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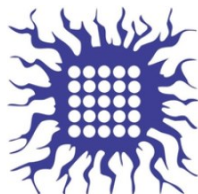
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**2<sup>nd</sup> International Conference on Chemo and Bioinformatics**

**ICCBIKG\_2023**



# BOOK OF PROCEEDINGS





2<sup>nd</sup> International Conference on Chemo and Bioinformatics  
ICCBIKG 2023

# BOOK OF PROCEEDINGS

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Kragujevac, Serbia

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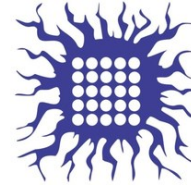
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## Table of contents

<b>PLENARY LECTURERS</b> .....	<b>1</b>
THE IMPORTANCE OF CHEMOMETRICS IN DRUG DISCOVERY FROM MEDICINAL PLANTS .....	2
A REVIEW OF THE APPLICATION OF THE FINITE ELEMENT SMEARED CONCEPT TO BIOMEDICAL ENGINEERING PROBLEMS .....	6
IS DEUTERIUM BIOLOGICALLY SIGNIFICANT? SOME UNEXPECTED DEUTERIUM SPECTROSCOPIC DATA .....	7
TARGETING DEPRESSION VIA COMPUTATIONAL APPROACHES TO DESIGN NEW COUMARIN-BASED SEROTONIN RECEPTOR ANTAGONISTS/AGONISTS AND DEVELOP RELIABLE MODELS OF G PROTEIN-COUPLED RECEPTORS.....	10
ALGORITHMS AND WEB SERVERS FOR PROTEIN BINDING SITES DETECTION IN DRUG DISCOVERY .....	14
TOWARD QUANTITATIVE RAMAN SPECTROSCOPY.....	22
SYNTHETIC DATA GENERATION FOR BIOMEDICAL DEEP LEARNING: METHODS, CHALLENGES, AND OPPORTUNITIES .....	26
<b>SECTION LECTURERS</b> .....	<b>34</b>
BENZENE AND WATER – DIFFERENT OR SIMILAR? .....	35
THE HYDROGEN ECONOMY: CHALLENGES AND PROSPECTIVES .....	39
MULTIPARAMETER MONITORING OF CARDIOVASCULAR FUNCTION .....	43
DB.3D-QSAR.COM. THE FIRST 3D QSAR MODELS DATABASE.....	51
IRM@Be <sup>2+</sup> - QUANTUM CHEMISTRY BETWEEN BAVARIA AND ŠUMADIJA.....	53
APPLICATION OF CARBON-BASED NANOCOMPOSITE SYSTEMS AS PHOTOSENSITIZERS FOR PHOTODYNAMIC THERAPY.....	61
CONFUSION ABOUT THE CHOICE OF EVALUATION METRICS FOR MODEL PERFORMANCE ASSESMENT IN CHEMOINFORMATICS, BIOINFORMATICS AND IN GENERAL .....	67
HISTORY OF RADIOLOGICAL PROTECTION AND EVOLUTION OF DOSIMETRIC QUANTITIES .....	73
<b>APPLIED SCIENCE AND TECHNOLOGY</b> .....	<b>81</b>
ENTROPY DYNAMICS FOR A PROPELLER-SHAPED QUANTUM BROWNIAN MOLECULAR ROTATOR .....	82
BIOCORROSION, BIOFOULING AND HEALTH RISK: BIOLOGICAL ACTIVITY REACTION TESTS OF SELECTED BRACKISH GROUNDWATER OCCURRENCES IN SERBIA.....	86
BACTERIA IN DRINKING AND BATHING MINERAL WATERS OF SERBIA WITH POLYMER-DEGRADING POTENTIAL .....	91
MODELING AND SIMULATION OF A POLYMER OPTICAL FIBER HUMIDITY SENSOR FOR THE SKIN MICROENVIRONMENT .....	96
COMPARISON OF ORGANIC SUBSTANCE CONTENT IN PELOIDS FROM SUTOMORE AND IGALO (MONTENEGRO) .....	100
DRIFT SPECTROSCOPY AND PERMUTATION IMPORTANCE ALGORITHM IN QUANTITATIVE ANALYSIS OF ORGANIC MATTER IN SOIL MODEL SYSTEMS .....	104
THE INFLUENCE OF PYROCATECHOL ADDED IN PRE-OSCILLATORY PERIOD ON THE DYNAMICS OF THE BRAY-LIEBHAFSKY REACTION.....	108
ENVIRONMENTAL IMPLICATIONS OF FINANCIAL DEVELOPMENT IN CEE COUNTRIES.....	112
GREENHOUSE GAS EMISSIONS AND DIGITAL COMPETITIVENESS IN CEE COUNTRIES .....	116
ANTIFREEZE WITH COFFEE TASTE .....	120
THE HYDRATION AND ANTIMICROBIAL PROPERTIES OF SELECTED IMIDAZOLE-BASED IONIC LIQUIDS WITH A HOMOLOGOUS SERIES OF CHLORIDE OXYANIONS .....	124
INFLUENCE OF THE IONIC LIQUIDS-BASED ELECTROLYTES ON THE TOMATO ( <i>SOLANUM LYCOPERSICUM</i> L.) AND CUCUMBER ( <i>CUCUMIS SATIVUS</i> L.) GROWTH, DEVELOPMENT AND OXIDATIVE STRESS .....	128
SOLUBILITY AND STRUCTURAL ORGANIZATION OF TAURINE MOLECULES IN WATER .....	132
SELECTING CRITICAL FEATURES FOR BIOMEDICAL DATA CLASSIFICATION .....	136
THROMBOPHILIA PREDICTION USING MACHINE LEARNING ALGORITHMS .....	140
SIMULATION OF DNA DAMAGE USING THE “MOLECULARDNA” EXAMPLE APPLICATION OF GEANT4-DNA.....	144
DEVELOPMENT OF NANOMATERIALS FOR SUSTAINABLE FOOD PACKAGING APPLICATIONS.....	148
BIOACCUMULATION POTENTIAL OF 'MEEKER' AND 'WILLAMETTE' RASPBERRY ( <i>RUBUS IDAEUS</i> L.) FRUITS TOWARDS MACRO- AND MICROELEMENTS AND THEIR NUTRITIONAL EVALUATION .....	152
<i>IN VITRO</i> AND <i>IN SILICO</i> ASSESSMENT OF ANTI-INFLAMMATORY ACTIVITY OF COCOA POWDERS .....	156

COMPARISON OF THE LUMINESCENCE PROPERTIES OF PHOSPHATE-TUNGSTEN BRONZE AND CERIUM DOPED PHOSPHATE-TUNGSTEN BRONZE .....	160
THE COMPARISON OF TWO METHODS USED TO OBSERVE A NONLINEAR SYSTEM: POTENTIOMETRY AND HOLOGRAPHY .....	164
RADIOACTIVITY LEVELS AND HEALTH RISKS ASSOCIATED WITH HIMALAYAN SALT CONSUMPTION .....	168
PREVALENCE OF RADON AND METALS IN NATURAL SPRINGS IN THE SOKOBANJA AREA .....	172
INVESTIGATION OF THE POSSIBILITY OF INTERACTION BETWEEN LITHIUM FLUORIDE CLUSTERS AND BORON USING LDI MS.....	176
<i>IN VITRO</i> BIOLOGICAL EFFECTS OF CLONAL RED WINES .....	180
APPLIED MACHINE LEARNING IN EXPLORING KEY FEATURES OF CRAYFISH POPULATIONS .....	184
DOSE COMPENSATION ALGORITHM IN RADIOTHERAPY PLANNING.....	188
A PROTOCOL FOR THORACIC RADIATION THERAPY IN PATIENTS WITH CARDIAC IMPLANTABLE ELECTRONIC DEVICES.....	193
DISTRIBUTION OF DOSES TO ORGANS AT RISK IN CERVICAL CANCER HIGH DOSE RATE BRACHYTHERAPY USING TANDEM AND OVOIDS OR VAGINAL CYLINDER.....	197
ASSESSMENT OF RADIOACTIVITY LEVELS IN SOIL SAMPLES ON ZLATIBOR MOUNTAIN.....	201
INFLUENCE OF DIFFERENT PRODUCTION SYSTEMS AND TOMATO GENOTYPES ON THE .....	205
CHALLENGES IN RADIOTHERAPY PLANNING IN PATIENTS WITH SYNCHRONOUS RECTAL AND PROSTATE CANCER AND HIP PROSTHESIS..	209
EXPLORING THE PHARMACOKINETIC PROPERTIES OF (NH <sub>4</sub> ) <sub>4</sub> [Fe(1DADTC) <sub>2</sub> ]: <i>IN SILICO</i> BIOLOGICAL SCREENING AND ADMET ANALYSIS .....	213
THE INFLUENCE OF DIFFERENT PLASTICIZERS ON THE MECHANICAL PROPERTIES OF ACTIVE EDIBLE BILAYER FILMS .....	217
PATCH CLAMP PIPETTE GIGA SEAL FORMING SUCCESS ON THE NANOSURGERY-OBTAINED FILAMENTOUS FUNGI PROTOPLASTS.....	221
ANALYSIS OF HEAVY METALS IN THE SOIL IN THE IBAR RIVER VALLEY IN THE DISTRICT OF KOSOVSKA MITROVICA .....	225
WATER QUALITY ANALYSIS IN THE DISTRICT OF KOSOVSKA MITROVICA.....	229
THE EFFECT OF CONSUMER ETHNOCENTRISM ON THE COMPETITIVENESS OF THE ECONOMY OF THE REPUBLIC OF SERBIA.....	232
THE ROLE OF SOCIALLY RESPONSIBLE BUSINESS IN IMPROVING THE COMPANY'S MARKET POSITIONING .....	236
CHEMOMETRIC APPROACH TO THE INVESTIGATION OF MICROELEMENTS AND POTENTIALLY TOXIC ELEMENTS IN THE SOIL.....	241
APPLICATION OF CHEMOMETRICS IN MONITORING OF SPATIAL AND TEMPORAL VARIATIONS IN RIVER WATER QUALITY AND WATER CLASSIFICATION .....	245
MECHANOCHEMISTRY: OPTIMIZATION OF THE SYNTHESIS OF DITHIOCARBAMATE DERIVATIVES.....	249
CAPACITIVE BEHAVIOUR OF BIOMASS-DERIVED ACTIVATED CARBON IN AL-ION-CONTAINING ELECTROLYTES .....	253
THE INTERDEPENDENCE OF STRUCTURAL PROPERTIES AND PSEUDOCAPACITIVE BEHAVIOR OF BIOMASS-DERIVED ACTIVATED CARBON	257
ELUCIDATING HEALTH-ENHANCING PROPERTIES OF NATURAL PRODUCTS: A JOURNEY FROM EXTRACT ISOLATION TO QUANTUM MECHANICS (QM) CALCULATIONS.....	261
A COMPUTATIONAL MODEL OF THE LEFT VENTRICLE – APPLICATION IN CARDIOMYOPATHY DISEASE .....	265
STATUS AND QUALITY OF LIFE OF PEOPLE WITH CELIAC AND PEOPLE ON A GLUTEN-FREE DIET .....	269
MODELING OF CIRCULATING TUMOR CELL (CTC) AND PLATELET INTERACTION IN CAPILLARIES.....	274
<b>BIOINFORMATICS AND APPLIED BIOLOGY .....</b>	<b>279</b>
ABUNDANCE, SPECIES RICHNESS AND DIVERSITY OF EARTHWORMS (LUMBRICIDAE) IN SEVERAL HABITATS OF THE NORTHERN PART OF JASTREBAC MOUNTAIN .....	280
A NEW RECORD OF <i>DENDROBAENA SERBICA</i> KARAMAN, 1973 (CLITELLATA; LUMBRICIDAE) FROM SERBIA.....	284
POTENTIALLY TOXIC ELEMENTS IN THE EDIBLE PART OF TROUT ( <i>SALMO TRUTTA</i> L.) FROM THE UPPER REACHES OF THE RAŠKA AND STUDENICA RIVERS .....	288
DIET COMPOSITION AND FEEDING HABITS OF COMMON BLEAK ( <i>ALBURNUS ALBURNUS</i> L.) IN THE GRUŽA AND GAZIVODE RESERVOIRS .....	292
IDENTIFICATION OF PROTEIN TARGET MOLECULES FOR [Pd(DACH)Cl <sub>2</sub> ] COMPLEX IN HELA CERVICAL CARCINOMA CELLS .....	296
EDIBLE MUSHROOMS AS PROMISING ANTIOXIDANTS .....	300
ANTIMICROBIAL POTENTIAL OF MUSHROOMS <i>MACROLEPIOTA PROCERA</i> AND <i>CHLOROPHYLLUM RHACODES</i> .....	304
OBESITY AS A RISK FACTOR FOR COVID- 19 MORTALITY: AN OVERVIEW OF PUBLISHED META-ANALYSES .....	308
CLASSIFICATION AND ANALYSIS OF KEY PARAMETERS IN PREDICTING THE STATE OF FACULTATIVE OLIGOTROPHS IN TWO DIFFERENT RESERVOIRS .....	312



ECOLOGICAL APPLICATIONS BASED ON BACTERIAL COMMUNITY ABUNDANCE IN RESERVOIRS USING AN ARTIFICIAL NEURAL NETWORK APPROACH.....	317
OXIDATIVE DNA DAMAGE PREVENTIVE ACTIVITY OF ESSENTIAL OILS OF THREE <i>PINUS</i> SPECIES: <i>P. MUGO</i> , <i>P. SIBIRICA</i> , AND <i>P. SILVESTRE</i> .....	321
COMPARATIVE ASSESSMENT OF FISH DIVERSITY INDICES IN PROTECTED VLASINA RESERVOIR AND UNPROTECTED GRUŽA RESERVOIR .....	326
ASSESSMENT OF DIFFERENT MACHINE LEARNING TOOLS EMPLOYED IN LIPIDOMICS .....	330
SLIGHT COOLING DURING GROWTH INDUCED CHANGES IN FILAMENTOUS FUNGI HYPHA MITOCHONDRIAL MORPHOLOGY .....	334
STRUCTURAL SIMULATIONS PREDICTING PROTEIN FOLDING IN ALZHEIMER'S DISEASE .....	338
A MACHINE LEARNING APPROACH COMBINING OMICS DATA FOR ALZHEIMER'S DISEASE ANALYSIS .....	342
<b>BIOMEDICAL ENGINEERING .....</b>	<b>346</b>
NUMERICAL MODELING OF NEW 4,7-DIHYDROXYCOUMARIN DERIVATIVE DIFFUSION WITHIN FINITE ELEMENT LIVER MODEL.....	347
UV-BLOCKING SUSTAINABLE FOOD PACKAGING BASED ON POLYHYDROXYALKANOATE AND BACTERIAL PIGMENT PRODIGIOSIN .....	351
USING NUMERICAL MODELING TO ANALYZE THE BEHAVIOR OF CANCER CELLS AFTER DIVERSE CO-TREATMENTS.....	355
OVERVIEW OF LEFT VENTRICULAR SEGMENTATION IN ULTRASOUND IMAGES .....	359
FINITE ELEMENT ANALYSIS OF STRESS DISTRIBUTION IN 3D TOOTH MODEL WITH EXTENSIVE CAVITIES RESTORED WITH DIRECT AND INDIRECT COMPOSITE RESTORATION .....	363
MULTISCALE MODELLING OF THE EFFECTS OF TEMPERATURE ON CARDIAC TWITCHES .....	367
ANALYTICALLY COMPUTED FRACTIONAL FLOW RESERVE BASED ON CORONARY CT ANGIOGRAPHY.....	371
A FINITE ELEMENT MODEL FOR STRUCTURAL OPTIMIZATION OF PARAMETRIZED LATTICE SCAFFOLDS .....	375
APPLICATION OF MACHINE LEARNING ALGORITHMS IN MEDICAL DATA PROCESSING .....	379
<b>BIOORGANIC, BIOINORGANIC AND MEDICINAL CHEMISTRY.....</b>	<b>382</b>
STRUCTURAL, SPECTROSCOPIC, AND MOLECULAR DOCKING ANALYSIS OF ISOPROTERENOL.....	383
MOLECULAR DOCKING STUDY OF RUTHENIUM- <i>p</i> -CYMENE COMPLEXES WITH ISOTHIAZOLE DERIVATIVES AS SARS-COV-2 MAIN PROTEASE INHIBITORS .....	387
SYNTHESIS, SPECTROSCOPIC, AND QUANTUM-CHEMICAL ANALYSIS OF MONONUCLEAR Ru(II)-NAPHTHYLHYDRAZINE COMPLEX .....	391
SYNTHESIS, SPECTROSCOPIC, AND THEORETICAL ANALYSIS OF Ru(II)-PHENYLHYDRAZINE COMPLEX .....	395
DNA/BSA BINDING STUDY OF MONONUCLEAR GOLD(III) COMPLEXES WITH CLINICALLY USED AZOLES.....	399
DNA/BSA INTERACTION OF PLATINUM(II) COMPLEXES WITH PHENOTHIAZINE AND <i>N</i> -METHYLPHENOTHIAZINE .....	403
THE INTERACTION STUDIES OF NOVEL DIAMINOPHENAZINE GOLD(III) COMPLEX AND BOVINE SERUM ALBUMIN (BSA-IBUPROFEN AND BSA-EOZINE Y) .....	407
THE INFLUENCE OF STRUCTURAL MODIFICATION OF Pd(II) Pincer-TYPE COMPLEXES ON THE KINETICS OF SUBSTITUTION REACTIONS. ....	411
<i>IN VITRO</i> CYTOTOXIC ACTIVITY OF A MONOLACUNARY WELLS-DAWSON NANOCUSTER AGAINST CERVICAL CARCINOMA HELA CELLS .....	415
THE INFLUENCE OF Fe(III) INCORPORATION ON ANTI-CANCER POTENTIAL OF A WELLS-DAWSON NANOCUSTER .....	419
DFT APPROACH OF THE REDOX PROPERTIES OF BRIMONIDINE AND VARENICLINE.....	423
THEORETICAL AND EXPERIMENTAL STUDY OF BILASTINE IONIZATION .....	427
NEW VANADIUM COMPLEXES WITH POTENTIAL BIOLOGICAL ACTIVITY.....	431
SYNTHESIS OF SCHIFF BASES BETWEEN SOME FIVE-MEMBERED HETEROCYCLIC ALDEHYDES AND THIOCARBOHYDRAZIDE (TCH) AND OPTIMIZATION OF REACTION CONDITIONS .....	435
SYNTHESIS, STRUCTURE AND ANTICANCER ACTIVITY OF Zr(IV) COMPLEXES WITH SCHIFF BASES DERIVED FROM 8-HYDROXYQUINOLINE .....	439
IONIC PALLADIUM(II) COMPLEXES WITH NITRO AND HALOGEN DERIVATIVES OF 8-HYDROXYQUINOLINE .....	443
A NOVEL SILVER COMPLEX WITH 4-HYDROXYCOUMARIN DERIVATIVE: SYNTHESIS, STRUCTURE, AND BIOLOGICAL ACTIVITY .....	447
ANTICANCER GALLIUM(III) COMPLEXES WITH HALOGEN- AND NITRODERIVATIVES OF 8-HYDROXYQUINOLINE.....	451
<i>IN SILICO</i> DRUG-LIKENESS, PHARMACOKINETIC AND OTHER ADME PROPERTIES OF 2-(AMINOMETHYL)CYCLOPROPANE-1,1-DICARBOXYLIC ACID.....	455
BSA BINDING OF 2-(AMINOMETHYL)CYCLOPROPANE-1,1-DICARBOXYLIC ACID .....	459
INVESTIGATION OF BINDING MODE OF NOVEL 2,4-DIKETO ESTERS TO BSA .....	463

SR FTIR SPECTROSCOPY INVESTIGATION OF Pd@S-CD NANOCOMPOSITE SYSTEM EFFECTS ON BIOMOLECULES IN CERVICAL CARCINOMA CELLS .....	467
THE EFFECTS OF A SELECTED METHOXY SUBSTITUTED CHALCONE IN HUMAN MELANOMA CELLS IRRADIATED WITH $\gamma$ -RAYS .....	471
<i>IN SILICO</i> ESTIMATION OF COX-2 AND 5-LOX INHIBITORY POTENTIAL OF SOME NOVEL THIOUREA DERIVATIVES OF NAPROXEN .....	475
MOLECULAR DOCKING STUDY OF DESIGNED N-MYRISTOYL TRANSFERASE INHIBITORS.....	479
PLATINUM(II) COMPLEXES WITH EPOXIDE DERIVATIVE OF 1,10-PHENANTHROLINE IN INTERACTION WITH HUMAN SERUM ALBUMIN .	483
ANALYTICAL VALUES OF BEESWAX FROM MONTENEGRO AND DETECTION OF ADULTERATION .....	487
PHENOLIC <i>N</i> -ACYL HYDRAZONE DERIVATIVES: <i>IN SILICO</i> ASSESSMENT OF POTENTIAL ANTIBACTERIAL ACTIVITY AGAINST SELECTED G <sup>+</sup> AND G <sup>-</sup> STRAINS .....	491
<i>IN SILICO</i> ANTIBIOFILM POTENCY OF PHENOLIC <i>N</i> -ACYL HYDRAZONES AGAINST SELECTED BACTERIAL STRAINS .....	495
TiO <sub>2</sub> NANOPARTICLES AND TiO <sub>2</sub> NANOPARTICLES SURFACE MODIFIED WITH SALICYLIC ACID AFFECT NEUROLOGICAL FUNCTIONS AND OXIDATIVE STRESS MARKERS IN THE EYES OF ADULT RATS .....	499
SYNTHESIS AND CYTOTOXIC ACTIVITY OF SELECTED DUAL COX-2 AND 5-LOX INHIBITORS IN HELA AND MIA PaCa-2 HUMAN CANCER CELL LINES .....	503
SYNTHESIS, CHARACTERIZATION AND HSA INTERACTIONS OF A NEW PIANO-STOOL RUTHENIUM(II) COMPLEX CONTAINING A THIOAMIDE-TYPE LIGAND .....	507
HPLC/UV PROFILE AND DETERMINATION OF TOTAL PHENOLIC AND FLAVONOID CONTENTS OF LICHEN <i>UMBILICARIA CRUSTULOSA</i> GROWING IN SERBIA .....	511
LICHENO-CHEMICAL ANALYSIS AND <i>IN VITRO</i> ANTIOXIDANT ACTIVITY OF EXTRACTS AND GYROPHORIC ACID FROM LICHEN <i>UMBILICARIA GRISEA</i> .....	515
BIOLOGICAL ACTIVITY OF THIENYL-TERPYRIDINE Ru(II) COMPLEX IN THE PRESENCE OF BIOCOMPATIBLE IONIC LIQUIDS .....	519
KINETIC STUDIES OF THE Ru(II) POLYPYRIDYL COMPLEX WITH BIOLOGICALLY RELEVANT LIGANDS .....	523
SYNTHESIS AND PHYSICO-CHEMICAL CHARACTERISATION OF THE Ni(II) COMPLEX WITH 3-(4-CHLOROPHENYL)-1H-PYRAZOLE LIGAND	527
NORMAL AND REVERSED PHASES THIN-LAYER CHROMATOGRAPHY OF ARYLIDENE 2-THIOHYDANTOIN DERIVATIVES .....	531
INVESTIGATION OF THE ANTICANCER ACTIVITY OF 2-AMINO-6-METHYLBENZOTHAZOLE AND CORRESPONDING Pd(II) COMPLEX USING MOLECULAR DOCKING SIMULATIONS .....	535
DNA BINDING AND MOLECULAR DOCKING OF FOUR PALLADIUM(II) COMPLEXES WITH <i>O, O'</i> -DIALKYL ESTERS OF ( <i>S, S</i> )-PROPYLENEDIAMINE- <i>N, N'</i> -DI-2-(2-BENZYL) ACETIC ACID .....	539
MACRO AND MICROELEMENTS IN THE LEAF AND EXTRACT OF NETTLE FROM DIFFERENT LOCALITIES OF MONTENEGRO .....	543
SYNTHESIS AND ANTIOXIDANT ACTIVITY OF NOVEL VANILLIN-BASED FERROCENYL CHALCONES .....	547
A CONTRIBUTION TO THE KNOWLEDGE OF THE SPECIES <i>DIPSACUS SYLVESTRIS</i> HUDS. ....	551
QUALITATIVE CONTENT OF SELECTED PHENOLIC COMPOUNDS IN DIFFERENT EXTRACTS OF PLANT SPECIES <i>IRIS PUMILA</i> L. ....	555
BUILDING A 3D QSAR MODEL WITH ISOPROPYLIDENE ANALOGS OF CYTOTOXIC STYRYL-LACTONES .....	559
VALIDATION OF GRAVIMETRIC METHOD FOR DETERMINATION OF CLAY IN SOIL .....	563
PYRAZOLE/TACRINE DERIVATIVES AS POTENTIAL CHOLINESTERASE INHIBITORS.....	567
THE INFLUENCE OF THE METHANOL EXTRACT OF <i>GALIUM VERUM</i> ON CARDIAC OXIDATIVE DAMAGE IN HYPERTENSIVE RATS IN A MODEL OF GLOBAL ISCHEMIA .....	571
CAN A THREE-WEEK ADMINISTRATION OF METHANOL EXTRACT OF WILD GARLIC MODULATE SYSTEMIC REDOX STATE IN HYPERTENSIVE RATS? .....	575
<b>CHEMOINFORMATICS, CHEMOGENOMICS AND MOLECULAR DESIGN .....</b>	<b>579</b>
HIGH-THROUGHPUT SCREENING OF NOVEL HYDROGEN STORAGE MATERIALS – ML APPROACH .....	580
3D-QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP AND DESIGN OF NOVEL RHO-ASSOCIATED PROTEIN KINASES-1 (ROCK1) INHIBITORS .....	584
VIRTUAL DOCKING, DESIGN AND <i>IN SILICO</i> ADMET PROFILING OF NOVEL RHO-ASSOCIATED PROTEIN KINASES-1 (ROCK1) INHIBITORS .....	589
A METRIC FOR PAIRWISE SIMILARITY ANALYSIS OF BINARY CHEMINFORMATICS DATA .....	593
COUMARINS AS PROMISING PPAR $\alpha$ AGONISTS. NOVEL <i>IN SILICO</i> INSIGHTS .....	597
COMBINED <i>IN SILICO</i> APPROACH TO IDENTIFY NEW TERPENOID PPAR $\alpha$ AGONISTS.....	601

<i>IN SILICO</i> SCREENING OF <i>SOLANUM LYCOPERSICUM</i> CAROTENOIDS FROM CAROTENOIDS DATABASE FOR CANDIDATES PPARA AGONISTS .....	605
NUMERICAL SIMULATIONS OF THE OSCILLATORY DYNAMICS IN THE BRAY-LIEBHAFSKY REACTION PERTURBED BY L-TYROSINE.....	609
THE ASSESSMENT OF THE ANTIOXIDANT CAPACITY OF THE SELECTED VANILLIN-BASED PYRIDO-DIPYRIDINES USING DPPH ASSAY: <i>IN SILICO</i> APPROACH .....	613
INHIBITORY POTENTIAL OF BARBARIN AND ITS PLATINUM(II) COMPLEX TOWARDS PBP1A PROTEIN .....	617
MODELING ION- $\pi$ INTERACTIONS OF TRANSITION METAL COMPLEXES .....	621
SUBSTITUENT EFFECTS ON STACKING INTERACTIONS OF AROMATIC LIGANDS IN ORGANOMETALLIC COMPOUNDS – CHEMOINFORMATICS AND QUANTUM CHEMICAL STUDY .....	625
COMPUTATIONAL STUDY ON THE INTERACTIONS OF QUERCETIN 3-O-RUTINOSIDE WITH HUMAN DPP III .....	629
NONCOVALENT INTERACTIONS OF HALOGEN ATOMS IN HALOGENATED BIPYRIDINES .....	633
REPULSIVE WATER-WATER CONTACTS FROM CAMBRIDGE STRUCTURAL DATABASE .....	637
COMPUTER-AIDED DESIGN OF NEW DRUGS AGAINST BREAST CANCER.....	641
STACKING INTERACTIONS AT LARGE HORIZONTAL DISPLACEMENTS—COMPARISON OF VARIOUS RING TYPES.....	645
INFLUENCE OF COORDINATION ON OH/ $\pi$ AND NH/ $\pi$ INTERACTIONS .....	649
RELATIVISTIC DFT CALCULATION AND THEIR EFFECT ON THE ACCURACY OF RESULTS .....	653
ANALYSIS OF PREDICTION OF WATER SOLUBILITY AND LIPOPHILICITY OF COUMARINS BY FREE CHEMINFORMATICS TOOLS .....	657
INFLUENCE OF PHTHALIMIDE SUBSTITUTION ON THE INTERACTION WITH CARBON NANOTUBE .....	662
INTERACTION ENERGY AND DECOMPOSITION OF INTERACTION ENERGY OF HALO-SUBSTITUTED PHTHALIMIDE WITH CARBON NANOTUBE .....	666
IDENTIFICATION OF SMALL MOLECULE BINDING SITES USING CMDOCK .....	670
A COMPREHENSIVE <i>IN SILICO</i> PROTOCOL FOR FAST AUTOMATED MUTAGENESIS AND BINDING AFFINITY SCORING OF PROTEIN-LIGAND COMPLEXES .....	674
WORKFLOW AUTOMATION OF HIGH-THROUGHPUT INVERSE DOCKING USING PHARMMAPPER .....	678
INVESTIGATING THE POTENTIAL INHIBITORY EFFECT OF THE MEGAPHONE (MOLECULE) ON NASOPHARYNGEAL CANCER GROWTH FACTOR RECEPTORS .....	682
GREEN SYNTHESIS OF CHROMENO-PYRIMIDINE DERIVATIVES – PART I.....	686
CHROMENO-PYRIMIDINE-TYPE COMPOUNDS (PART II): <i>IN VITRO</i> EVALUATION OF ANTIOXIDANT POTENTIAL .....	690

## TiO<sub>2</sub> nanoparticles and TiO<sub>2</sub> nanoparticles surface modified with salicylic acid affect neurological functions and oxidative stress markers in the eyes of adult rats

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**Abstract:** Titanium dioxide nanoparticles (TiO<sub>2</sub>NPs) are widely used in pharmaceuticals, food products and cosmetics. Besides numerous beneficial outcomes, they also induce toxic effects in different organs, including the eyes. The recent findings report that some surface modifications can attenuate TiO<sub>2</sub>NPs toxicity. Thus, the aim of this study was to compare the effects of acute oral treatment with commercially available, bare TiO<sub>2</sub>NPs and TiO<sub>2</sub>NPs surface modified with salicylic acid (SA-TiO<sub>2</sub>NPs) using adult Wistar rats as model organisms. Control animals were gastrically intubated with vehicle (0.01 M HCl), while others were treated with either TiO<sub>2</sub>NPs or SA-TiO<sub>2</sub>NPs (1000mg/kg dissolved in vehicle). Afterward, the mortality rate as the acute toxicity parameter and parameters of neurological function were assessed. Animals were sacrificed on the 14th day following treatment. In the eye crude synaptosomal fraction, the effects of treatments on oxidative stress markers such as prooxidant/antioxidant balance (PAB) and lipid peroxidation (LPO) were compared. According to the obtained results, the mortality was 0 in all experimental groups. TiO<sub>2</sub>NPs and SA-TiO<sub>2</sub>NPs treatments displayed mild effects on spontaneous activity and pacing and had no impact on the visual placing reflex. Moreover, TiO<sub>2</sub>NPs and SA-TiO<sub>2</sub>NPs exposure significantly elevated PAB levels, when compared to controls. Animals treated with SA-TiO<sub>2</sub>NPs had similar LPO levels as controls, while in TiO<sub>2</sub>NPs group LPO levels were significantly increased. The presented data showed that both examined nanoparticles exerted similar outcomes referring to most of the investigated parameters, however, surface binding of SA decreased the level of LPO and thus, mitigated some of TiO<sub>2</sub>NPs toxicity in the eyes.

**Keywords:** Titanium dioxide nanoparticles (TiO<sub>2</sub>NPs) and surface modification with salicylic acid (SA-TiO<sub>2</sub>NPs), neurological function, oxidative stress, eye, rat

### 1. Introduction

Titanium dioxide nanoparticles (TiO<sub>2</sub>NPs) are widely used as a white pigment in daily consumer products, like food, toothpaste, sun cream, cosmetics, and plastics. They are also exploited in surgery, dentistry, and pharmacy; in antimicrobial and antibiotic therapies; as photosensitizers in photodynamic cancer therapy; and can potentially be used as a drug delivery system [1]. Unfortunately, toxic impacts of TiO<sub>2</sub>NPs, provoked by oxidative stress (OS) and inflammation, are recognized in the brain, liver, kidneys, spleen, and eyes [2]. Their toxicity might be reduced by various modifications, including surface bounding of naturally occurring compounds with a wide range of biological activities and therapeutic applications. Since previous studies showed that some surface modifications can attenuate TiO<sub>2</sub>NPs toxicity [3], we compared the effects of bare TiO<sub>2</sub>NPs and SA-TiO<sub>2</sub>NPs (TiO<sub>2</sub>NPs surface modified with salicylic acid, SA) in the eyes of adult Wistar rats.

## 2. Materials and methods

For the purpose of the experiment, we used commercially available, bare TiO<sub>2</sub>NPs (Sigma Aldrich Co., USA, sized 25 nm) with maximum absorption wavelength of 380 nm and SA-TiO<sub>2</sub>NPs, synthesized and characterized at the Department for Radiation Chemistry and Physics, VINČA Institute of Nuclear Sciences - National Institute of the Republic of Serbia, University of Belgrade, with maximum absorption of 600 nm. The estimated concentration of SA bound to the surface of TiO<sub>2</sub>NPs was 5 %.

All procedures were approved by the Ministry of Agriculture, Forestry and Water Management - Veterinary office of the Republic of Serbia (protocol 323-07-03626/2021-05). Adult Wistar rats, maintained under standard conditions, were randomly divided into 3 groups (n = 4 per group): controls treated with vehicle (2.5 ml, 0.01 M HCl) (V); animals treated with either TiO<sub>2</sub>NPs or SA-TiO<sub>2</sub>NPs (1000 mg/kg dissolved in 2.5 ml vehicle). All treatments were applied intragastrically in a single dose. During the 14-day rest period, the mortality rate as the acute toxicity parameter was monitored daily. On the last day, sensory-motor parameters, including spontaneous activity, pacing and visual placing reflex were assessed, as indicators of neurological function. Animals were then sacrificed, and their eyes were isolated on ice and stored at -80°C for further processing. Whole eyes were homogenized in 5 volumes of solvent (50 mM Tris-HCl, 0.25 M sucrose, 1 mM EDTA, pH 7.4) to isolate crude synaptosomal fraction [4]. Evaluation of eyes' oxidative status was conducted using modified spectrophotometrical methods for prooxidant/antioxidant balance (PAB) and lipid peroxidation (LPO) [5]. Obtained results are presented as a percentage of V and expressed as mean ± SEM. The GraphPad Prism 5 (GraphPad Software, Inc., USA) was used for statistical analysis, with one way analysis of variance (ANOVA) and Tukey's multiple-comparison post hoc test (statistical significance was p < 0.05).

## 3. Results and discussion

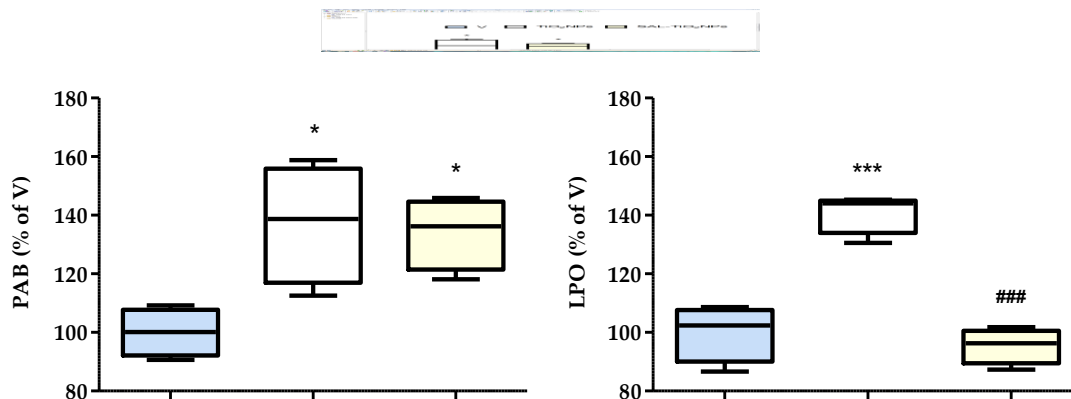
During the 14-day rest period, the mortality was 0 in all experimental groups, pointing to nonlethal effect of applied NPs (data not shown). As shown in Table 1., the investigated neurological parameters were unaffected by vehicle treatment. Both TiO<sub>2</sub>NPs and SA-TiO<sub>2</sub>NPs treatments caused noticeable, but mild effects on spontaneous activity and pacing, indicating neurological deficits that tempered animal behavior. The visual placing reflex was unchanged and showed no difference between groups, suggesting that the eye function probably remained intact following TiO<sub>2</sub>NPs and SA-TiO<sub>2</sub>NPs treatments.

**Table 1.** Assessment of neurological parameters of rats subjected to acute oral treatment with vehicle (V), bare titanium dioxide nanoparticles (TiO<sub>2</sub>NPs) or titanium dioxide nanoparticles surface modified with salicylic acid (SA-TiO<sub>2</sub>NPs).

Neurological parameters/groups	V	TiO <sub>2</sub> NPs	SA-TiO <sub>2</sub> NPs
Spontaneous activity	-	+	+
Pacing	-	+	+
Visual placing reflex	-	-	-

"- " no effect; "+" mild effect

In the eye crude synaptosomal fraction, the treatments' effect on OS markers: PAB and LPO were tested. As illustrated in Figure 1 both TiO<sub>2</sub>NPs treatments significantly elevated PAB levels compared to V ( $p < 0.05$ ), while the LPO level was significantly increased only in the TiO<sub>2</sub>NPs group ( $p < 0.001$ ). Animals treated with SA-TiO<sub>2</sub>NPs had decreased LPO levels when compared to TiO<sub>2</sub>NPs ( $p < 0.001$ ).



**Figure 1.** Levels of oxidative stress markers: prooxidant/antioxidant balance (PAB) (left) and end lipid peroxidation products (LPO) (right) in the eye crude synaptosomal fraction of rats, subjected to acute oral treatment with vehicle (V), bare titanium dioxide nanoparticles (TiO<sub>2</sub>NPs) or surface modified with salicylic acid (SA-TiO<sub>2</sub>NPs). Values are presented as percentage of V and expressed as mean  $\pm$  SEM, with ANOVA and Tukey post hoc test statistical analysis.

Statistically significant difference between V and other experimental groups is represented as \* (\*  $p < 0.05$ , \*\*\*  $p < 0.001$ ) and between TiO<sub>2</sub>NPs and SA-TiO<sub>2</sub>NPs as # (###  $p < 0.001$ )

Based on presented results, it can be assumed that TiO<sub>2</sub>NPs and SA-TiO<sub>2</sub>NPs have different mechanisms of OS induction. TiO<sub>2</sub>NPs-induced OS is associated with oxidative

changes of lipids, as also previously reported [6], while SA-TiO<sub>2</sub>NPs in the eyes of rats do not affect lipids, but most likely their effects are accomplished through some other mechanisms of action.

### 3. Conclusions

Although TiO<sub>2</sub>NPs and SA-TiO<sub>2</sub>NPs exert similar outcomes referring to most of the investigated parameters, surface binding of SA reduces the level of lipid peroxidation and thus, at least partially, suppresses TiO<sub>2</sub>NPs toxic effects in the eyes. Further research is needed to reveal unknown mechanisms of TiO<sub>2</sub>NPs and SA-TiO<sub>2</sub>NPs actions and to investigate the benefits associated with positive outcomes resulting from the implementation of other TiO<sub>2</sub>NPs modifications.

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