for their clinical application in medical practice.

**Aim.** The aim of our study was to evaluate the *Equisetum arvense* extract for its antimicrobial, antioxidant and antiapoptotic activity on endothelial cell culture.

**Material and methods.** The effect against gram positive, gram negative bacteria and *Candida albicans* by disc diffusion test and minimum inhibitory concentration (MIC) was evaluated. Oxidative/antioxidative and inflammatory status in addition with caspase-3 and 8 activities and their interaction with two doses of *Equisetum arvense* L. extract, on osmotic stress *in vitro*, were investigated.

**Results.** Our results demonstrate that there is an antimicrobial effect on gram-positive cocci. The effects of *Equisetum arvense* L. extract (catechin and caffeic acid) on endothelial cell exposed to hypertonic medium was different and depended on the concentration used. Low concentrations of tested compounds exerted an antioxidant effect, but in high doses, *Equisetum arvense* L. extracts had a prooxidant effect and induced apoptosis.

**Conclusions.** These experimental findings suggest that *Equisetum arvense* L. has antibacterial effect on gram-positive cocci and, administered in low dose, may be a new therapeutic approach for diseases associated with hypertonic conditions or oxidative stress and apoptosis.

**Keywords:** *Equisetum arvense* L., hyperosmotic stress, antimicrobial effect, oxidative stress, inflammation, apoptosis

## MATERNAL HIGH-FAT DIET INFLUENCES THE IMMATURE RAT HIPPOCAMPUS EXPOSED TO PERINATAL ASPHYXIA

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**Introduction.** Recent scientific literature has shown that the intrauterine environment has a fundamental impact on fetal development with subsequent consequences on the onset of diseases in adulthood. Maternal high-fat enriched diet is a common detrimental habit that acts as a multisystem injury enhancer. A high-fat diet (HFD) not only creates health problems for expectant mothers, but it also alters the neurodevelopment and cognitive function of the child. Moreover, HFD has been reported to have harmful systemic consequences, including low-grade, long-lasting inflammation.



**Aim.** Considering that perinatal asphyxia (PA) increases neuroinflammation and neuronal injury in the immature hippocampus and modifies hippocampal epigenetic programming, we aimed to establish the impact of maternal HFD on offspring hippocampus exposed to PA.

**Material and methods.** Postnatal day 6 Wistar rat pups were exposed to a hypoxic-hypercapnic environment at 37°C for 90 min, conditions that mimic PA. The rats were divided into 2 groups: PA group (mothers receiving standard diet) and HFD group (mothers receiving high-fat supplemented diet). Meanwhile the control pups were held for 90 min in atmospheric air at 37°C. Pups were sacrificed and the hippocampi were dissected and isolated at 24 or 48 hours post-exposure. Hippocampal neuroinflammation magnitude was assessed by ELISA measurement of TNF $\alpha$  and IL-1b levels in the tissue homogenate, while neural injury was quantified by determining the S-100B level. The expression of specific microRNAs (miR124, miR132, miR134, miR146 and miR15a) as epigenetic markers of hippocampus response to PA was determined 24h post-asphyxia. Metabolic activity was measured by resazurin test in hippocampal cell suspension obtained 24 h after PA.

**Results.** Our results indicate that maternal HFD additionally increases hippocampal TNF $\alpha$ , IL-1b and S-100B after PA. Also, PA associated with maternal HFD induces miR124 up-regulation and miR132 down-regulation relative to PA alone. Metabolic activity was increased in hippocampal cells from pups whose mothers received HFD.

**Conclusion.** HFD increases the PA-induced neuroinflammation and neuronal injury, while epigenetically influences homeostatic synaptic plasticity and neuronal tolerance to asphyxia, processes associated with a higher hippocampal cellular metabolism.

## CHLORIDE TRANSPORTATION MODULATION IMPACTS ON NEURONAL VIABILITY IN MATURE HIPPOCAMPAL CULTURES EXPOSED TO OXYGEN-GLUCOSE DEPRIVATION AND REOXYGENATION

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**Introduction.** Brain hypoxia leads to disruption of the excitability-inhibition balance due to alterations in ionic homeostasis. The intracellular chloride level, generally dictated by the cell membrane transportation mechanisms, is of particular interest in excitotoxic conditions like hypoxia/ischemia. By using the in vitro oxygen-glucose deprivation (OGD) model to mimic cerebral ischemia, we investigated the changes in cellular metabolism after modulating the activity of chloride co-transporters NKCC1 and KCC2, and ligand-gated chloride channel GABAA.

**Material and methods.** Primary hippocampal cultures were obtained from Wistar rats on postnatal day 0. After 7 days in vitro, neuronal cultures were exposed to 2h OGD or control conditions (normoxia and glucose-containing medium). Evaluation of cellular metabolism was performed for 3h during reoxygenation using the resazurin test. Part of the cells were treated with the NKCC1-antagonist bumetanide or KCC2-antagonist DIOA, either during OGD or reoxygenation. Other cells received Gabazine which inhibits the GABAA receptor. Cellular viability post-OGD and reoxygenation exposure was compared to control viability, considered as 100%.

**Results.** Our results show that bumetanide treatment increased cellular metabolism during OGD, in contrast with the DIOA metabolism decreasing effect ( $p < 0.05$ ). Treatment with bumetanide or DIOA during reoxygenation didn't impact on cellular viability. Regarding the modulation of the GABAA receptor, gabazine during reoxygenation significantly decreased cell viability ( $p < 0.05$ ).

**Conclusions.** The potential neuroprotective effect of bumetanide could be explained by the blockage of Cl<sup>-</sup> inward transport via NKCC1. Following the same algorithm, the detrimental effects of DIOA-treatment might be due to the blockage of Cl<sup>-</sup> outward transport via KCC2 and a supplementary increase in intracellular Cl<sup>-</sup> concentration. The response to GABAA receptors inhibition post-OGD might be a result of a triggered switch from inhibitory to excitatory function of the neurotransmitter, but further research is necessary to clarify these changes in excitability.

## CURING AMBROSIA ALLERGY ONE STEP AT A TIME. AN INSIGHT INTO Amb A 6 ALLERGEN EXPRESSION

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**Introduction.** During the last few years the number of allergies caused by *Ambrosia artemisiifolia* throughout Romania and also the vast majority of Europe has reached a peak value. It has, therefore, become a serious health issue which requires us to address our entire attention. OncoGen center is the first to tackle this important health issue in Romania through the INSPIRED Project which aims to perform detailed characterization of *Ambrosia artemisiifolia* allergens by using recombinant allergens. Amb a 6 is one out of 12 described ragweed allergens, is considered as a minor allergen and belongs to a non-specific lipid transfer proteins family.

**Material and methods.** For approaching the recombinant expression of Amb a 6 allergen, we decided to use insect cells system, considering the glycosylation sites of the molecule. After transfection of *Spodoptera frugiperda* (Sf9) line of insect cells, the supernatant was collected, put under dialysis, and then purified (using Ni-NTA Agarose columns for His-tagged proteins). Also a final step of concentration was done using 3,000 NMWL Amicon filter units, and concentration was measured using a protein assay kit. For confirmation of recombinant protein reactivity we tested it against the sera of 90 patients with Ambrosia allergy using ELISA test.

**Results.** The Amb a 6 presence was confirmed both on SDS-Page stained with Coomassie and also on Western blot revealing a consistent band at 10 KDa. The final concentration of recombinant protein was about 150-180 µg/ml. The results of ELISA test shows 29% IgE reactivity, which corresponds to the data from literature.

**Conclusion.** Using insect cells expression system, Amb a 6 was expressed as recombinant protein in our laboratory. The obtained allergen is planned to be used for improving the diagnosis kits and for targeted therapy for the patients allergic to *Ambrosia artemisiifolia*.

**Keywords:** allergy, Ambrosia, recombinant allergen expression

## SIGNALING PATHWAYS INVOLVED IN CHEMOPREVENTION WITH BIOMATERIALS BASED ON SILVER NANOPARTICLES IN ORAL DYSPLASTIC KERATINOCYTES

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**Introduction.** Oral squamous carcinoma is the 11th most common malignancy in the world with a high risk of invasion, rapid metastasis and increasing occurrence, especially in young people. Early detection, the prevention as well as the development of safe, effective targeted therapies are very important strategies in this pathology. The current study aims to find the safety and efficacy of silver nanoparticles coated with *Cornus mas* L. or *Sambucus Nigra* L. fruit extracts as a therapeutic tool against dysplastic oral keratinocytes.

**Material and methods.** Dysplastic oral keratinocytes (DOK) were treated with silver nanoparticles functionalized with Cornus mas (AgCM) or Sambucus Nigra (AgSN) or only extracts. Untreated cells were used as controls. Viability (MTS assay) was determined. TEM was used to determine intracellular localization of the AgNPs at 4h and 24h of incubation time. Apoptosis was evaluated through FACS (annexin-PI staining), western blot (p53, Bcl-2, Bax, Akt activation,  $\gamma$ H2Ax) and for inflammatory changes TNF $\alpha$  and TRAIL were measured through ELISA. Oxidative stress damage induction was evaluated by malondialdehyde (MDA) level.

**Results.** Silver nanoparticles exhibited significant decreases of cell viability at doses higher than 20  $\mu$ g/ml and diminished MDA levels. TEM analysis demonstrated the internalization of silver nanoparticles and their accumulation, especially in lysosomes. AgCM and AgSN induced in DOK time dependent ultrastructural changes (vacuoles, autophagosomes, endosomes) and exhibited an anti-inflammatory effect, especially AgCM. AgCM and AgSN determined cellular death by different mechanisms: AgSN and SN increased  $\gamma$ H2AX, a marker of early apoptosis, while AgCM induced apoptotic levels of p53.

**Conclusions.** Both silver nanoparticles induced cellular death by different mechanisms depending on the type of functionalization and did not correlate with oxidative stress damage.

## HEPATOPROTECTIVE POTENTIAL OF DIFFERENT NATURAL COMPOUNDS IN EXPERIMENTAL-INDUCED LIVER FIBROSIS

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Liver fibrosis, a common condition occurring during the evolution of almost all chronic liver diseases, is the consequence of hepatocyte injury that leads to the activation of Kupffer cells and hepatic stellate cells (HSC). Reactive oxygen species (ROS) and some cytokines are among the most potent activators of HSC. There are a lot of experimental models to induce liver fibrosis and we performed two of them: CCl<sub>4</sub>-induced fibrosis and bile duct ligation (BDL).

We aimed to evaluate different protective strategies with natural compounds using these experimental models in order to establish their potential to inhibit the initiation and the progression of liver fibrosis: Silymarin (Si), an herbal product, Silymarin coated gold nanoparticles, Chitosan (CS) a polysaccharide obtained from chitin and silver nanoparticles loaded with chitosan. To quantify liver injury and protective effects in early and late phases of fibrosis we assessed: hepato-cytolysis (aminotransferases and LDH), oxidative stress (malondialdehyde, protein carbonyls, GSH/GSSG ratio), inflammation (different interleukins and intracellular pathways), fibrosis (histological score, hyaluronic acid), transforming growth factor TGF- $\beta$ 1, markers of HSC activation ( $\alpha$  – SMA expression by western blot) and activation of Kupffer cells (CD 68) by immunohistochemistry. We have also used the immunohistochemical assay for cytocheratin 19 and proliferating cell nuclear antigen (PCNA).

Our data showed the protective effects of Silymarin, in different doses, in early and late phases of liver fibrosis, the protective effects of chitosan during the early stages after BDL and no clear beneficial effects of silver nanoparticles loaded with chitosan and Silymarin coated gold nanoparticles in the early stages of liver cholestasis.

**Keywords:** liver fibrosis, hepatoprotection, Silymarin, Chitosan, nanoparticles

## COMPARATIVE EFFECTS OF CHLOROGENIC ACID AND RESVERATROL ON OXIDATIVE STRESS INDUCED BY EXPERIMENTAL INFLAMMATION

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**Introduction.** Chlorogenic acid and resveratrol are natural compounds with protective effects. The aim of this study was to evaluate the oxidative stress produced during inflammation in rats previously treated with chlorogenic acid, resveratrol or indomethacin.

**Material and method.** Adult male rats, Wistar breed, received for 14 days 0.5 ml/day of medication through oral gavage: chlorogenic acid 100 mg/kg/day, chlorogenic acid 150 mg/kg/day, resveratrol 50 mg/kg/day diluted in carboxymethyl cellulose, or indomethacin 1 mg/kg/day. On day 14, the animals were intraplantar injected with 0.2 ml carrageenan 1% in the posterior right paw to produce paw inflammation. Measurements for paw's inflammation were done using a plethysmometer, at 2 hours and at 24 hours after injection. On day 14, blood samples and inflamed paws' tissues were taken for determination of oxidative stress parameters: malondialdehyde, glutathione, glutathione disulfide.

**Results.** Plethysmometry showed a significant decrease of inflammation in rats that received chlorogenic acid and indomethacin. In inflamed tegument, the administered medication reduced the oxidative stress, while in serum, only indomethacin presented antioxidant effects.

**Conclusion.** Chlorogenic acid presented better anti-oedematous and antioxidant effects compared to resveratrol.

**Keywords:** chlorogenic acid, resveratrol, indomethacin, inflammation, oxidative stress

## EVALUATION OF BIOCOMPATIBILITY *IN VIVO* OF TWO ANTIFUNGAL AGENTS DERIVED FROM KETOCONAZOLE

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**Introduction.** Mycotic infections are a health problem due to the increased frequency, especially with associated illnesses, developing resistance to the existing antifungal products and long term treatment toxicity, that mainly affects the liver. Therefore, our research aimed to design new antifungal agents with increased efficiency and biocompatibility, derived from Ketoconazole (KET). KET has poor water solubility, leading to a high dosage needed to achieve therapeutic effect. This increases toxicity. Therefore, we synthesized two new solid forms, starting from KET: ketoconazole-fumaric acid (KET-FUM) and ketoconazole- p-aminobenzoic acid (KET-PABA). Solubility, antifungal efficiency and biocompatibility were studied.

**Material and methods.** New solid co-crystal forms of Ketoconazole with fumaric acid and PABA were obtained by solvent drop grinding method. Co-crystal formation was confirmed by powder X-ray diffraction, FT-IR and ss-NMR

spectroscopy, and differential scanning calorimetry. Antifungal activity was evaluated on *Candida* species (ATCC). Acute general toxicity was evaluated on Wistar rats, using 3 doses: 1.5 mg/kg bw, 0.8 mg/kg bw and 0.3 mg/kg bw. Evaluation was done at 30 min, 24h and 7 days after administration. Hematology, biochemistry and histopathology exams of collected samples were done.

**Results.** Both co-crystals showed good suspension stability, improved solubility and antifungal activity compared to KET. All animals tolerated well the compounds. Hematology and biochemistry measurements showed no consistent modifications. Liver toxicity was mainly shown at 24h through increased transaminases, however, this effect was minimal or absent at 7 days. Interestingly, on histopathology exam, there was only a slight, transient vasodilatation in liver vessels, without other modifications.

**Conclusion.** Co-crystallization with fumaric acid and PABA of Ketoconazole increased the antifungal effect of ketoconazol, without diminishing the biocompatibility. Therefore, these new co-crystals seem promising for developing improved antimicrobial agents.

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## EFFECTS OF THIAZOLIDINEDIONES ON NERVE FUNCTIONS IN EXPERIMENTAL DIABETIC PERIPHERAL NEUROPATHY

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**Background.** Diabetic peripheral neuropathy (DPN) is a debilitating complication of diabetes mellitus (DM) which in turn increases the risk of other diabetes complications such as foot ulcers and amputation. This study was designed to investigate the neuroprotective effect of synthetic thiazolidinediones compound (TZDs) administration on mechanical nociceptive thresholds, nerve conduction velocity and behavioral indices in diabetic rats.

**Methods.** Type 1 DM was induced in Wistar rats by intraperitoneal administration of STZ (60 mg/kg). The control non-diabetic rats and diabetic rats were orally treated for 5 weeks with quercetin (30 mg/kg body weight/day), pioglitazone (30 mg/kg body weight/day), insulin (10 UI/kg body weight/day) or TZDs (30 mg/kg body weight/day), respectively. Sensory and motor DPN was evaluated by: nerve conduction velocity measurements, electrophysiological assessment and behavioral tests.

**Results.** Six weeks STZ diabetic rats developed neuropathy which was evident from significant reduction in sensory and motor nerve conduction velocities (SNCV and MNCV) and increased mechanical hyperalgesia. Diabetic trained rats treated with TZDs exhibited a significant amelioration in SNCV, MNCV and hyperalgesia.

**Conclusions.** The results of the present study suggest the potential neuroprotective effect of TZDs in experimental DPN.

**Keywords:** sciatic nerves, oxidative stress, quercetin, glitazones



## THE DUAL ROLE OF METFORMIN AS AN ADJUVANT IN PHOTODYNAMIC THERAPY AGAINST MELANOMA

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**Introduction.** Despite the latest advances, melanoma therapy is challenging. Metformin (Metf) used as an adjuvant may bring therapeutic advantages. The present study has evaluated the effects of photodynamic therapy (PDT) mediated by a metal substituted phthalocyanine - Gallium phthalocyanine chloride (GaPc) combined with Metf, against a metastatic melanoma cell line M1/15, in vitro. Herein we analyze the anti-melanoma efficacy of GaPc-PDT, uncover antitumor mechanisms and weight the antiproliferative properties of Metf combination with PDT.

**Material and methods.** Melanoma cells (M1/15) previously subjected to Metf exposure were treated with GaPc-PDT. Following the different exposure regimens, cells were tested for viability; oxidative stress induction: malondialdehyde-MDA, superoxide dismutase-SOD; angiogenesis: vascular endothelial growth factor-VEGF; hypoxia inducible factor 1 alpha -HIF-1 $\alpha$ ; inflammation and proliferation: tumor necrosis factor alpha-TNF $\alpha$ , nuclear factor kappa B-NF- $\kappa$ B activation, melanin quantification; cell death: TNF-related apoptosis-inducing ligand-TRAIL and flow cytometry.

**Results.** Preliminary results of our work have suggested that GaPc was a valuable photosensitizer. Oxidative stress was increased by GaPc-PDT. Metf addition to GaPc-PDT irradiation induced apoptosis via inhibition of NF- $\kappa$ B pathway and TRAIL activation. However, the combined regimen diminished the beneficial anti-angiogenic effect of GaPc-PDT. The combined regimen induced a strong inhibitory effect on melanin production.

**Conclusions.** GaPc-PDT in combination with Metf as an antineoplastic adjuvant, induced a notable but limited effect on M1/15 melanoma cells. Even though the combined regimen has increased tumor cell killing through enhanced oxidative damage and induction of proapoptotic mechanisms, Metf has also altered the PDT anti-angiogenic effects.

**Keywords.** melanoma, metformin, photodynamic therapy, phthalocyanines

## CHEMOPREVENTIVE EFFECTS OF TWO ANTIOXIDANTS, THE GRAPE SEED EXTRACT BURGUND MARE AND CURCUMIN, ON ORAL CARCINOGENESIS

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**Introduction.** Despite the recent research results oral cancer remains a common cancer worldwide. Being a multifocal problem arising from premalignant lesions and modulated by endogenous and exogenous factors it is difficult to manage. Therefore chemoprevention appears as an important approach. Since antioxidants showed chemopreventive properties we compared the effect of the grape seed extract Burgund Mare (BM) on oral carcinogenesis with that of curcumin (CU).

**Material and methods.** Six groups (n=10) of Wistar rats received: 4-nitro-quinoline-1-oxid (4NQO) to induce oral carcinogenesis - groups 1 to 5; BM and CU during initiation group 2 and 3 respectively and groups 4 and 5 BM and CU respectively during postinitiation of carcinogenesis; group 6 was the negative control group. We assayed: total malondialdehyde (MDA) and reduced glutathione (GSH) (fluorometrically) in oral tissue (gingival, jugal, palatal, lingual mucosa) and serum. We performed histopathological exam (H&E) and gave a dysplasia score to each oral mucosal lesion. We evaluated Ki67, cyclin D1, p63, Bcl2 and p53 (immunohistochemical).

**Results.** BM and CU reduced tissue MDA values elevated by 4NQO (p=0.000). CU and BM acted significantly different in the initiation (p=0.02) but not in the postinitiation of carcinogenesis (p=0.58). They didn't significantly modified

tissue GSH levels decreased by 4NQO ( $p < 0.001$ ). Serum MDA levels increased by 4NQO ( $p = 0.000$ ) were significantly lowered by CU ( $p = 0.04$ ) and BM ( $p = 0.04$ ) during initiation and by CU during postinitiation of carcinogenesis ( $p = 0.01$ ). CU was more effective than BM during postinitiation of carcinogenesis ( $p = 0.01$ ). Serum GSH lowered by 4NQO ( $p = 0.55$ ) was significantly decreased by BM and CU ( $p < 0.012$ ) with no significant difference between groups receiving BM or CU. Moderate dysplasia was the most advanced dysplasia induced and gingiva was the most frequent involved site. Both BM and CU lowered dysplasia scores with BM being the most efficient during postinitiation of carcinogenesis ( $p = 0.001$ ). Ki67, cyclin D1, p63, Bcl2 and p53 expression increased with the dysplasia scores.

**Conclusion.** BM reduced the local and general oxidative stress and the intensity of dysplasia during initiation and postinitiation of oral carcinogenesis showing chemopreventive properties. During postinitiation of carcinogenesis BM and CU had similar effects.

**Keywords:** oral carcinogenesis, grape seed extract Burgund Mare, curcumin, malondialdehyde, glutathione, dysplasia

## THE SPHINGOLIPIDS SIGNALING PATHWAY - NEW DIAGNOSTIC TOOL FOR HEPATOCELLULAR CARCINOMA

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**Introduction.** Early diagnosis of hepatocellular carcinoma (HCC) based on  $\alpha$ -fetoprotein (AFP) serum levels could sometimes be misleading because of increased AFP is also detected in cirrhotic patients. In the struggle to discover more specific biomarkers, metabolomics has a key role in providing a better understanding of the factors involved in the oncogenic processes of the HCC. Recently, sphingolipids have gained the attention by being involved in cell proliferation and drug resistance.

**Aim.** The aim of our study is to improve the HCC diagnosis by determining a more reliable biomarker and correlate it with the overall survival.

**Material and methods.** We conducted a cross-sectional study in which 104 patients were included: 54 with early HCC (BCLC stages 0, A and B) and 50 with compensated cirrhosis. Analysis of the metabolites from the serum of each patient was carried out using mass spectrometry. For the identification of the possible biomarkers we used MetaboAnalysis, performing univariate and multivariate statistical analysis. The performance of the biomarkers to detect early HCC was evaluated using semi-quantitative assessment and through a leave-one-out cross-validation based on area under the receiver operating characteristics (ROC) curve.

**Results.** There were 15 metabolites identified, from which sphingolipids, especially C16 sphinganine (C16-SPH), were the most upregulated in the HCC subjects. C16-SPH had a 4.869 times higher concentration in HCC group than in cirrhotic patients ( $p < 0.005$ ). The area under the curve (AUC) of C16-SPH for the diagnosis of HCC was significantly higher compared to AFP [0.969 (95%CI, 0.923- 1) vs. 0.544 (95%CI, 0.415-0.673),  $p$  (deLong test)  $< 0.001$ ].

**Conclusion.** We discovered that sphingolipids show a considerable upregulation in HCC patients and may help discriminate HCC patients from those with chronic liver disease. Therefore, C16-SPH could be considered as a novel/potential biomarker for the early detection of HCC.

**Keywords:** metabolomics, biomarkers, sphingolipids, hepatocellular carcinoma



## FIRST INTER-MEDICAL SCHOOL PHYSIOLOGY QUIZ

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The Department of Physiology at the “Iuliu Hațieganu” University of Medicine and Pharmacy in Cluj-Napoca together with the Student Scientific Circle of Physiology intended to increase the involvement of medical students in physiology-oriented learning activities. A great step in achieving this goal was the organization for the first time in Europe of the 1st Edition of an Inter-Medical School Physiology Quiz whose origins are attributed to Prof. Dr. Cheng Hwee Ming from the University of Malaya in Kuala Lumpur. The contest brought together 24 teams from 7 medical university centers in Romania, some of the participants being of other nationalities or minorities. The quiz fixture comprised three rounds divided into question sessions; during every session, the teams in front of the Auditorium listened to Prof. Cheng's questions and tried to respond to each in 30 sec. The participating teams and also the audience were deeply delighted by the dynamics of this event and the organizing committee aims to attract as many teams as possible in future editions. The manner in which questions brought to light delicate aspects in physiology has also triggered debates between students and the wish to read more. We think this is an alternative method in increasing the impact of medical physiology in student communities but is also a trigger in increasing the quality of learning and teaching physiology in medical centers in Romania, one special issue given by the event being the use of graphs to understand the dynamics of physiology processes.

**Keywords:** quiz, contest, teaching, learning

## OPTICAL PROPERTIES OF BLOOD IN A GROUP OF SUBJECTS WITH ISCHEMIC STROKE

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**Introduction.** Hemostasis is a complex physiological process that stops bleeding at the site of a vascular injury. Although the majority of vascular accidents are ischemic, the role of hypercoagulable state and stroke needs further investigation.

**Aims.** The purpose of this study is to dynamically evaluate the optic properties of the coagulating blood in a group of subjects with ischemic stroke compared to a group of clinically healthy subjects.

**Material and methods.** Fresh whole blood was taken from 61 acute ischemic stroke patients and compared to 18 healthy subjects and investigated with optical coherence tomography imaging after initiating coagulation. We used an OCT1300SS system (Thorlabs) and did 3D scans. We then processed the images with ImageJ. For each image mean, integrated density, skewness and kurtosis of gray values were analyzed.

**Results.** We found changes in the reflectivity of blood samples, even at the start of the recording. This difference only got bigger as the reaction continued, showing an intrinsic difference between the two groups. Mean gray value

and integrated intensity of sampled data showed an intrinsic difference detected with OCT. This difference was further confirmed by the data distribution analysis.

**Conclusions.** The mean gray value and integrated intensity of sampled data showed an intrinsic difference detected by OCT. It suggests that normal blood coagulation is not due to a random reaction while in the case of stroke patients, the relatively symmetrical distribution of gray values brings coagulation closer randomized process.

**Keywords:** cerebral ischemia, coagulation, optical coherence tomography

## AQUAPORIN 4 AND THE CENTRAL NERVOUS SYSTEM GLIA SCARRING

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Edema represents one of the earliest markers of central nervous lesions. New insights into water metabolism in the brain have opened the way for molecular targeted treatment, with aquaporin 4 channels (AQP4) taking center stage. Our aim was to evaluate the histopathological effects of a nonfunctional AQP4 channel, on the overall glial scar. A chemical channel blocker was given to the animals 20 minutes after a cortex lesion was made. Rotarod motor testing and neuropathology examinations were next performed. Evaluation of the blood vessels revealed thicker basement membranes colocalizing with exudated albumin in the treated animals, suggesting that inhibition of AQP4 blocks fluid flow towards the parenchyma in the paravascular drainage pathways of the interstitial fluid. Our data show that blocking water diffusion after central nervous system lesion, leads to a higher neuronal survival.

## IN SILICO INSIGHT INTO EPIGENETIC AND TRANSCRIPTION CHEMOPREVENTIVE SIGNALING MECHANISM IN ORAL CANCER

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**Introduction.** Recent studies give insights about coordination between metabolism and epigenetics mechanisms (the activity of histone modifying enzymes) and shown that epigenetic processes are sensitive to changes in the metabolic state of a cell. Metabolic and epigenetic dysregulation play a critical role in tumor development. The central hypothesis of this study is that alterations in metabolism can affect the epigenetic pathways of a cell by changing the level of critical cofactors required. Our work further contributes to the current understanding of the complex signaling networks underlying

OSCC (oral squamous cancer cells), and may aid in the development of novel means of cancer chemoprevention.

**Material and methods.** The expression of PI3K-AKT, WNT and p53 signaling pathways were examined by *in silico* methods. Source data sets. For this study, we employed gene list corresponding to the expression data obtained from SABiosciences Qiagen (for each signaling pathways we did 84 interrogations in KEGG and UniProt, to infer genes and underline pathways). *In silico* analysis was performed by employing online tools: geneMANIA and esyN (build network interactively).

**Results.** Gene predicted maps of the oncogene expression assessed in the study (PI3K, AKT, mTOR, Rad, Myc, HIF1) lead to PPI (protein-protein-interaction) and gene mapping that involved other 20 genes.

**Conclusions.** These results suggest that dysregulation of these signaling networks may be the driving force behind the early stages of OSCC tumorigenesis as well could be target molecules for chemotherapy that will be further investigated in wet lab work.

**Keywords:** OSCC, *in silico*, PI3K-AKT, WNT, p53, geneMANIA, esyN

## INTEGRITY – THE INTEGRAL DIMENSION OF EXCELLENCE IN RESEARCH

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**Introduction.** In the past few years, cases and issues of Research and Integrity have gained visibility, and became an important topic of debates and public investigations. Now, ethics and integrity in research are widely acknowledged as core conditions for credibility and trust in scientific research. But why is it important to talk about integrity in scientific research nowadays? Is there a relation between medicine, generally speaking, and research integrity?

**Material and methods.** As objectives of this presentation we set up the following: presenting some notorious cases of frauds in research reported in the last years; analyzing the consequences of these cases for the academic community and for society; identifying some solutions and ethical orientations in order to avoid and prevent frauds. As methods we will use cases analyze and ethical deliberations. Also we will present the current legal framework in the EU and the further legal proposal regarding these practices.

**Results.** Cases about conflict of interests and plagiarism are reported, in Romania. Plagiarism practices had as outcomes a legislative proposal of the Legal Commission of the Romanian Senate, in March 2016, calling for punishment of plagiarism by imprisonment from 6 months to 3 years or a fine, and Ph.D. theses or scientific works found to be plagiarized becoming null and void. On January 30th 2018, the Minister of National Education approved an order for the inclusion of ethics and integrity courses in the curricula for all academic programs in the higher education institutions of the national education system. Some universities already started to improve their curricula for students with courses on Integrity and Ethics regarding the Research.

**Conclusion.** We need to be aware about its importance, especially in Academia. At present, the EU institutions have initiative and take measures in this field. It is important to have a plan and procedures in order to be able to correct and prevent such practices.

**Keywords:** research, integrity, ethics, responsibility

## STEM CELLS RESEARCH AND THERAPY – ETHICAL AND LEGAL ISSUES

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**Introduction.** Medicine is an ever-changing science. Stem Cells Research and Therapy are nowadays part of the medicine. After developments and trials for decades, in 1988 James Thomson announced that he had derived and cultured human embryonic stem cells, researchers advanced the idea that a variety of diseases and injuries would be cured, such as: cancer, diabetes, Parkinson's, spinal cord injuries and many others. But, as the human embryo status is much debated, the trials were put on hold. In 2007, a team of researchers from Japan (Takahashi et al., 2007; Yu et al., 2007) published very good news: the possibility to create induced pluripotent stem cells, derived from somatic cells, easily used to establish any disease-specific cell line. And researches are going on.

**Material and methods.** The purpose of this presentation is: 1) to familiarize professionals with current debate on the stem cells research and therapy; 2) to provide main legal standards and regulations concerning this specific area; 3) to summarize ethical issues raised by stem cells research and therapy.

**Results.** Cases about patients who are moving to certain countries to benefit from treatments with stem cells in order to treat diabetes, AIDS, multiple sclerosis, muscular dystrophies and many others are already known. Also, scientists who are claiming to patent treatments with stem cells are judged and analyzed by Courts in Europe. Some countries adopted laws and regulations in order to become transparent in their practices, and other countries prefer to have no regulations. Romania is in this second category. Ethical issues are grouped in three categories: Integrity and frauds in stem cell research and therapy; the debate on Human Embryo Status in the case of using human embryonic stem cells; and Stem Cell Tourism.

**Conclusion.** Our conclusion is that in a hand from we are facing with legal and ethical issues, but science should go on and looking for solutions and progress. At this moment, "Science can only ascertain what is, but not what should be," Albert Einstein said, "and outside of its domain value judgments of all kinds remain necessary."

**Keywords:** stem cell research, stem cell therapy, human embryo status, stem cell tourism

## OLD ROADS WITH NEW CONNECTIONS: LANDMARKS IN DIAGNOSIS AND PATHOPHYSIOLOGICAL MECHANISMS IN RARE DISEASES, FOCUS ON TREATABLE NEURO-METABOLIC DISORDERS

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The classical inborn errors of metabolism (IEM) are defects in enzymes or transporters involving the metabolism of amino acids, carbohydrates, fatty acids, or in mitochondrial energy metabolism; the clinical picture of these disorders (750

*types have been described so far*) is often non-specific, and 85% are presenting predominantly neurologic manifestations. One reason is the fact that, the building and maintaining the normal structure and function of the brain is due to the involvement of many genes; besides, this tissue seems to possess restricted capabilities for repair. Due to the development of basic sciences and advances in technology (metabolic and genetic analyses), we gained insights in the molecular basis of these diseases, about 300 “new” disorders being described in the last 5 years. Our experience includes NMR spectroscopy and chromatography investigations used as a selective screening on a research base for children/adults suspected for IEM; we identified defects in amino acid metabolism (including urea cycle disorders- UCD), organic acidurias, carbohydrate defects, ketolysis abnormalities. <sup>1</sup>H-NMR spectroscopy shows the majority of proton-containing compounds and gives a characteristic ‘*fingerprint*’ of almost all hydrogen nuclei in a metabolite.

During the last decades, many therapeutic approaches were developed, a specific dietary restriction helps for the defective pathway or for the avoidance of catabolic states. Pharmacological doses of chaperons, vitamins have been useful in deficiencies that affect the brain, i.e.: cobalamin and biotin defects. The discoveries of substances that remove nitrogen in the form of alternative conjugates are essentials for treatment of UCD, preventing the brain damages. The major progress in the last years has been made with the introduction of enzyme replacement therapy in several storage disorders or even in phenylketonuria. Other future options are: inhibition of substrate synthesis, administration of neurotransmitters precursors or inhibitors, chaperon-mediated enzyme enhancement, transplant-ation of stem cells, and even the gene therapy or genome editing procedures.

In this manner, these disorders - that need rapid diagnosis and prompt treatment (if available) - continue to be a scientific challenge to modern medicine.

Our work was partially supported by Merck group Romania.

**Keywords:** inborn errors of metabolism (IEM), <sup>1</sup>H-NMR spectroscopy, treatable neuro-metabolic disorders

## **PSORIASIS: INTERLEUKIN-17 GENE POLYMORPHISMS ASSOCIATION WITH SEVERITY AND RESPONSE TO TREATMENT**

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Psoriasis is a chronic, inflammatory disease with a complex pathogenesis that is not yet fully understood. Although it is a multifactorial disease, the genetic factor has a major role in the pathogenesis of psoriasis. Genome wide association studies have identified over 50 genetic loci associated with psoriasis risk. Beside TNF- $\alpha$  or IL-23, the IL-17 family is a newer group that has proven implications in the pathogenesis of psoriasis. The most important members of the family, with pro-inflammatory qualities, are IL-17A and IL-17F. These interleukins are produced by a varied number of cells, but by far the most important are Th17 cells. A percent of 20 to 30 of the patients present moderate-to-severe psoriasis therefore systemic medication (phototherapy, methotrexate, cyclosporine, acitretin or biologic agents) is mandatory. The necessity of an individualized treatment plan, for each patient, is imperative in order to establish the best strategy for non-responders to classical treatment or to other biologic treatments. The discovery of Th17 pathway improved the treatment and prognosis of psoriasis. Anti-psoriatic agents against IL-17 or its receptors are a novel group of biologic agents; these include ixekizumab, secukinumab and brodalumab. Polymorphisms of IL-17 family have been correlated with the severity and response to treatment in psoriasis, and also with the risk of inflammatory, infectious, autoimmune or neoplastic pathologies. The significant difference in the presence or absence of susceptibility loci in different population is due to genetic background and environmental factors that have a major impact on disease predisposition.

## NANOTECHNOLOGY FOR IMPROVEMENT OF HUMAN DENTAL FOLLICLE DERIVED STEM CELLS DIFFERENTIATION INTO RETINAL PROGENITORS

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**Introduction.** The purpose of this study was to investigate innovative mesenchymal stem cell therapies combined with the administration of growth factors (basic FGF, IGF and NGF) in retinal degenerative diseases using as vehicle for initiation of differentiation gold nanoparticles.

**Material and methods.** Mesenchymal stem cells isolated from human dental follicles have been used since these cells have several advantages: they are of human origin, are easy to isolate, accessibility of dental tissues. These cells were characterized phenotypically, genetically and functionally for their capacity of multipotentiality. The differentiation protocol consisted of 6-stage specific differentiation stages over 50 days. A serum-free basal medium was used DMEM/F-12 supplemented with growth factors or regulatory molecules depending on each step of differentiation. Growth factors were administered via the gold nanoparticles functionalized with bFGF (basic Fibroblast Growth Factor), NGF (Nerve Growth Factor) and IGF (Insulin Growth Factor) either in the culture medium either embedded in a substrate consisting by fibronectin and laminin. Immunocytochemical staining for transducin and rhodopsin was performed. Genotyping was carried using RT-PCR for Oct-4, RPE65, Rho (rhodopsin) NLR, NR2E3, GNB3 and Calb1 expression.

**Results.** Immunocytochemistry showed the expression of rhodopsin and transducin in most groups in varied proportions. The genetic analysis revealed that differentiated cells were negative for Rho and positive for the other retinal specific genes.

**Conclusion.** The 50-day differentiation protocol, with increased activin concentration and the addition of new activating molecules such as DAPT, SU 5402, VIP and EGF in high concentrations, and finally retinoic acid induced a terminal differentiation stage with expression for rhodopsin and transducin. Functionalized NGF nanoparticles (AuNP-NGF) induced the most typical cell morphology in the case of cultures without substrates. Cells grown on the substrate exhibited a higher intensity of rhodopsin staining.

**Keyword:** mesenchymal stem cells, growth factors, gold nanoparticles

## CO-TRANSPLANTATION OF IMMUNOSTIMULATORY MACROPHAGES AND MESENCHYMAL STEM CELLS FOR THE REGENERATION OF THE OPTIC NERVE IN AN ANIMAL MODEL OF GLAUCOMA

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**Introduction.** Currently, glaucoma clinical treatment is aimed at lowering intraocular pressure (IOP). Both retinal ganglion cell loss and optic nerve atrophy may also occur even at normal IOP levels. The most worrying consequence is axonal dystrophy of the optic nerve. We proposed the development of an experimental in vivo rat model for the regeneration of the optic nerve in induced glaucoma using a co-transplant with macrophages and mesenchymal stem cells administered intravitreally.

**Material and methods.** Human and rat monocytes were isolated by centrifugation with Ficoll-Paque 1077. Isolated monocytes were activated with zymosan and characterized. Isolation, cultivation and characterization of mesenchymal stem cells from human umbilical cord stem cells and rat bone marrow was performed. Glaucoma was induced by injecting



paraformaldehyde fixed erythrocytes in the anterior chamber. Animals' follow-up was performed by measuring the intraocular pressure (IOP) and eye fundus view for suggestive changes for optic nerve atrophy. After 6 weeks glaucoma was confirmed and co-transplantation of PKH26 pre-stained stem cells/zymosan-activated monocytes was performed into the intravitreal space. Animals were sacrificed at 6 and 10 days post transplantation in general anesthesia by cervical dislocation. Eyeballs were harvested and fixed for classical histopathological analysis or immunohistochemical staining. The levels of circulating TGF $\beta$ 1 were measured by ELISA from the serum collected from animals at 6 and 10 days post-transplant.

**Results.** A comparison was made between allo-transplants and xeno-transplants with human fetal stem cells and human monocytes. The isolated stem cells in our study did not express HLA-DR, an important molecule in inducing the immune response in graft rejection. Clinical examination by IOP measurement and indirect ophthalmoscopy showed that the groups with allo co-transplant have evolved more favorably with decreasing IOP and ameliorating the eye fundus aspect. Pathological anatomy confirmed the clinical examination. The dynamic growth of TGF $\beta$ 1 levels was observed in allogenic co-transplantation, suggesting the best immune tolerance.

**Conclusion.** The evaluation of the local response by histological techniques confirmed the repair of lesions in allo-transplant groups and the minimization of these lesions in the xeno-transplantation groups.

**Keywords:** co-transplant, mesenchymal stem cells, monocytes, glaucoma

## A COMPARATIVE STUDY OF ANTITUMORAL EFFECTS OF NEW SOLID FORMS OF 5-FLUOROURACIL AND PIPERAZINE

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**Introduction.** The 5-fluorouracil (5-FU) is a chemotherapy drug used in some solid tumors such as colon cancers. The aim of our study was to test the antitumoral effect of two new forms of 5-FU, co-crystal and salt respectively, on three different cell lines: normal and tumoral cells.

**Materials and methods.** The new solid forms of antineoplastic agent 5-FU in combination with an antihelminthic compound (piperazine), were obtained by liquid crystallization methods as co-crystal (5-FU BM2) and salt (5-FU SL). We studied the toxicity of 5-FU and its compounds on a normal cell line (HUVEC- endothelial cells) and two tumoral cell lines: DLD1 and HT-29 (both colorectal adenocarcinoma). The cytotoxicity was studied by MTT assay and cell proliferation assay. Data obtained were expressed as EC 50 (half maximal effective concentration). Samples were assessed with Biotech plate reader at 570 nm. Statistics were performed with GradPad Prism program.

**Results.** We found that the co-crystal form of 5-FU (5-FU BM2) exerts a selective cytotoxic effect on tumoral cells (especially on HT-29 cells), in contrast with the resistance showed by the normal endothelial cell line. For the soluble form (5-FU) and the salt (5-FU SL) the effects on tumoral and normal cells are similar.

**Conclusions.** The comparative study between the three forms of 5-FU showed that the best antitumor selective response is obtained for the co-crystal solid form of the drug.

**Keywords:** 5-Fluorouracil, cytotoxicity, tumoral cells, endothelial cells



## RECOMBINANT Amb A 8, A CANDIDATE FOR THE IMPROVEMENT OF RAGWEED ALLERGY DIAGNOSIS AND THERAPY

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**Introduction.** Ragweed (*Ambrosia artemisiifolia*) pollen is known for its high potential to cause type I allergic reactions, representing a major health problem in many countries. Currently, ragweed allergy diagnostic is based on pollen extract, with variable allergens and allergen concentration. Therefore, using recombinant allergens would be a good alternative for accurate diagnosis and therapy.

**Material and methods.** The DNA sequence encoding Amb a 8 with a polyhistidine tag was subcloned into an expression vector with kanamycin resistance. The plasmid was transformed into BL21 E. coli cells, and protein expression was induced with IPTG. After expression, recombinant Amb a 8 (rAmb a 8) was purified under denaturing conditions using Ni-NTA affinity chromatography. The presence of the purified protein was verified on SDS-PAGE. The concentration of the protein was measured using fluorescence spectroscopy. IgE reactivity was determined in ELISA using sera from 90 ragweed allergic patients. Amb a 8 specific IgG antibodies were induced upon immunization in rabbits.

**Results.** The SDS-PAGE analysis showed a band at 14 kDa for the recombinant allergen. The expression and purification resulted in a pure rAmb a 8 with a concentration of 200-400 µg/mL. The IgE binding frequency of the rAmb a 8 was 30%, as previously stated in the literature. Immunization with rAmb a 8 induced a robust immune response in rabbits.

**Conclusions.** We managed to produce recombinant profilin from ragweed pollen in an E.coli expression system, which behaved comparably with the naïve form. Therefore, both the recombinant allergen and the specific IgG obtained in rabbits will be used to develop a diagnostic kit and to improve the therapy.

**Keywords:** allergy, ragweed, recombinant allergen, E.coli expression system

## A NEW APPROACH IN THE TREATMENT OF EXPERIMENTAL CHOLESTASIS USING SILYMARIN COATED NANOPARTICLES

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**Introduction.** A new Silymarin formula, coated on gold nanoparticles, was used in order to assess its hepatoprotective and antifibrinogenic properties after bile duct ligation in rats. Blood tests and liver histopathology results were compared with the standard administration of silymarin in order to assess the new formula.

**Material and methods.** Forty male Wistar rats with a weight of 180±20 g were randomly divided into 4 groups. Group 1 only with laparotomy (SHAM), group 2 with bile duct ligation (BDL), group 3 with BDL and a daily dose of orogastric silymarin administration for 7 days and group 4 with BDL and a daily administration of Silymarin coated gold nanoparticles, also for 7 days. On the 8th day each animal was sacrificed and blood samples and liver tissue were collected in order to assess the liver injury and the silymarin effects.

**Results.** Silymarin-coated gold nanoparticles improved liver function, reduced cholestasis and oxidative stress parameters while increasing the antioxidant liver support. It also helped by reducing the inflammation and fibrosis in the liver of rats with extrahepatic cholestasis as compared to non-treated animals. The increased Silymarin cellular intake provided by the nanoparticles, showing a more efficient absorption, delivered the substance into the cells more efficiently comparing to the standard administration.

**Conclusion.** Our data showed that silymarin coated gold nanoparticles administration have beneficial effects in the early stages of experimental cholestasis.

**Keywords:** Silymarin, cholestasis, nanoparticles

## Posters



## PROPOLIS - THE NATURAL BIOREGULATOR IN DIABETES AND FOR IMPROVEMENT OF GONADOTROPIC HORMONES

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**Background.** Genetic repression is an important action of certain hormones such as estrogens and glucocorticoids. Some flavonoids in the propolis contain such hormone-like actions that have a very close structural resemblance to some hormones, which could explain their common action. The bioregulatory effect of propolis occurs through the ability of the body to function, defend and adapt to the disorder of glucose metabolism. Administration of this valuable apiculture product has a role in health maintenance, being devoid of harmful or secondary effects sometimes produced by pharmaceutical preparations.

**Material and methods.** Researches were performed on laboratory white rats, body weight 170-230 g, divided into 4 groups: one control and three experimental. The model of experimental diabetes was made by introducing 5% alloxan solution. Testing of hormones - by the immunofermentative method.

**Obtained results.** Research data show that due to the chemical composition, rich in vitamins, microelements and amino acids, propolis tincture possesses stimulating properties on the functional activity of endocrine and gonadal pancreas through the tendency of normalizing hormones in the blood, which plays an important role in stopping the occurrence of complications in experimental diabetes. By examining the estradiol content on the background of alloxane, we observed a relative decrease to  $77.65 \pm 5.85$  pg/ml compared to the control group that records  $209.51 \pm 3.8$  pg/ml. When administering propolis tincture on the background of alloxan, we notice a relative normalization trend of estradiol up to  $120, 19 \pm 2.33$  pg/ml. The same effect is seen in the alloxan group on propolis tincture, where the testosterone concentration reaches  $3.08 \pm 0.18$  ng/ml, compared to the alloxan group which is  $2.53 \pm 0.19$  ng/ml.

**Conclusions.** The experimental study reports that propolis tincture has a hypoglycemic effect and can be included in the list of natural preparations used in the treatment of glucose metabolism disorders. It can also be concluded that the sanogenic effects of propolis are beyond doubt, and it can be successfully used in sanocreatology to maintain and strengthen health by modifying the vector to regulate reactions and processes in the body, organ systems, thus maintaining the vital potential of the body within the limits of physiological norms.

**Keywords:** diabetes, pancreas, propolis, gonads

## MODIFICATIONS OF CORTICOSTERONE IN EXPERIMENTAL DIABETES IN THE CONTEXT OF PROPOLIS TINCTURE ADMINISTRATION

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**Background.** Diabetes influences on adrenal glands, which is manifested by a hyperproduction of glucocorticoids and catecholamines, which causes the occurrence of hyperglycemia. Investigating the corticosterone level, we observed an increase of up to  $179.35 \pm 2.616$  nmol/l in the experimental group, compared to the control -  $87.53 \pm 0.148$  nmol/l. This confirms the diabetogenic factor of glucocorticoids, although it may also have an adaptive character in the early stages of diabetes. The above data allow us to assume the participation of glucocorticoids in the pathogenesis of spontaneous diabetes. The degree of manifestation of the changes described above is in direct dependence on the level of insulin deficiency.

**Material and methods.** Researches were performed on laboratory white rats, body weight 170-230 g, divided into 4 groups: one control and three experimental. Model of experimental diabetes - by introducing 5% alloxan solution. Testing of hormones - by the immunofermentative method.

**Obtained results.** The induction of experimental diabetes, followed by the installation of persistent hypoinsulinemia and hyperglycaemia, results in a substantial increase of the plasmatic corticosterone level. This statistically significant increase is 62% in relation to the corticosterone levels up to injection of alloxane. When administering propolis tincture on the background of alloxanic diabetes, there is a reduction of corticosterone level -  $130.34 \pm 2.505$  nmol/l, in relation to the alloxanate diabetes group -  $179.35 \pm 2.616$  nmol/l, which allows us to emphasize the positive role of the propolis tincture in the treatment of diabetes.

**Conclusions.** Based on the data presented above, we assume that the differences in the activity of cortical substances of adrenal glands in diabetes are closely related to the peculiarities of diabetes evolution and reflect a different level of development of adaptation to metabolic stress disorder. It is proven that the evolution of diabetes is related to changes in the cortical layer of adrenals. Intraperitoneal administration of alloxane contributed to the establishment of hyperglycemia in rats, by changes in clinical, laboratory and hormonal indices. The propolis tincture, on the background of alloxanic diabetes, determines a positive influence on all mentioned indices and on the functional status of the adrenal cortex by their relative improvement.

**Keywords:** diabetes, adrenal glands, corticosterone, propolis

## CARDIOVASCULAR RESPONSE IN SLEEP DEPRIVED SUBJECTS

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**Introduction.** The aim of our study was to assess the impact of sleep deprivation cardiovascular parameters in sleep deprived doctors after on call duty.

**Material and methods.** We compared 34 patients between 20-35 years old of both gender who performed an intense effort during emergency on call duty. All subjects consumed caffeine and individual consumption was expressed as caffeine units. All cardiovascular parameters were analyzed using impedance cardiography recordings (ICG-M501 from Physiology Department I of University of Medicine and Pharmacy Carol Davila, Bucharest, Romania), ECG and arterial blood pressure measurements. Several parameters were recorded and analyzed: cardiac output, cardiac index, stroke volume, peripheral vascular resistance, ventricular pre-ejection time. Data analysis was performed using IBM SPSS statistics (SPSS software, version 20.0, Inc., Chicago, IL, USA). Continuous variables were reported as mean ( $\pm$ SD) or median (range) and categorical variables are presented as n (%). Statistical significance was set to  $p < 0.05$ .

**Results.** We found a paradoxical cardiovascular response in group of sleep deprived cases who consumed caffeine versus those who did not consumed. This response consisted of a significant decrease in stroke volume (from 68.5 mL to 60.5 mL,  $p < 0.05$ ), cardiac output (from 6.25 L/min to 5.2 L/min,  $p < 0.05$ ), peripheral resistance ( $1888.2 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$  to  $2301.23 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$   $p < 0.05$ ). Systolic blood pressure had also significantly decreased (136.42 mm Hg before versus 124.5 mmHg,  $p < 0.05$ ).

**Conclusions.** Sleep deprivation changes the cardiovascular adaptive response in sleep deprived persons in a paradoxical manner.

**Keywords:** sleep deprivation, cardiovascular response, impedance

## OXIDATIVE STRESS IS A KEY FACTOR IN PATIENTS WITH TRAUMATIC BRAIN INJURY

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**Introduction.** Our study evaluates the role of oxidative stress in the pathophysiology of the acute traumatic brain injury and was performed in the "St. Pantelimon" Emergency Hospital – Bucharest. Our results sustain literature data about oxidative stress and antioxidant enzymes activities in this category of patients.

**Methods.** 61 patients with acute traumatic brain injury and 10 control cases were studied after admission in hospital. Clinical examination, data laboratory and imaging (CT and MRI) was performed for all cases. Plasma measurements of superoxide dismutase (SOD), catalase and total antioxidant capacity (TAC) of plasma together with inflammatory tests were performed. Statistical analysis was performed using T Test, with a significance threshold for  $p < 0.05$ .

**Results.** After comparison, we identified increased values for inflammatory markers (fibrinogen, CRP, ESR), reduced TAC and decreased activity of SOD and CAT activities.

**Conclusion.** Oxidative stress and inflammation appeared to be significant factors in patients with TBI versus control.

**Keywords:** brain trauma, oxidative stress, inflammation

## STUDY OF CIRCADIAN CHANGES OF HEMOSTASIS AT BIRTH

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**Introduction.** The lack of information about circadian variation of hemostasis at birth has prompted our interest in this problem, which can be speculated for diagnostic and therapeutic purposes.

**Material and methods.** The study was conducted on five lots of newborns, classified according to G.A. (gestation age), birth weight, and APGAR score, which determined different hemostasis parameters at two moments of the day (a.m. 6.00-8.00 and p.m. 6.00-8.00).

**Results.** In neonatal newborns with APGAR above 8, the values of the investigated parameters differed significantly depending on the period of the day when the birth occurred. At premature, there are no signs of a circadian rhythm of hemostasis.

**Conclusions.** Hemostasis shows statistically significant circadian variation only in normoponderal newborns with APGAR scores above 8.

**Keywords:** circadian rhythm, hemostasis, newborn



## CHRONIC ADMINISTRATION OF ACEI AND ARBs MAY IMPROVE SCOPOLAMINE-INDUCED MEMORY IMPAIRMENT IN MICE

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**Introduction.** A large number of patients worldwide are currently using medicines for various cardiovascular diseases and angiotensin-converting enzyme inhibitors / ACEI and angiotensin receptor blockers / ARBs are the most commonly used due to their ease of administration, favorable outcomes and good tolerance. Recent studies argue that these therapeutic classes acting on Angiotensin II, including at the cerebral level, have beneficial effects on cognitive performances (short and long term memory), especially in patients with various types of dementia. Angiotensin II plays an important neuromodulatory role by interacting with different neurotransmitters such as acetylcholine, catecholamines, serotonin and other peptides. In this context, our aim was to study the possible protective role of some ACEI ( ramipril) and ARBs (losartan) that were administered for eight consecutive days in a scopolamine-induced dementia animal model.

**Material and method.** The experimental protocol was performed on six groups of Swiss male mice (n=8 animals/group), weighing 30 g on average, randomly assigned to the study groups. Scopolamine was administered at a dose of 0.5 mg / kg body weight/day (i.p.) in order to induce memory impairment, after the selected groups were previously protected with ACEI or ARBs. Administration of scopolamine, ACEI and ARBs was conducted daily for a period of 8 days. The behavioral tests consisted in the evaluation of the working and reference memory in the eight arm radial task.

**Results and discussion.** Our results showed a protective effect of these compounds administered prior to scopolamine treatment by decreasing the number of working and reference errors, particularly for the losartan + scopolamine and ramipril + scopolamine treated groups versus the scopolamine only treated group.

**Conclusions.** The present study suggests that ACEI and ARBs are involved in mitigating the cognitive impairment mediated by scopolamine. These results are promising for (future) developing (of) new therapeutic strategies in patients with various types of dementia.

**Keywords:** ACEI, ARBs, scopolamine, cognitive disorders

## OSTEOPOROSIS, INFLAMMATION AND PERIODONTAL DISEASE

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Decreased bone density is a phenomenon that characterizes osteoporosis. Bone density may be a determining factor in the prognosis of tooth preservation and periodontal disease. The literature associates systemic inflammatory syndromes or localized inflammatory outbreaks with systemic or localized osteoporosis episodes. To maintain bone homeostasis, a balance between two fundamental processes is needed: bone resorption and bone apposition. This balance ensures the

maintenance of bone density within physiological limits. Two examples of disorders in which an imbalance occurs in this process are osteoporosis and periodontal disease. Osteoporosis has been considered a disease of the elderly for a long period of time, but it is now known that the disease can occur at any age, being caused by multiple and various factors. Its etiology involves hormonal, nutritional, metabolic factors that compromise bone strength, making the patient more prone to fractures even in the case of minor trauma. Recently, the relationship between inflammatory syndromes and osteoporosis is mentioned in the literature. The mechanism underlying this association is based on pro-inflammatory cytokines. The disruption of the balance between resorption and apposition is generated by the activation of the humoral and cellular immune responses, which stimulates osteoclastogenesis and inhibits osteoblastogenesis. The role of cytokines in the resorption-apposition imbalance and the way periodontal disease alters the serum concentrations of these cytokines are resumed in the present paper.

## LIPID FRACTIONS THAT CORRELATE WITH INSULIN RESISTANCE IN NEWLY DIAGNOSED TYPE 2 DIABETES PATIENTS

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**Introduction.** In persons with type 2 diabetes either insulin resistance or insulin deficiency predominates. Given the physiological pleiotropic effects of insulin on lipid metabolism we proposed to determine which of the lipid fractions correlate mostly with insulin resistance evaluated by calculation of HOMA-IR index. It is well-known that insulin resistance is a leading cause of dyslipidemia by lack of inhibition of adipose tissue hormone sensitive lipase.

**Materials and method.** Therefore in 240 newly diagnosed diabetes mellitus patients we performed lipid profile analysis: total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, non HDL-cholesterol and triglycerides/ HDL-cholesterol ratio. The inclusion criteria were: patients over 18 years old that gave their consent for participation in the study and patients who were not receiving any lipid modifying treatment in the past 6 months. For every patient we calculated the HOMA-IR index using the formula:  $\text{HOMA1-IR} = (\text{FPG (mmol/L)} \times \text{FPI (mU/L)}) / 22.5$ .

**Results.** The parameters that correlated statistically significant with insulin resistance were: triglycerides ( $p=0.0004$ ), non HDL-cholesterol ( $p=0.0008$ ), triglycerides/HDL-cholesterol ratio ( $p=0.003$ ). Total cholesterol, LDL-cholesterol and HDL-cholesterol did not correlate with insulin resistance. Patients were further divided as insulin resistant or non-insulin resistant based on their HOMA-IR index; a cut-off value of 2.5 was used. Patients with HOMA-IR greater than 2.5 showed statistically significant greater values of lipid fractions only for triglycerides but all the other lipid fractions had greater values but without statistic significance.

**Conclusion.** High values of plasma triglycerides represent the most significant lipid fraction that correlates with insulin resistance Triglycerides/HDL ratio and non HDL-cholesterol can also serve as useful proportions for orientating the clinician concerning the predominance of either insulin resistance or insulin deficiency in the etiology of type 2 diabetes.

## ECG CHANGES IN ACUTE CO POISONINGS

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**Objectives.** Poisoning is a major public health problem, both through the high costs of hospitalizations and by temporary or permanent withdrawal of patients from the workplace, and their comorbidities. Carbon monoxide (CO)

poisoning has an important place among asphyxiating poisoning, due to its lethal potential but mainly due to the difficulty of detecting CO, especially in accidental exposures, which are the most common. The purpose of this paper is to determine the impact that CO poisoning may have on the cardiovascular system by means of an electrocardiogram.

**Material and method.** This study was conducted on a group of 22 patients of both sexes admitted to the SUUB ER diagnosed with CO intoxication. Paraclinic investigations included complete blood counts; parameters of acid-base balance; ECG; systolic and diastolic blood pressure; heart rate; oxygen saturation of peripheral blood.

**Results and discussions.** Measuring HR in young people (16-40 years) revealed statistically significant higher values than in the elderly (41-68 years). Analysis of the PQ interval, the QRS axis and the QRS duration revealed statistically insignificant differences between the two age groups. 41% of elderly patients had changes in QRS appearance of left ventricular hypertrophy, rotation and increased duration. 90% of the younger patients did not have ST segment changes and 42% of the elderly had, possibly ischemic, ST changes. 30% of young patients experienced T-wave changes, while 50% of elderly patients experienced T-wave changes of probably ischemic nature. The QT and corrected QT interval values were in normal range, with no statistically significant differences between the two age groups.

**Conclusions.** CO poisoning does not cause statistically significant changes between the young and the elderly of the investigated biochemical parameters, nor of normal cardiac rhythm or atrio-ventricular conduction time. CO poisoning has led to a statistically significant increase in heart rate in young patients, both as a value and as proportions of tachycardic patients. All patients with CO poisoning had higher blood pressure, both systolic and diastolic, in younger patients compared to the elderly, probably due to a higher reactivity of the CV system at sympathetic -adrenergic discharge. CO poisoning caused more pronounced changes in the terminal phase compared to QRS changes. Consequently, oxygen deficiency in CO patients is particularly noticeable on the ventricular repolarization step.

## THE INFLUENCE OF BODY MASS INDEX ON RETINAL VASCULAR CALIBER IN PATIENTS WITH ARTERIAL HYPERTENSION

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**Introduction.** The association between retinal microvascular abnormalities and hypertension is well described. Retinal vessels, as a part of central circulation system, are small blood vessels that can be studied in detail by direct viewing in vivo, noninvasively and accessible.

**Purpose.** To measure retinal vessel caliber using optical coherence tomography (OCT) and to describe the relationship between body mass index and retinal vascular caliber in patients with arterial hypertension.

**Methods.** The study included 43 patients, men and women, with mean age of 59.79 years (range 33-82). After pupil dilation, the width of retinal vessel was measured with OCT; body mass index (BMI) was also measured. Associations between BMI and arteriolar and venular caliber were assessed with linear regression models, in subjects with hypertension.

**Results.** Retinal arteriolar caliber decreased with 1,162  $\mu\text{m}$  for every unit increase in BMI. We found no correlation between retinal venular caliber and BMI.

**Conclusions.** Measuring retinal vascular caliber with OCT may be an alternative method to the fundus imaging. OCT data may be an attractive approach for clinical studies, and retinal vascular width can be correlated with body mass index considered an important cardiovascular risk factor.

**Keywords:** retinal vessel caliber, hypertension, body mass index, optical coherence tomography

## THERAPEUTIC POTENTIAL OF INTRAVENOUS CURCUMIN ADMINISTRATION IN EXPERIMENTAL MIGRAINE

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**Background.** Migraine is characterized by an imbalance between oxidative molecules and antioxidants resulting in oxidative stress. Curcumin is considered to have antioxidative properties and therefore can be used in a number of diseases, as it influences diverse cellular pathways. Our aim was to assess the efficacy of curcumin solution combined with sumatriptan (ST) treatment in nitroglycerin (NTG) induced migraine in rats.

**Methods.** We examined 5 groups, each consisting of 9 rats: control group with no migraine (1 ml intraperitoneal saline solution), group with NTG induced migraine (1 ml intraperitoneal NTG | 1 mg/100 g body weight), group with NTG induced migraine and ST treatment, group with NTG induced migraine, ST and additional intravenous curcumin 1 (1 mg /100 g body weight) and finally a group with NTG, ST and additional intravenous curcumin 2 (2 mg /100 g body weight). The parameters that were assessed were: plasma total oxidative stress (TOS), malondialdehyde (MDA), nitric oxide (NOx), thiol levels and total antioxidative capacity (TAC). The number of flinches and shakes after formalin test was used as an assessment for the nociceptive process.

**Results.** The plasma levels of oxidative stress parameters (TOS, MDA, NOx) were significantly lower in groups that were treated with ST and curcumin compared to ST treatment alone. Moreover, thiol and TAC levels, which quantify the antioxidant capacity of the treatment, were significantly increased in groups who received ST and curcumin treatment in comparison to groups who only received ST treatment. The number of flinches and shakes was also significantly reduced in the groups where curcumin was added to ST treatment compared to ST alone.

**Conclusion.** The antioxidative properties of curcumin not only can be beneficial in migraine treatment when given in addition to sumatriptan treatment, but can also serve as a foundation for future studies involving this antioxidant substance in various pathophysiological processes.

**Keywords:** rats, migraine disorder, oxidative stress, curcumin

## IS P-gp A CAUSE OF THE INTERACTION BETWEEN AMIODARONE AND FUROSEMIDE?

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**Introduction.** The purpose of this pilot study was to evaluate plasma concentrations of amiodarone in patients with AF and to identify possible drug-drug interactions between amiodarone and concomitant medications.

**Material and methods.** A prospective observational study was conducted in 27 consecutive patients treated with amiodarone from May to July 2017 in a Clinical University Hospital. The patients included met our inclusion criteria. HPLC-MS was the device used to determine the plasma concentration of amiodarone.

**Results.** Only 51.8% of the patients had amiodarone's plasmatic concentration in the therapeutic interval (500-2500 ng/ml). The drugs associated to amiodarone in the therapeutic plan belonged to: diuretics, beta blockers, statins, antiplatelets, fluoroquinolones, non-steroidal anti-inflammatory drugs. It was observed a statistically significant difference between the plasmatic concentrations of amiodarone in patients treated with furosemide vs patients concomitantly treated with other drugs. Interactions between other mentioned drugs and amiodarone weren't registered.

**Conclusion.** We can report an underuse of amiodarone for more than 50% of the patients. Also, a significant interaction between furosemide and amiodarone was found, most likely through the interaction with MDR. Furosemide may

influence the pharmacokinetics of P-gp-interfering drugs. However, the relevance of these findings needs to be confirmed and further research is needed to characterize the interaction between amiodarone and furosemide.

**Keywords:** furosemide, amiodarone, plasma concentration, drug interaction, P-glycoprotein

## **THE IMPORTANCE OF Q-T INTERVAL CHANGES IN PATIENTS WITH ATRIAL FIBRILLATION**

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Atrial fibrillation is one of the major heart rhythm disorders responsible for a high rate of cardiovascular and cerebrovascular morbidity and mortality, being a major health problem. Atrial fibrillation may coexist with many other comorbidities, such as hypertension, hyperlipidaemia, ischemic heart disease, heart failure, anemia, diabetes mellitus, arthritis, chronic obstructive pulmonary disease. Finally, it is well known as a risk factor for myocardial infarction, heart failure and stroke, which in some cases may be the first manifestation of arrhythmia. The study was attended by patients who presented to the Emergency Unit of the Bucharest University Emergency Hospital between January 2018 and July 2018 for atrial fibrillation. The study included 74 patients. In many patients, heart failure and atrial fibrillation coincide. These are related to similar risk factors and share a common pathophysiology. They can cause and exacerbate each other through mechanisms such as structural cardiac remodeling, activation of neurohormonal mechanisms and left ventricular function deficiencies. The duration and amplitude of the T wave were within normal limits. Regarding the morphology of the ST segment, we found the presence of ST segment depressions. ST-T abnormalities reflect the presence of hypertrophy, fibrosis or ventricular conduction abnormalities and ischemia, and these conditions may lead to diastolic dysfunction of the ventricle and atrial remodeling. The QT interval may be a predictor of atrial fibrillation. Individuals with prolonged atrial fibrillation may also represent a distinct subtype of patients with atrial fibrillation with abnormal repolarization, and future investigations may determine whether identifying this subtype is useful in selecting particular therapeutic strategies. Q-T interval, atrial fibrillation.

## **CORTICAL OSCILLATIONS IN AN ANIMAL MODEL OF DYSTONIA CAUSED BY CEREBELLAR DYSFUNCTION**

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Synchronies of neuronal activity in the sensorimotor cortices play a crucial role in motor skills and learning. They can be modulated through upstream activity in the cerebello-cortical network. Yet, the dialog between the cerebral cortex and the cerebellum remains poorly understood. Our aim is to study the contribution of the cerebellum to brain oscillatory activities, in particular in the case of dystonia, a very disabling motor disease associated with altered sensorimotor coupling. We used a kainic-induced dystonia model to evaluate the cortical oscillatory activity and connectivity during dystonic episodes. We performed microinjections of low doses of kainic acid into the cerebellar vermis in mice and examined

activities in somatosensory, motor and parietal cortices. We showed that repeated applications of kainic acid into the cerebellar vermis, for five consecutive days, generate constant and reproducible dystonic motor behavior. No epileptiform activity was recorded on electrocorticogram during the dystonic postures or movements. We investigated the EcoG (electrocorticogram) power spectral density and coherences between motor cortex, somatosensory and parietal cortices before and during dystonic attacks. During baseline condition, we found a phenomenon of permanent adaptation with a change of baseline locomotor activity coupled with an EcoG gamma band increase in the motor and somatosensory cortices. Additionally, after kainate administration, we observed an increase in muscular activity, but less signs of dystonia together with modulations of the EcoG power spectra with an increase in gamma band in motor, parietal and somatosensory cortices. Moreover, we found a reduced coherence for all frequency bands between the motor cortex and somatosensory or parietal cortices during dystonia. In conclusion, examination of cortical oscillatory activities in this animal model of chronic dystonia caused by cerebellar dysfunction reveals a disruption of the coordination of neuronal activity across the cortical sensorimotor/parietal network, which may underlie deficits in motor skills.

**Acknowledgements.** This work was supported by the PN-II-RU-TE-2014-4 project/UEFISCDI to Daniela Popa.

## THE PATHOPHYSIOLOGY OF SMOOTH UTERO-TUBULAR MUSCLES

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The uterus is a fibromuscular organ belonging to the female reproductive apparatus. It is responsible for maintaining the product of conception, beginning with the laying of the egg and until the birth of the fetus. It is also due to menstrual function and at the same time has endocrine, sexual roles and in keeping pelvic structural statics. The structure of the endocrine wall is made up of the uterine endometrium or mucosa, myometrium and peritoneum. Myocardial contractility is increased by substances that increase intracellular calcium levels (ocitocin, angiotensin II, prostaglandins, estrogens, adrenergic agonists), whereas relaxation of the uterine muscle occurs when the calcium concentration decreases in the presence of beta-adrenergic agonists, progesterone and relaxin. At the uterus, oxytocin contracts the myometrium, both in vitro and in vivo, the effect being greater in the pregnant uterus due to the fundamental morpho-functional transformations of the muscle fiber that occur during pregnancy. Experimentally, on isolated myometric fragments, only phase shrinkage is obtained, therefore unaccompanied by the increase in basal tone. Its growth can only be recorded on isolated uterus. The explanation of the phenomenon could be the existence of mechanisms of myometrial contraction modulation, which act strictly in the uterine integrity conditions, in which extrauterine mechanisms can also be added in vivo. Of all angiotensins, the most important is angiotensin II, which has a pronounced vasopressor effect. Stimulates aldosterone secretion, interfering with blood pressure regulation. Angiotensins are synthesized starting from a precursor called angiotensinogen. Angiotensinogen formation is stimulated by glucocorticosteroids, thyroid hormones, angiotensin II, and contraceptive medication.

**Keywords:** uterine muscle, contraction, tocolytic effect, oxytocics, angiotensins



## RENAL DENERVATION IMPACT UPON THE BAROREFLEX CONTROL OF THE HEART RATE IN THE MODEL OF REDUCED RENAL MASS, SALT SENSITIVE VOLUME-OVERLOAD HYPERTENSION

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**Introduction.** Increased systemic arterial blood pressure (ABP) is a major issue in terms of clinical implications and mechanisms involved. Beyond lowering ABP in hypertensive patients, renal denervation (RDNx) has also been shown to improve heart control by autonomic nervous system, especially in sympathetically mediated cardiovascular disorders. But little is known about renal nerve ablation efficiency in dysfunctions that are not sympathetically mediated. We studied RDNx influence on heart control by the autonomic nervous system in a classical hypertension model; salt sensitive, volume-overload hypertension developed after surgical reduction of renal mass (RRM) by 75-80% and salt loading.

**Methods.** This study, performed at Grigore T. Popa University of Medicine and Pharmacy Iași, is an elaborate analysis of heart rate data from a study we have recently published; telemetry data in freely moving rats, according to the protocols detailed there (Tudorancea et al., Front Physiol 2018; 9:455, p. 1-11). Dynamic time-dependent cardiac autonomic system analyses, such as the baroreflex sensitivity (BRS), the power of the fluctuations of the heart rate in high frequency range (0.75-3Hz, HF power), and both short and long term beat-to-beat variability, were calculated from continuously recorded cardiac cycles before and after surgical RRM by 80%, including here RDNx and central sympathoinhibition with clonidine.

**Results.** The BRS decreased significantly throughout the entire 2 weeks of the development of salt-sensitive, volume overload hypertension induced after surgical RRM and high salt diet. The HF power decreased during the first 7 days after RDNx, paralleling the alterations of both long and short term heart rate variability. Global sympathoinhibition after clonidine administration significantly improved cardiac autonomic nervous system, as reflected by the substantial enhancement of the BRS, the HF power and both short and long term heart rate variability.

**Conclusions.** The present results indicate that in salt-sensitive, volume overload hypertension, the cardiac autonomic nervous system is impaired and these alterations are not improved over the long term by RDNx. On the contrary, central sympatho-inhibition after clonidine administration following RDNx significantly improved BRS, the HF power and both short and long term beat-to-beat variability.

**Keywords:** hypertension, renal denervation, cardiac autonomic nervous system, baroreflex, heart rate variability

## CYTOKINES IN BRONCHO-OBSTRUCTIVE AIRWAYS DISEASES

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**Introduction.** Cytokines are key mediators in airways inflammatory diseases. The role of IL-31, a cytokine which belongs to IL-6 family, in atopic skin diseases has already been demonstrated, but there are conflicting results regarding its role in airways inflammatory disorders. IL-10 is an important immunoregulatory cytokine determining mainly the suppression of immune response. The present study aims to evaluate IL-31 and IL-10 plasmatic levels in patients with asthma and COPD and their correlation with clinical and lung function parameters.

**Material and method.** 50 consecutive patients (pts) with broncho-obstructive diseases (32 pts with asthma and 18 pts with COPD) were included in the study. The evaluation included: number of exacerbation in the last year, disease's severity, spirometry. Plasmatic levels of IL-31 and IL-10 were determined in all patients.

**Results.** IL-31 was significantly higher in patients with asthma [median 1269 (338.36-2785.99)] pg/ml versus COPD [median 481.79 (178.74-1402.72)] pg/ml ( $p=0.015$ ). IL-31 was positively correlated with the number of exacerbation in the last year ( $R=0.456$ ,  $p=0.033$ ) and asthma severity ( $R=0.541$ ,  $p=0.009$ ) and negatively correlated with FEV1 ( $R=-0.413$ ,  $p=0.05$ ) and IL-10 plasmatic level ( $R=-0.459$ ,  $p=0.032$ ) in patients with asthma. In patients with COPD the number of

exacerbation was negatively correlated with vital capacity ( $R=-0.523$ ,  $p=0.026$ ), but there were no correlations between IL-31 level and clinical, functional parameters or with plasmatic level of IL-10.

**Conclusions.** IL-31 has an increased plasmatic level in patients with asthma. IL-31 may play a role in the severity and regression of lung function in asthmatic patients, but not in COPD patients.

## EVALUATION OF SERUM TRANSAMINASES IN HYPOXIA

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**Introduction.** The release of transaminases (ALT/AST) after induced hypoxia shows a non-specific impairment of membranous integrity and permeability. The serum level of transaminases (ALT/AST) in induced hypoxia is an important indicator of liver status. In the liver was found the hepatocyte necrosis after hypoxia with later necrosis of the organ. It is difficult to estimate the severity of the hypoxic injury only after enzymatic tests.

**Material and methods.** The study included two groups: Control group (five immature Wistar rats) and Hypoxia 3 hours group (five immature Wistar rats). We determined the serum transaminases by spectrophotometric methods. The results are expressed in U/l.

**Results.** The results indicate a significant increase of ALT Hypoxia 3 hours group ( $26.4 \pm 1.81$ ) compared with ALT Control group ( $20.20 \pm 1.39$ ) and AST Hypoxia 3 hours group ( $48.6 \pm 3.6$ ) compared with AST Control group ( $24 \pm 1.52$ ).

**Conclusion.** Serum transaminases (ALT/AST) in hypoxia show significant increases in their activity over the Control group, especially AST. The increased AST activity indicates an advanced injury probably involving mitochondrial membranes. The study confirms liver damage after induction of hypoxia. Measurement of ALT and AST as parameters of hepatocellular destruction also indicates changes in cell permeability. Expansion of hypoxic injury can be correlated with increased serum transaminases.

## MOTOR BEHAVIOR IN MICE DURING DYSTONIA INDUCED BY CEREBELLAR KAINIC ACID APPLICATION

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DENISE CM ZAHIU, VLAD PETRU MOROZAN, ADRIAN PANA, ALEXANDRU ȚÂRLEA,  
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In our experimental model of dystonia we obtained abnormal motor behavior in mice by administering kainic acid on the cerebellar vermis. For the examination, we used wireless electrocorticography and video tracking in freely moving mice and then correlated the electric activity of the brain with the animal behavior. The mice were recorded for six consecutive days, the administration being started in the second day. Comparing with the total time of recording, our results showed an active wake decrease in all days of kainic acid administration. In our assessment we also gave a dystonia score for each 10 minutes of post-administration period and found that the motor alterations reached their maximum after 50 minutes, soon being followed by a constant downtrend for all period of examination. No epileptiform activity was identified during the experiment. To conclude, we found an important drop in the level of activity displayed by the mice during dystonia and the intensity of the symptoms increased gradually in the first hour after the kainic acid administration.

In this study we demonstrated that this model of dystonia can be further used to better understand the pathophysiology of dystonia and to find superior new therapies.

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## **EFFECT OF IMPLANTED NANOPARTICLES OF POLYLACTIC ACID (NPLLA) ENRICHED BONE CEMENT ON A FEMORAL EXPERIMENTAL DEFECT IN RATS – PRELIMINARY RESULTS**

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**Introduction.** Bone cement (BC) is a biomaterial used in orthopedics disorders and bone reconstruction, being biocompatible and providing increased mechanical resistance at the site of the lesion. In vivo bone defects certify the biocompatibility, mechanical resistance and safety in using biomaterials in regenerative medicine. The aim of the research was to evaluate the biocompatibility of newly synthesized bone cement formed by a mixture of nPLLA, calcium phosphate and hydroxyapatite.

**Material and methods.** Research was performed on 15 adult male Wistar rats that were divided in three groups (n=5): group 1- reference group; group 2- unfilled cavities; group 3- BC filled cavities. Groups 2 and 3 were subjected to a non critical femoral defect. Computed tomography was applied for investigation of bone architecture at 1, 14 and 30 days after surgical intervention. Blood samples were collected and complete blood counts (CBC) as well as biochemical analysis (alkaline phosphatase, calcium and phosphorus) were determined.

**Results.** The imagistic exam revealed the lack of bone substance, therefore the defect in group 2, as well as the increase in bone density and the absence of periosteal inflammatory reactions in group 3 after 14 and 30 days. The CBC did not reveal changes characteristic of an associated inflammatory process, and biochemical analysis have showed an increase in alkaline phosphatase and calcium concentration in the bone cement group, which can be attributed to hydroxyapatite bioactivity and / or to the bone regeneration.

**Conclusions.** Our most significant finding based on the CT analysis attested the lack of the bone resorption and inflammation, showing the materials stability and integration level. The synthesis bone cement provided a good biocompatibility in Wistar rats' bone defect, creating at the same time an optimal basis for the bone regeneration.

**Keywords:** bone cement, nPLLA, bone defect, Wistar rats, biocompatibility, biochemistry

## **POSSIBLE BENEFITS OF SELENIUM SUPPLEMENTATION IN AUTOIMMUNE THYROIDITIS**

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**Introduction.** This study was done in the context of permanent intense developments in the field of oxidative stress and of antioxidants for medical use, including the roles played by selenium (Se) via the multitude of selenoproteins. Various research groups from the Grigore T. Popa University of Medicine and Pharmacy Iași (1) and from the Alexandru Ioan Cuza University Iași (2) frequently collaborate in oxidative stress research. For example in the present study (Preda et al., Rev

Chim (Bucharest) 2017; 68(7):1617-21), which was designed simply to evaluate, in euthyroid subjects with autoimmune thyroiditis, the effect of Se supplementation upon the following: thyroid stimulating hormone (TSH), antiperoxidase antibodies (TPOAb), and glutathione peroxidase 1 (GPx1).

**Methods.** 100 euthyroid women with autoimmune thyroiditis, from the same region, were randomized to receive daily 100 µg selenomethionine (n=50) or placebo (n=50) for 3 months. Serum concentrations of Se, TPOAb and TSH were measured in each patient initially and after 3 months. GPx1 activity was also measured in the interventional group before and after Se supplementation.

**Results.** After 3 months TSH presented a significant increase in patients treated with Se (2.49 vs. 2.09 UI/mL;  $p=0.001$ ) and in patients not treated with Se (2.38 vs. 1.91 UI/mL;  $p=0.008$ ). TPOAb decreased by 15.2% in patients treated with Se ( $p=0.002$ ) and did not change in patients not treated with Se. At the end of the study Se and TPOAb were in direct insignificant correlation ( $r=+0.267$ ,  $p=0.105$ ). GPx directly and significantly correlated with Se both initially and after 3 months, but GPx1 did not show significant changes after Se supplementation. After 3 months of Se supplementation results showed a mild decrease of TPOAb and a weak negative correlation of these antibodies with Se levels.

**Conclusions.** The impact upon TPOAb suggests that Se treatment may improve the course of thyroid autoimmunity, so we discuss our results in terms of optimal dose and duration for Se treatment of autoimmune thyroiditis.

**Keywords:** selenium, glutathione peroxidase, autoimmune thyroiditis, oxidative stress

## TOPICAL APPLICATION REINFORCED BY LOW-LEVEL LASER THERAPY ON AN ANIMAL MODEL OF HAIR REGROWTH - NEW ZEALAND RABBITS

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Low-Level Laser Therapy (LLLT) induces hair regrowth by altering cell metabolism, increasing microcirculation, regulating apoptosis and generating cell proliferation. Topical minoxidil determines hair regrowth by stimulating the mesenchymal cells from the follicular dermal papilla of the hair follicle and inducing vasodilation. The aim of the study was to evaluate on an animal model (New Zealand Rabbits) the hair regrowth effect of LLLT as monotherapy or concomitant therapy with topical application of Minoxidil 2% solution, Minoxidil 5% foam, Aminexil and Spectral DNC solution (containing Minoxidil 5%, aminexil, retinol, B2, plant extracts, etc). Skin areas of 4 squared cm each were denuded on the dorsal part of 10 New Zealand rabbits, one for control, the rest for daily topical treatment (with 0.5 ml of Minoxidil 2%, Minoxidil 5%, Aminexil or Spectral DNC), daily LLLT treatment (HairMaxProfessional 12, for 1 minute 30 seconds) or combined treatment (each topical compound with LLLT exposure). The hair regrowth effect was evaluated after 3 months by macroscopical images (photographs), trichoscopy (with a dermatoscope) and histopathological assessment. At the beginning and at the end of the experiment, the systolic blood pressure was measured and the tested areas were examined by a Doppler ultrasound study. Our results showed no modification of the systolic blood pressure throughout the experiment. Vasodilation was significantly increased in the areas treated with Spectral. The best hair regrowth effect was induced by Spectral DNC treatment and LLLT. This study proves that combined therapy is more efficient than the single use of LLLT or topical treatment.

**Keywords:** hair regrowth, Minoxidil, Aminexil, Spectral, LLLT, trichoscopy, New Zealand rabbits, systolic blood pressure, Doppler ultrasound study

## SUCCESS OF CARDIAC RESYNCHRONIZATION IN A PATIENT WITH ISCHEMIC CARDIOMYOPATHY. A CASE REPORT

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**Aim.** The global mechanical performance of the heart is affected by the atrio-ventricular, interventricular or intraventricular conduction disorders, which lead to the de-synchronization of the electrical activity in patients with heart failure, the effective cardiac resynchronization therapy improves the clinical and hemodynamic status of these patients.

**Material and method.** We present the case of a responder patient to the cardiac resynchronization therapy, which was showed by the improvement in the quality of life, by the diminishing symptoms and by the increased effort capacity.

**Results.** Our presentation includes a 66-year-old patient, former smoker, hypertensive with maximum pressure values of 250 mmHg since 1999, with diabetes since 2004 in treatment with oral antidiabetic drugs, also known with inferior myocardial infarction in 1996, anterior myocardial infarction in 2013, with ambulatory treatment correctly taken, who came to the cardiology service for dyspnea of rest with orthopnea, accompanied by fatigue, headache and dizziness. The coronarography showed important trivascular lesions, graftable vessels. Thus, “off pump” surgical myocardial revascularization (with high risk) and subsequently implanting a defibrillator cardioverter with cardiac resynchronization therapy were taken into account.

**Conclusion.** The effectiveness of the cardiac resynchronization therapy for this patient was shown by lowering NYHA class, by improving the effort capacity and, also, by improving the left ventricle’s hemodynamics.

**Keywords:** heart failure, haemodynamic status, conduction disorders, cardiac resynchronization therapy

## INTERVENTIONAL THERAPY IN MITRAL REGURGITATION AS AN ALTERNATIVE TO SURGICAL TREATMENT? A CASE REPORT

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**Aim.** Mitral regurgitation is a common valvulopathy, being on the second place in Europe after aortic stenosis. The transcatheter repair of the mitral valve provides a therapeutic alternative to patients with mitral regurgitation and increased surgical risk.

**Material and method.** We present the case of a responder patient to MitraClip therapy based on Alfieri surgical technique for repairing the mitral valve by suturing the free edges of the two leaflets, this system is transcatheter implanted.

**Results.** Our presentation includes a 56-year-old patient, a former smoker, suffering from dyslipidemia, hypertensive, with inferior-posterolateral lateral myocardial infarction, with BMS on MG I with moderately severe VS systolic dysfunction (LVEF = 25-30%), after the coronary angiography reevaluation was performed the implantation of a pharmacologically active stent in the IVA II was decided. The patient had repeated cardiac decompensations, a history of moderately severe mitral regurgitation, so, it has been decided to interventionaly reduce the mitral regurgitation by MitraClip implantation and subsequently the implantation of a heart defibrillator was decided due to the presence of episodes of NSVT. After that, the patient had a favorable evolution, improving the severity of the mitral regurgitation, increasing the functional capacity and reducing the left ventricular remodeling.

**Conclusion.** Although valvular surgery remains the standard care in patients with symptomatic severe mitral regurgitation, this presentation demonstrates that the use of interventional procedure is a viable solution for patients who are not candidates for surgery.

**Keywords:** heart failure, mitral regurgitation, MitraClip, interventional procedure



## EARLY MARKERS FOR CARDIOVASCULAR DAMAGE IN PATIENTS WITH PULMONARY SILICOSIS BEFORE THE OCCURRENCE OF CHRONIC PULMONARY HEART

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**Introduction.** Silicosis is a collagen pneumoconiosis caused by long-term inhalation of inorganic powders that contain high concentrations of silicon dioxide. The purpose of this study was to identify correlations in electrocardiographic and echocardiographic changes in patients with silicosis prior to the occurrence of chronic pulmonary heart disease.

**Materials and method.** We conducted an analytical prospective, descriptive observational study, in which we included a group of 89 patients consecutively admitted to the Occupational Medicine Clinic between 01.12.2017 - 01.05.2018. There was an electrocardiographic evaluation for each patient as well as a right ventricle echocardiographic evaluation (volume, weight, function). A control group, including 45 patients with benign minor diseases that requires a cardiologist consultation, was also used.

**Results.** From the electrocardiographic point of view, slight changes were observed regarding the waves of electrical activity of the right ventricle. Taking into account the degree of ventilator dysfunction, changes in right heart echocardiographic parameters were identified. Thus, values at the upper limit of normal were recorded in most patients with moderate and severe ventilator dysfunction in what the most important right ventricular assessment parameters, including the tricuspid annular plane systolic excursion (TAPSE) or the RV index of myocardial performance (RIMP), were concerned.

**Conclusions.** Values of the right heart echocardiographic parameters at the upper limit of normal, correlated with the degree of ventilator dysfunction, are early markers for cardiovascular damage in patients with pulmonary silicosis prior to the occurrence of chronic pulmonary cord.

**Keywords:** pulmonary silicosis, echocardiographic parameters, ventilator dysfunction

## THE EFFECT OF THREE DIFFERENT DOSES OF RHODIOLA ROSEA, ON INTENSE PHYSICAL STRESS

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**Background and aim.** Rhodiola rosea (RR) is recognized for its antistress effects. The objective of the study was to highlight the effect of three different doses of RR on anxiety (A) and malondialdehyde (MDA) in intense and short term physical-stress.

**Methods.** Chosen subjects (n=24 healthy sedentary males) were selected according to the requirements of the study and divided into four groups: control (C); who received one dose (RR1), two doses (RR2) and respectively three doses (RR3) of RR per day. Stress was represented by an intense and short term physical effort: running 12 min on a treadmill. Analyzed indicators were A and MDA: immediately pre-effort (T1), immediately (T2) and 4 hours (T3) post-effort. Statistical evaluation was made on the basis of Student test.



**Results.** Parameters were significantly reduced: A at T1 and T2, but more at T2; and MDA at T2 and T3, but more at T2. For all doses, the effect was more important on A than on MDA. The most important and significant effect was at RR3 for both A and MDA. For both A and MDA, the significant difference between RR groups was between RR1 and RR2, and RR1 and RR3. The difference between RR2 and RR3 was not significant.

**Conclusions.** 1) The effect on A was more important pre-stress and more important than on MDA. 2) RR1, RR2 and RR3 influence of was more intense on A than on MDA. 3) The most useful dose, both as efficacy and economic aspect, would be RR2. 4) The RR used may be an effective, safe and accessible modulation path for stress caused by intense and short term physical effort on sedentary persons, but more in-depth studies could bring more detail.

**Keywords:** Rhodiola rosea, stress, intense and short term physical effort, anxiety, malondialdehyde

## EFFECT OF SCHISANDRA CHINENSIS ON HEART RATE, GLYCEMIA AND MALONDIALDEHYDE, IN EXERCISE STRESS

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**Background.** Schisandra chinensis (SC) is known for its many beneficial adaptogenic effects.

**Aims.** The objective of the study was to evaluate the effect of SC on heart rate (HR), glycemia (G) and malondialdehyde (MDA), in exercise-stress.

**Methods.** 12 healthy volunteer men were randomly assigned to two groups: control (C), who did not receive therapy; and who received SC product for one week before exercise (SCP). For both groups the stress was an intense and short-term exercise on Monark 839E cycle ergometer; analyzed parameters were heart rate (HR), glycemia (G) and malondialdehyde (MDA). Parameters were analyzed: 10 min before (T1), 30 min (T2) and 4 h (T3) after the exercise. Statistical evaluation was done using Student test.

**Results.** HR changes were anticipatory, pre -stress (T1). For both C and SCP: HR was significantly increased to T1 compared to T2 and T3, the most at C; G and MDA were significantly increased to T2 compared to T1 and T3, the most at C. The most significant differences between C and SCP were: at T1 for HR, at T2 for HR, G and MDA, and at T3 for G and MDA. SC was effective on all parameters, but the most intense effect was on HR, and the lowest on MDA.

**Conclusions.** 1) The dynamics of the parameters was similar for C and SCP. 2) The effect of SC on HR was more intense pre stress; and on G and MDA, it was more intense post stress. 3) At administered doses, SC was effective on all analyzed parameters, but especially on HR. 4) SC can provide an antistress protection in intense and short-term exercise in sedentary subjects, but studies of other doses and parameters would be recommended.

**Keywords:** Schisandra chinensis, rate, glycemia, malondialdehyde, stress, intense and short-term exercise

## INFLUENCE OF ASTRAGALUS VERSUS PLACEBO, ON ANXIETY AND GLYCEMIA IN PSYCHOLOGICAL-MENTAL STRESS

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**Background.** Astragalus is useful for stress situations.

**Aims.** The objective was to highlight the Astragalus (AS) influence versus placebo on anxiety (A) and glycemia (G) in psychological-mental stress.

**Methods.** Subjects (n = 30 healthy males ) were organized into three groups: control (C=10), no treatment; who received placebo (P=10); who received AS product (ASP=10). Placebo and AS were given for 21 days, before stress. Psychological-mental stress for all groups: a verbal arithmetic mental effort. A and G measurements: 15 min before stress (T1); 30 min (T2), 120 min (T3) after stress. Assessments: anxiety with Beck inventory; glycemia with glucometer. Statistical evaluation was based on Student test.

**Results.** T2 compared to T1: A decreased significantly at ASP versus C and P; G increased significantly, more at C and P versus ASP. T3 compared to T1: A decreased, but not significantly at C and P, and significantly at ASP. T3 compared to T2: G decreased, but not significantly at C and P, and significantly at ASP. The AS influence was more intense on A, than on G.

**Conclusions.** 1) Astragalus reduced the anticipatory effect of stress, on A. 2) Astragalus reduced the hyperglycemic effect of stress, immediately and 120 minutes post-stress. 3) Astragalus acted more intense on A than on G. 4) Astragalus product may be useful to modulate A and G on psychological-mental stress, but evaluations in other mental stress forms and parameters, would be useful.

**Keywords:** Astragalus, anxiety, glycemia, psychological-mental stress

## EXPLORATION SCINTIGRAPHY IN PARATHYROID PATHOLOGY

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The parathyroid glands can be visualized with the aid of multiple imaging methods: scintigraphy, echography, CT and MRI; the most used are echography and scintigraphy, the rest being utilized as additional imagistic methods. Hyperparathyroidism (HPT) is characterized by an increased synthesis and release of parathormone (PTH), which is responsible for the calcium and phosphorus homeostasis in the organism.

**Material and method.** In this paper we exemplify a few illustrative cases of primary, secondary and tertiary hyperparathyroidism; the explorations were realized in the Nuclear Medicine Department of Hiperdia Brasov. Parathyroid scintigraphy is an imagistic method of visualizing pathological parathyroid glands, utilizing radioactive isotopes (99mTc-Sestamibi). 99mTc-Sestamibi is faster absorbed by the hyperfunctional parathyroid gland compared to the normal one, phenomenon correlated with the count and activity of mitochondria in oxyphile cells which have a great avidity for sestamibi. We used 99mTc-Perchnetate for the thyroid gland and 99mTc-Sestamibi for the parathyroid glands, the study of the latter being followed by that of the thyroid gland. The image acquisition was realized with a (SIEMENS) Symbia E double detector gamma camera, recording planar static images both early and late, which was then supplemented with SPECT acquisitions.

**Discussion.** Following our examinations we found out that the most frequent cases were those of primary hyperparathyroidism (by adenomas, including ectopic sites), secondary and tertiary hyperparathyroidism being less

frequent. The imagistic methods allow a good visualization and localization of pathologically modified parathyroid glands; normal parathyroid glands are non-observable. Scintigraphy and echography are the dominant imaging methods used in investigating primary HPT. Scintigraphic study of parathyroid glands allows a correct evaluation of parathyroid pathology. Conclusions: Imaging methods allow the visualization and localization of pathologically modified and/or ectopically parathyroid glands. US and parathyroid scintigraphy with methoxyisobutylisonitrile (sestamibi) [8] are the dominant imaging techniques used in the setting of primary hyperparathyroidism.

## WHEN NATURE DOES NOT HELP PHYSIOLOGY – THE USE OF RECOMBINANT ALLERGENS FOR THE STUDY OF THE ALLERGIC IMMUNE RESPONSE

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**Introduction.** Amb a 1 is the major allergen from ragweed (*Ambrosia artemisiifolia*) pollen, which sensitizes an important fraction of people, creating a large health and economic burden in Romania. 95% of ragweed allergic patients show IgE binding to Amb a 1 in RIA, and have positive skin prick tests to Amb a 1. There are five known isoforms of Amb a 1, with different sequence homologies between 63 and 87% and with distinct patterns of IgE binding and immunogenicity. This study aims to produce recombinant Amb a 1 isoforms and to investigate the allergic immune response induced by them.

**Materials and methods.** Amb a 1 isoforms 01 and 02 were expressed as recombinant proteins using Sf9 insect cells. The gene sequence was introduced into a vector, after inclusion of a His-tag, and then the vector was introduced DH10 competent *E. coli* cells for amplification. The colonies were screened for product insertion by antibiotic sensitivity and PCR, and the bacmid DNA was amplified, isolated and purified using a Midiprep kit. The DNA was then used for the transfection of the Sf9 insect cells, after which the proteins were purified and concentrated. Protein production was measured semi-quantitatively by Western blot. The antigenicity of the proteins was then analyzed by ELISA with sera from patients previously sensitized to ragweed pollen.

**Results.** Amb a 1 isoforms 01 and 02 were obtained as recombinant proteins. The protocol that yielded the most amounts of protein used supernatant from the Sf9 cells, and no dialysis. The obtained proteins are properly folded, as they react with sera from patients allergic to ragweed.

**Conclusions.** Recombinant Amb a 1 isoforms are adequate tools for understanding the immunological and allergenic properties of individual Amb a 1 isoforms found in natural ragweed pollen, which is of great importance for the development of efficient products for diagnosis and therapy of ragweed pollen allergy.

## EXPERIMENTAL ORTHODONTIC BRACKET BONDING MATERIAL TESTING

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**Introduction.** Orthodontic bonding materials are easy to use materials, usually they are thermo-, auto- or photo-polymerized and despite all their advantages, due to their polymethylmethacrylate (PMMA) component they can cause irritation, inflammation and allergic reactions in the oral mucosa. AIM: The purpose of the study was to evaluate and compare the cytotoxicity of 1 new experimental graphene based resin modified composite with 3 commercial orthodontic

bonding materials, glass-ionomer.

**Material and method.** Samples of each bonding and experimental material were obtained after polymerization of 40 seconds at each end of the mold. No grinding or polishing was performed on the resin samples. The composite samples were incubated with medium, the obtained extract was filtered sterile through a 20nm syringe filter, then used immediately for the experiments, Viability assays, cell lysis and oxidative stress assays were performed.

**Results.** Cell viability was affected for all bonding agents but the experimental material showed similar results to commercial ones. Different concentrations of extracts presented higher variations of cell viability for two of the commercial bonding agents than for the experimental. SOD and MDA assays were significantly increased for the experimental material.

**Conclusions.** All tested materials presented cytotoxic effects as well as oxidative stress. However, there can be multiple interpretations as to why the results show convergence in respect with cell viability and divergence when assessing oxidative stress and further investigations are to be required.

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**Keywords:** orthodontics, bonding agents, cell viability

## BIOCHEMICAL MODIFICATIONS DURING PREGNANCY IN PATIENTS WITH MISCARRIAGES

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**Objectives.** Free-beta HCG and PAPP-A may be modified by a series of well-defined factors. WE speculated that free-beta HCG and PAPP-A may be modified by a previous miscarriage.

**Methods.** We enrolled 626 women requesting a first trimester combined risk. We included only singleton spontaneous pregnancies of healthy women. Gestational diseases and fetal major disorders, including abnormal karyotype, were excluded at follow-up. During the screening, information about previous miscarriages were included in the dataset.

**Results.** We individualized two groups of women: 420 who did not have any miscarriage and 206 who had at least one miscarriage. Women who had experienced a previous miscarriage had a higher statistically significant value of PAPP-A MoM than women without miscarriage.

**Conclusions.** Previous miscarriage may influence PAPP-A MoM and it should be reported. However, further study is necessary to understand the causative association described in this abstract. We need larger series to produce likelihood ratios to apply in a screening setting in case of a previous miscarriage.

## FETAL CYSTIC HYGROMAS IN THE FIRST TRIMESTER

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**Objectives.** To describe the association of abnormal outcome with fetal cystic hygroma detected when Crown – rump length 45-84 mm.

**Methods.** We performed study of six fetuses with first trimester hygroma in 2017 - 2018. The definition of cystic hygroma is hypoechoic space at the back of the fetal neck, extending along the length of the fetal back and in which septations are visible.

**Results.** A total of six fetuses were included. The median nuchal translucency was 6.2 mm with a range of 3.8 mm and 10.3 mm. Karyotype results were available for the all fetus with this abnormal: Trisomy 18, Trisomy 21 and S Turner and major structural anomaly above all cardiac anomalies.

**Conclusion.** Cystic hygroma are associated with a high rate of adverse outcomes. A detailed anatomic assessment and fetal echocardiography are important components after the diagnosis of cystic hygroma.

## MANAGEMENT OF TUBAL ECTOPIC PREGNANCY

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**Objectives.** To investigate the success rate of expectant management of ectopic pregnancy by avoiding administration of methotrexate as first line management.

**Methods.** Retrospective audit of all patients diagnosed with an ectopic pregnancy from 2016 – 2017 were identified. Scan diagnosis, biochemical results and management and treatment details were recorded.

**Results.** 41 women were diagnosed with a tubal ectopic pregnancy. Of these, 19 (46.3%) women had expectant management, 3 (7%) methotrexate and 19 (46.3%) surgical management as first line management. 2 (66%) out of the 3 treated first line with methotrexate required surgery. Overall, successful treatment modalities of tubal ectopic pregnancies were 58% surgical, 36% expectant and 6% methotrexate.

**Conclusions.** Our national published guidelines advise methotrexate or surgical management of ectopic pregnancy. However, successful expectant management in ectopic pregnancies avoided the need for this chemotherapeutic agent. First line expectant management is comparable to first line methotrexate management for avoiding surgical intervention for the treatment of ectopic pregnancy in suitable cases.

## TREATMENT OF LIGATURE-INDUCED PERIODONTITIS IN RATS WITH NATURAL REVEALERS AND PHOTODYNAMIC THERAPY

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The effects of a photodynamic therapy are based on three components: light, revelator, and the presence of oxygen. Development of new revelatory can be a positive factor for this treatment

**Objective.** This study aims at biological testing of essential oils-based photosensitizers and curcumin extract on rat-induced periodontal disease treated with photodynamic therapy (PDT).

**Material and methods.** Periodontal disease was ligature-induced at the first mandibular molar of 20 rats. After 7 days, the ligature was removed and animals were randomly divided into 5 groups: M (n=5) was left without surgical intervention and represented the control group, P (n=5) was operated and left without treatment, GC (n=5) was treated with a Curcumin revelator and PDT, GO (n=5) was treated with Oregano revelator and PDT and L (n=5) treated only with PDT. The animals were humanly euthanatized after 4 weeks of study. The radiographic, hematologic and histological values were statistically analyzed.

**Results.** The radiographic, hematologic and histopathological analysis in this study demonstrated a greater magnitude of inflammatory response and severe destruction of periodontal ligaments when rats received no treatment after ligature removal and it was evident that ligature was effective in the development of experimental periodontal disease.

**Conclusions.** PDT was an effective adjuvant treatment of induced periodontitis in groups treated with natural photosensitizers.

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## BIOCOMPATIBILITY EVALUATION OF THE EXPERIMENTAL DENTAL COMPOSITES

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**Objective.** The purpose of the present study is to evaluate the biocompatibility of the experimental dental composites on animal tests.

**Material and methods.** In the present study, the biological compatibility of experimental composite material composed of a visible light-curing monomer mixture (Bis-GMA+TEGDMA) as a matrix and hydroxyapatite, bioglasses, colloidal silica as a reinforcing filler. The biological properties of the experimental dental composites were evaluated according to ISO 10993 standards. The biocompatibility was studied using the test of tolerance by the subcutaneous and intramuscular implantation on the rats (Wistar race). The specimens were light-cured with LED lamp. Irritation tests were performed and monitored: *primary irritation effects* - specimens were fixed under bandages on the skin for 48 h; *sensitizer potential* - specimens were applied for short periods every 24 h during 1 week and *systemic acute toxicity* - daily monitoring for toxic signs, behavior characteristics and food ingestion.

**Results and discussion.** The resin monomer TEGDMA, present in the composite composition, increased the amount of intracellular reactive oxygen species. Resin-based composites are cytotoxic before polymerization and immediately thereafter, whereas already set specimens cause almost no reaction. The test of tolerance showed that the composite materials do not contain any toxic, irritant substances or destructive ones for the living cells or tissues.

**Conclusion.** Biological tests lead to the conclusion that the elaborated composites are well tolerated by the organism without any systemic or local rejection manifestation.

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