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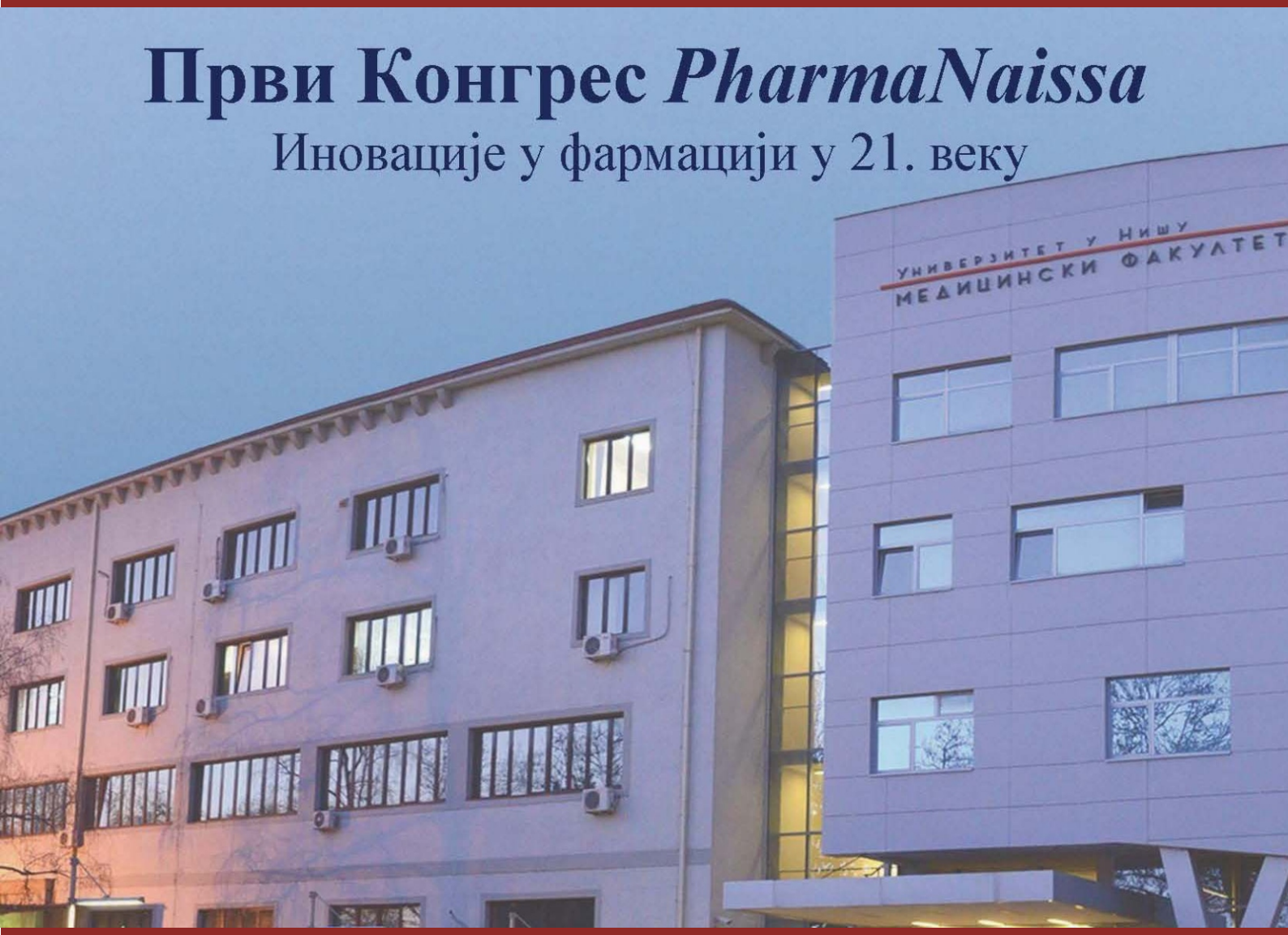
Први Конгрес *PharmaNaissa*

Иновације у фармацији у 21. веку



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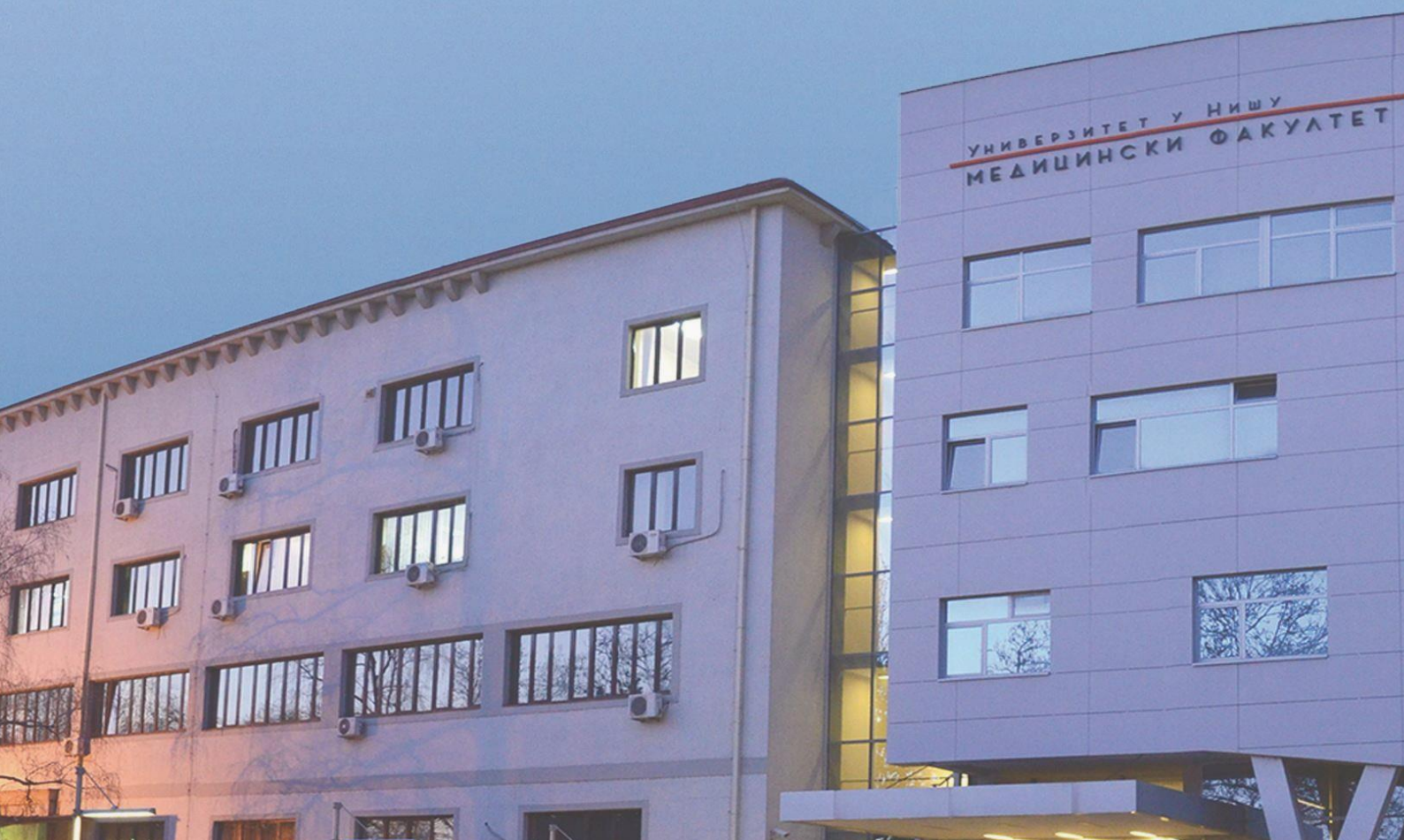
КЊИГА САЖЕТАКА

23. и 24.09.2022. године

Медицински факултет Универзитета у Нишу



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SAŽECI / ABSTRACTS

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PREDAVANJA

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THE PROGRESS OF PHARMACY IN THE 21st CENTURY

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The development and availability of biotechnology and information technologies have led to new discoveries such as precision medicine, M-Health, 3D printing, nanotechnology, artificial intelligence. In the last 20 years, after complete sequencing and mapping of the human genome (2003), accelerated development and research in pharmacogenetics has started. The pharmacogenetics is a scientific discipline the task of which is to study the association between individual genes and the PK/PD characteristics of drugs. Biological therapy, the most advanced therapeutic modality, has changed the standard principles of treatment, which has resulted in better therapeutic outcomes of many diseases such as tumors, autoimmune and chronic rheumatic diseases, diabetes, multiple sclerosis, and rare diseases for which therapeutic modalities were limited. The application of immune therapy has brought a revolution in the treatment of malignant diseases. Modern pharmacy strive for personalized solutions in order to achieve optimal therapeutic outcomes for each individual patient. Advancements in technology, sociopolitical changes, greater access to information and a shift to multi-disciplinary approach have contributed to a switch in the role of pharmacists. The primary role of the pharmacist to be an expert for medicines is now patient-oriented with the aim of providing high-quality pharmacotherapy (effectiveness, safety and quality). The pharmacist may have generic roles as an educator, manager, mentor, business/service developer, leader, researcher depending on their practice, experience, competencies, interests and other factors. By defining the core qualities of the role, appropriate selection, education, training and workforce planning are required. Pharmacists are expected to be competent and adaptive so they are able to develop their own practice and roles to meet the changing needs. A readiness to be more actively involved in decision making and take on greater leadership responsibilities will surely need to be the core of the role which will change throughout their careers.

Keywords: *pharmacy, progress, innovation, precision medicine, nanotechnology*

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NAPREDAK FARMACIJE U 21.VEKU

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Intenzivan razvoj i dostupnost biotehnologije i informacionih tehnologija doveie su do značajnih otkrića u 21. veku, kao što su: precizna medicina, M-Health, 3D štampa, nanotehnologija i veštačka inteligencija, koja imaju svoju primenu i u farmaciji. Poslednjih 20 godina, nakon kompletnog sekvenciranja i mapiranja humanog genoma, započet je ubrzani razvoj istraživanja u farmakogenetici, koji je doveo do otkrića ciljane terapije i imunoterapije. Uvođenjem biološke terapije, najnaprednijeg terapijskog modaliteta, izmenjeni su standardni principi lečenja, što je rezultiralo boljim terapijskim ishodima brojnih oboljenja, kao što su tumori, autoimune i hronične reumatske bolesti, dijabetes, multipla skleroza, kao i retke bolesti za koje su terapijske mogućnosti bile ograničene. Primena imunološke terapije dovela je do revolucije u lečenju malignih bolesti. Savremena farmacija personalizovanim rešenjima ostvarila je izuzetan progres u postizanju optimalnih terapijskih ishoda za svakog pacijenta pojedinačno. Razvoj nanotehnologije omogućio je korišćenje nanočestica i primenu novih formulacija zasnovanih na nanosistemima u lečenju brojnih oboljenja (upotreba nosača za lekove, koji se mogu isporučiti do tumora i gena). Primenom 3D modelovanja i printinga omogućena je proizvodnja lekova prilagođenih individualnim potrebama pacijenata, posebno najmlađim i najstarijim. Pandemija virusa COVID-19 direktno je pokazala značaj napretka i inovacija u farmaciji, kroz razvoj vakcina, dijagnostičkih testova i novih terapijskih opcija u lečenju infekcija izazvanih virusom COVID-19, u rekordnom vremenskom periodu. Tokom pandemije virusa COVID-19, farmaceuti su pokazali prilagodljivost i inovativnost, dajući značajan doprinos ukupnom zdravstvenom sistemu. Primarna uloga farmaceuta, od stručnjaka za lekove, sada je fokusirana na pacijenta, sa ciljem obezbeđenja visokokvalitetne farmakoterapije (efikasnost, bezbednost, kvalitet). Napredak u tehnologiji, društveno-političke promene, veća dostupnost informacija i multidisciplinarni pristup doprineli su promeni uloge farmaceuta. Farmaceut je u 21. veku edukator, menadžer, mentor, programer poslovanja/usluga, lider, istrazivač, itd. (zavisno od prakse, iskustva, kompetencija, interesovanja). To zahteva odgovarajuću selekciju, promene u obrazovanju, edukaciju i planiranje odgovarajućih profila farmaceuta. Od farmaceuta se očekuje da bude kompetentan i prilagodljiv novoj praksi i ulozi, spreman da se aktivnije uključi u donošenje odluka i preuzimanje liderske odgovornosti.

Ključne reči: *farmacija, napredak, inovacije, precizna medicina, nanotehnologija*

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PHARMACOGENETICS/PHARMACOGENOMICS IN SCIENCE AND PRACTICE - THE PRECISION MEDICINE ERA

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Most of drugs, which are in use nowadays, have been approved based on the pharmacokinetic and pharmacodynamic (PK/PD) studies in larger subject populations. However, interindividual differences in PK/PD of particular drugs may cause different therapeutic response or presence of adverse effects within the standard dosage regimen. Identification and consideration of variability factors of drug response in context of therapeutic algorithms may provide better therapeutic outcomes in most patients. Studies have shown that genetic factors significantly affect variability in disposition and clinical effects of drugs. Single nucleotide polymorphism in a DNA molecule, present in the genes of metabolic enzymes, transporters and target proteins, may contribute to their different individual activity and function. Cytochrome P450 (CYP) 3A5 gene polymorphism affects the functional activity or inactivity of this isoenzyme, whereas the carriers of functional enzyme require higher daily doses of tacrolimus in order to maintain drug concentrations within the optimal range. Besides CYP3A5 and tacrolimus, other gene/drug pairs may be of clinical significance: CYP2C19/clopidogrel, CYP2D6, CYP2C19/antidepressants, CYP2C9, VKORC1/warfarin, DPYD/fluoropyrimidines, etc. The introduction of pharmacogenetics in clinical practice contributes to the development of precision therapy, where the selection of a drug and/or dosage regimen is tailored to the genetics of an individual. The term "pharmacogenetics" primarily refers to the effects of single genes, while "pharmacogenomics" defines a broader field of genomics and genome-wide associations with drug response. A step forward in the development of precision medicine has been reflected in the cancer genomic profiling and the discovery of pharmacogenomic biomarkers (driver mutations). Analysis of the patient genome contributes to the understanding of the PK/PD characteristics of the drug in the organism, while the analysis of tumor DNA enables the identification of therapeutic drug's targets and predicts individual response to the drug. Clinical implementation of precision medicine provides larger availability of targeted therapies for oncology patients and contributes to the optimal health outcomes, improving treatment efficiency, safety and cost-effectiveness.

Keywords: *pharmacogenetics, pharmacokinetic variability, cancer pharmacogenomics, targeted therapy, precision medicine*

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FARMAKOGENETIKA/FARMAKOGENOMIKA U NAUCI I PRAKSI – ERA PRECIZNE MEDICINE

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Većina lekova, koji su danas u upotrebi, odobrena je na osnovu farmakokinetičkih i farmakodinamičkih (FK/FD) ispitivanja u većim populacijama ispitanika. Međutim, interindividualne razlike u FK/FD pojedinih lekova mogu usloviti različit terapijski odgovor ili pojavu neželjenih efekata pri standardnom režimu doziranja. U skladu sa tim, identifikovanje i razmatranje faktora varijabilnosti odgovora na lek, u kontekstu terapijskih algoritama, može omogućiti bolje terapijske ishode za većinu pacijenata. Studije su pokazale da genetski faktori značajno utiču na varijabilnost u dispoziciji i kliničkim efektima lekova. Zamena pojedinačnog nukleotida u molekulu DNK (genski polimorfizam), koja je prisutna u genima metaboličkih enzima, transportera i ciljnih mesta delovanja lekova, može doprineti njihovoj različitoj individualnoj aktivnosti i funkciji. Polimorfizam prisutan u citohrom P450 (CYP) 3A5 genu utiče na funkcionalnu aktivnost ili neaktivnost ovog izoenzima, pri čemu nosioci funkcionalnog enzima zahtevaju veće dnevne doze takrolimusa u cilju održavanja koncentracije leka u optimalnom terapijskom opsegu. Pored CYP3A5 i takrolimusa, drugi parovi gen/lek mogu imati klinički značaj: CYP2C19/klopidogrel, CYP2D6, CYP2C19/antidepresivi, CYP2C9, VKORC1/varfarin, DPYD/fluoropirimidinski antineoplastici i dr. Uvođenje farmakogenetičkih testova u kliničku praksu doprinosi razvoju precizne terapije, koja nalaže da se izbor leka i/ili doznog režima prilagodi genetici pojedinca. Termin "farmakogenetika" prvenstveno se odnosi na efekte pojedinačnih gena, dok termin "farmakogenomika" definiše šire polje genomike i ispituje povezanost celokupnog genoma sa odgovorom na lek. Značajan iskorak u razvoju precizne medicine ogleda se u genomskom profilisanju tumora i otkriću farmakogenomskih biomarkera (engl. *driver mutations*). Ispitivanje genoma pacijenta doprinosi razumevanju FK/FD karakteristika leka u organizmu, dok ispitivanje tumorske DNK omogućava identifikaciju terapijskih ciljeva (farmakogenomski biomarker) i predviđa individualni odgovor na lek. Klinička implementacija precizne medicine omogućava široku dostupnost ciljanih terapija namenjenih onkološkim pacijentima i doprinosi optimalnim zdravstvenim ishodima, unapređujući efikasnost, bezbednost i isplativnost primenjenih terapija.

Ključne reči: *farmakogenetika, farmakokinetička varijabilnost, farmakogenomika karcinoma, ciljana terapija, precizna medicina*

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EFFICACY AND SAFETY OF PHARMACOTHERAPY FROM THE PHARMACIST'S POINT OF VIEW

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Patient-focused pharmacotherapy is essential for improving health outcomes, particularly in vulnerable patients such are geriatric, pediatric patients, pregnant and breastfeeding woman and patients undergoing immunosuppressive therapies.

Avoiding medication errors and achieving optimal health outcomes are the challenges both for physician and clinical pharmacist. The role of a pharmacist in individual approach is to fit dose regimen in accordance with characteristics of patients, presented disease and pharmacotherapy. Besides the knowledge regarding adverse effects, drug-drug interaction and toxicity potential of the chosen drugs, it is necessary to opt for an appropriate pharmacokinetic approach – a population, physiological or some other model, which give more information about inter- and intra-individual variability and important factors for drug clearance. Monitoring of patients, both biochemical and therapeutic, at the same time helps in avoiding under- and overdosing of vulnerable patients. Modern approach in therapy management includes the Monte Carlo simulation, a mathematical model that uses previous pharmacokinetic data for the prediction of risk/benefit ratio during drug exposure. Nowadays we are faced with machine learning as hi-tech solution for clinical questions.

Literature data and conducted studies confirm the importance of personalized approach in pharmacotherapy management. Pharmacokinetic approach together with clinical monitoring is required for optimal clinical outcomes. A pharmacist has knowledge and skills for pharmacotherapy optimization and monitoring of drug exposure, adverse effects and adherence level. Our results have shown a difference in drug exposure and adverse effect intensity regarding gender, dose regimen, number of drugs, which points to the importance of pharmaceutical care and pharmacokinetic data in kidney transplant patient approach. Clinical practice is in constant need for pharmacy-related information aimed at the optimization of medical treatment for vulnerable patient's population.

The interaction of physicians and pharmacists in clinical practice stands for an initiative to introduce the cutting edge knowledge in daily medical practice and make pharmacotherapy decisions, with focus on the patient.

Keywords: *pharmacotherapy optimization, clinical pharmacy, risk/benefit ratio*

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EFIKASNOST I BEZBEDNOST FARMAKOTERAPIJE IZ UGLA FARMACEUTA

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U cilju poboljšanja zdravstvenih ishoda, neophodna je farmakoterapija sa pacijentom u fokusu, posebno kod osetljivih populacija – gerijatrijskih, pedijatrijskih i imunokompromitovanih pacijenata, trudnica i dojilja. Zajednički profesionalni izazov za lekara i kliničkog farmaceuta predstavlja izbegavanje medicinskih grešaka i postizanje optimalnih ishoda. Uloga farmaceuta u individualnom pristupu pacijentu ogleda se u rukovođenju terapijom u skladu sa karakteristikama pacijenata, prisutnim bolestima i izabranim lekovima. Pored poznavanja neželjenih efekata, interakcijskog i toksičnog potencijala izabranih lekova, potrebno je odabrati odgovarajući farmakokinetički pristup – populacioni, fiziološki ili drugi model, u cilju dobijanja više informacija o interindividualnoj i intraindividualnoj varijabilnosti i važnim faktorima, koji vrše uticaj na farmakokinetiku leka. Istovremeno biohemijsko i terapijsko praćenje pacijenata može biti značajna pomoć u izbegavanju suboptimalnog ili prekomernog izlaganja leku kod vulnerabilnih pacijenata. Savremeni pristup upravljanju terapijom uključuje Monte Karlo simulaciju, matematički model, koji koristi postojeće farmakokinetičke podatke za predviđanje odnosa rizik/korist tokom terapije. Danas smo suočeni sa upotrebom veštačke inteligencije i mašinskog učenja, kao visokotehnološkim odgovorom na klinička pitanja.
Podaci iz literature i sprovedene studije potvrđuju važnost personalizovanog pristupa u rukovođenju farmakoterapijom. Farmakokinetički pristup, zajedno sa kliničkim praćenjem, predstavlja preduslov za optimalne kliničke ishode. Farmaceut poseduje ogovarajuća znanja i veštine za optimizaciju farmakoterapije i može da prati kako izloženost organizma leku, tako i stepen adherencije i specifične neželjene efekte. Rezultati naših istraživanja sprovedenih na pacijenatima sa transplantiranim bubregom, pokazuju da se izloženost leku i neželjeni efekti razlikuju u odnosu na pol pacijenta, dozni režim i broj lekova, što ukazuje na važnost farmakokinetičkih informacija i farmaceutske nege u tretmanu pacijenata sa kompleksnim stanjima. Klinička praksa konstantno pokazuje potrebu za farmaceutskim informacijama u cilju optimizacije terapije. Interakcija farmaceuta i lekara u kliničkoj praksi predstavlja inicijativu za implementaciju najnovijih saznanja u rutinsku praksu i donošenje farmakoterapijskih odluka, sa pacijentom u fokusu.

Ključne reči: *optimizacija farmakoterapije, farmaceutska nega, odnos rizika i koristi*

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TREATMENT OF CHRONIC VENOUS INSUFFICIENCY - A CHALLENGE FOR PHARMACISTS

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According to statistics of the World Health Organization, venous diseases belong to the group of major diseases affecting the modern man. Chronic venous insufficiency (CVI) is caused by incompetence of the valves in the superficial veins and it stands for a significant health and economic problem. It is defined by a group of symptoms resulting from increased pressure in the superficial and/or deep veins of the lower extremities (deep pain in the leaf muscles, fatigue, tingling, itching, bloating, venous claudication). The goal of CVI treatment is based on the simultaneous improvement of venous function and the reduction of symptoms and signs of the disease. The therapeutic approach must be tailored to the progressive nature of the disease in order to prevent worsening and progression. Treatment modalities for CVI include: compression therapy, medical treatment, surgical methods and physical therapy. Considering the complexity of development and progression of CVI, pharmacological therapy is unavoidable treatment modality and the basis of pharmacotherapeutic approach is the use of venoactive drugs. The role of these drugs is the clinical improvement of venous tone and contractility, reduction of oedema and inflammation, as well as in improving microcirculation. The active ingredients of venoactive drugs of plant origin belong to the groups of: saponosides, flavonoids, anthocyanins, coumarins or terpenes, while synthetic drugs include calcium dobesilate and sulodexide. Venoactive drugs are available as oral or topical preparations, with or without a prescription. In recent years, there has been a growing number of drugs for the prophylaxis and treatment of chronic CVI that are available without a prescription, which is why pharmacists face a new challenge in their daily professional work. In order to provide a high degree of efficacy and safety of CVI therapy, an active role of pharmacists is necessary, as members of the health team, which is reflected in patient's counselling and education regarding the proper use of compression therapy/drugs, prevention of side effects and interactions of venoactive drugs.

Keywords: *chronic venous insufficiency, pharmacist, venoactive drugs*

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TERAPIJA HRONIČNE VENSKE INSUFICIJENCIJE - IZAZOV ZA FARMACEUTE

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Prema statistici Svetske zdravstvene organizacije, venska oboljenja spadaju u grupu najmasovnijih oboljenja savremenog čoveka. Hronična venska insuficijencija (HVI) uzrokovana je inkompetencijom zalistaka u površinskim venama i predstavlja značajan zdravstveni i ekonomski problem. Definisana je grupom simptoma koji su posledica povišenog pritiska u površinskim i/ili dubokim venama donjih ekstremiteta (duboki bol u mišićima lista, zamor, trnjenje, svrab, nadutost, venske klaudikacije). Cilj lečenja HVI bazira se na istovremenom poboljšanju venske funkcije i umanjenju simptoma i znakova bolesti. Terapijski pristup mora biti prilagođen progresivnoj prirodi bolesti, sa ciljem sprečavanja pogoršanja stanja pacijenta i napredovanja bolesti. Modaliteti lečenja HVI obuhvataju: kompresivnu terapiju, medikamentozni tretman, hirurške metode i fizikalnu terapiju. Imajući u vidu kompleksnost nastanka i progresije HVI, medikamentozna terapija predstavlja nezaobilazni modalitet lečenja, a osnovu farmakoterapijskog pristupa čine venoaktivni lekovi. Uloga ovih lekova ogleda se u kliničkom poboljšanju venskog tonusa i kontraktilnosti, smanjenju edema i inflamacije, kao i poboljšanju mikrocirkulacije. Aktivni sastojci venoaktivnih lekova biljnog porekla pripadaju grupama: saponozida, flavonoida, antocijana, kumarina ili terpena, dok se u sintetske lekove ubrajaju kalcijum-dobesilat i sulodeksid. Venoaktivni lekovi dostupni su u vidu oralnih ili topikalnih preparata u režimu izdavanja sa lekarskim receptom ili bez lekarskog recepta. Poslednjih godina utvrđen je rastući broj lekova za profilaksu i lečenje hronične HVI, koji su dostupni bez lekarskog recepta, zbog čega se farmaceuti susreću sa novim izazovom u svakodnevnom profesionalnom radu. U cilju obezbeđivanja visokog stepena efikasnosti i bezbednosti terapije HVI neophodna je aktivna uloga farmaceuta, kao člana zdravstvenog tima, koja se ogleda u savetovanju i edukaciji pacijenata o pravilnoj primeni kompresivne terapije / lekova, prevenciji neželjenih reakcija i interakcija venoaktivnih lekova.

Ključne reči: *hronična venska insuficijencija, farmaceut, venoaktivni lekovi*

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TECHNOLOGICAL INNOVATIONS IN THE PHARMACEUTICAL AND COSMETIC INDUSTRIES

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The pharmaceutical industry is characterized by a very dynamic development. The development of new, original drugs and their placement on the global market are the goals of all innovative pharmaceutical companies. On the other hand, intensive work is being done on actives that have been on the market for many years, where new drugs/drug systems with improved characteristics compared to the existing ones are created on the basis of modern technological procedures and/or the use of new excipients and carriers. It is evident that the innovator and generic companies are being developed technologically and economically with the aim of creating "smart" products and production processes so that the new products, which are increasingly highly individualized and meet the needs of the patient, could be brought to the market in the shortest possible period of time. Through the process of drug formulation using innovative technological processes, the problems of low solubility and instability of drug substances, poor organoleptic properties, significant first-pass metabolism, non-specific biodistribution, side effects, and interactions with various biomolecules are being solved. The application of nanotechnology, primarily nanoemulsions and nanoparticles that are biocompatible, biodegradable, physically stable, with high solubilization capacity for lipophilic drugs and simple "scale up", leads to increased bioavailability, controlled release and targeted delivery of drugs. Using vesicular drug carriers (liposomes, transfersomes, nanosomes, ethosomes, invasomes) and the formulation of therapeutic systems with drugs incorporated into various micro- and nano-carriers, the more effective treatment of many diseases (reduction of disease symptoms, speeding recovery time, reduction of side effects and long-term consequences of treatment), as well as more comfortable treatment and consequently better adherence (compliance) of users are enabled.
The cosmetics industry follows the innovative solutions of the pharmaceutical industry, especially in the field of the development of carriers for cosmetically active substances; it increasingly applies ingredients of natural origin and markets innovative cosmetic products, which very often provide consumers with more than usual care, hygiene and beautification.

Keywords*: innovation, pharmaceutical industry, cosmetics industry*

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FARMACEUTSKO-TEHNOLOŠKE INOVACIJE U FARMACEUTSKOJ I KOZMETIČKOJ INDUSTRIJI

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Farmaceutsku industriju karakteriše veoma dinamičan razvoj. Novi, originalni lekovi i njihov plasman na globalno tržište cilj su svih inovativnih farmaceutskih kompanija. Sa druge strane, intenzivno se radi na lekovitim supstancama koje su na tržištu dugi niz godina, kako bi se savremenim tehnološkim postupcima i/ili primenom novih ekscipijenasa i nosača, pronašli načini kreiranja novih lekova / lekovitih sistema sa poboljšanim karakteristikama, u odnosu na postojeće terapeutike. Evidentan je tehnološki i ekonomski razvoj inovativnih i generičkih kompanija, koje rade na kreiranju "pametnih" proizvoda i procesa proizvodnje, kako bi na tržište dospeli novi proizvodi u što kraćem vremenskom periodu, a koji su sve češće visoko individualizovani i odgovaraju potrebama pacijenta.

Kroz proces formulacije lekova, primenom inovativnih farmaceutsko-tehnoloških procesa, rešavaju se najčešće problemi slabe rastvorljivosti i nestabilnosti lekovitih supstanci, loše organoleptičke osobine, značajan metabolizam prvog prolaza, nespecifična biodistribucija, neželjena delovanja i interakcije sa različitim biomolekulima.

Primena nanotehnologije, pre svega nanoemulzija i nanočestica, koje su biokompatibilne, biodegradabilne, fizički stabilne, sa visokim solubilizacionim kapacitetom za lipofilne lekovite supstance i jednostavanim *scale up*-om, dovodi do povećanja biološke raspoloživosti, kontrolisanog oslobađanje i ciljne isporuke lekovitih supstanci u različite organe. Uvođenjem vezikularnih nosača lekova (liposomi, transfersomi, nanosomi, etosomi i invasomi) i formulisanjem terapijskih sistema u kojima je izvršeno uklapanje lekovitih supstanci u različite mikronosače i nanonosače, omogućeno je delotvornije lečenje mnogih bolesti, smanjenjem simptoma bolesti, ubrzanjem vremena oporavka, smanjenjem neželjenih dejstava i dugoročnih posledica lečenja, kao i komfornije lečenje i sledstveno bolja adherencija (komplijansa) korisnika.

Kozmetička industrija prati inovativna rešenja farmaceutske industrije, posebno na polju razvoja nosača za kozmetički aktivne supstance, sve više primenjuje sastojke prirodnog porekla i plasira na tržište inovativne kozmetičke proizvode, koji vrlo često pružaju potrošačima više od uobičajene nege, higijene i ulepšavanja.

Ključne reči: *inovacije, farmaceutska industrija,kKozmetička industrija*

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THE APPLICATION OF QUALITY BY DESIGN CONCEPT IN THE DEVELOPMENT OF MEDICINES

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The quality by design (QbD) concept is a modern approach in pharmaceutical drug development based on the identification and definition of quality target product profile (QTPP) using the existing scientific knowledge (International council for harmonisation – ICH Q8(R2), 2009) and risk analysis. It starts with defining the target quality profile of the product/medicine and continues with the consideration and identification of critical quality attributes (CQA). An advanced concept may further include identifying critical material attributes (CMA) and critical process parameters (CPP), as well as establishing functional relationships between these characteristics and critical product quality attributes. The combination and interaction of CMA and CPP provides the definition of a design space.

The final goal of QbD concept application in the pharmaceutical industry is the most efficient definition of the range of values of critical material attributes and process parameters whose application leads to a medicine with defined quality target profile. As the quality of a pharmaceutical product is determined by its stability, safety and efficacy, the application of this concept emphasizes patient safety and the identification of critical attributes that a medicine should have in order to be safe for use.

By applying the QbD concept, the medicine production process can be completely controlled so that the production of medicines/products of constant quality is ensured.

By applying this concept, the optimization of the pharmaceutical development process and a better understanding of the production process are achieved, which actually enables more efficient development of a pharmaceutical product of predefined quality. The quality by design concept is defined in the guidelines of the International Conference on Harmonization and provides risk management for the quality of the new medicine.

Keywords: *quality by design concept, critical attributes, pharmaceutical development*

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PRIMENA KONCEPTA DIZAJN KVALITETA U RAZVOJU LEKOVA

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Koncept dizajn kvaliteta (engl. *Quality by design* – QbD) predstavlja savremen pristup u farmaceutskom razvoju lekova, koji se bazira na identifikaciji i definiciji ciljanog profila kvaliteta proizvoda (engl. *Quality target product profile – QTPP*), korišćenjem postojećih naučnih saznanja (Internacionalnog saveta za harmonizaciju, engl. *International council for harmonisation* – ICH Q8(R2), 2009) i analizom rizika. Ovaj proces započinje definisanjem ciljanog profila kvaliteta proizvoda/leka, a nastavlja se razmatranjem i identifikovanjem kritičnih atributa njegovog kvaliteta (engl. *Critical quality attributes* – CQA). Unapređen koncept može dodatno da uključuje identifikovanje kritičnih atributa materijala (engl. *Critical material attributes* – CMA) i kritičnih procesnih parametara (engl. *Critical process parameters* – CPP), kao i utvrđivanje funkcionalnih veza između ovih karakteristika i kritičnih atributa kvaliteta proizvoda. Kombinacija i interakcija CMA i CPP obezbeđuje definisanje prostora dizajna (engl. *Design space*).

Krajnji cilj primene koncepta QbD u farmaceutskoj industriji je najefikasnije definisanje opsega vrednosti kritičnih atributa materijala i procesnih parametara, čijom se primenom dolazi do leka definisanog, ciljanog profila kvaliteta. Kako je kvalitet farmaceutskog proizvoda određen njegovom stabilnošću, bezbednošću i efikasnošću primenom ovog koncepta akcenat se stavlja na sigurnost pacijenata i identifikaciju kritičnih atributa, koje lek treba da poseduje kako bi bio bezbedan za upotrebu.

Primenom QbD koncepta proces proizvodnje leka može biti potpuno kontrolisan, čime se obezbeđuje proizvodnja lekova/proizvoda konstantnog kvaliteta.

Primenom ovog koncepta, postiže se optimizacija procesa farmaceutskog razvoja i bolje razumevanje proizvodnog procesa, što, zapravo, omogućava efikasniji razvoj farmaceutskog proizvoda, unapred definisanog kvaliteta. Koncept dizajn kvaliteta definisan je u skladu sa smernicama Internacionalne konferencije za harmonizaciju i obezbeđuje upravljanje rizikom za kvalitet novog leka.

Ključne reči: *koncept dizajn kvaliteta, kritični atributi, farmaceutski razvoj*

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SKIN AND COVID-19 PANDEMIC: THE PHARMACIST'S PERSPECTIVE

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Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus, in its hardest form, is followed by severe pneumonia, acute respiratory distress syndrome, septic shock and multiple organ failure. Although COVID-19 is present in a milder form more often, it affects many organs, including the skin, by dysregulating many areas of metabolism alongside the skin lipidome. Skin manifestations are numerous and could be a consequence of the disease itself, but also of the preventative measures taken to avoid the infection. A variant of acne, so called ''maskne'' (term coined during pandemic), is very common in general population and associated with personal protective equipment. Hygiene measures (hand sanitizer gels, hand washing) have been mandatory, and their use increased the frequency of associated skin disorders. Various exanthems and cutaneous findings are attributed to the viral infection itself, and also new manifestations of cutaneous eruptions have been reported. Dermatological adverse reactions to prescribed or to over-the-counter treatment regimens have been reported as well.
The COVID-19 pandemic has affected every area of life. The greatest challenge has been to adapt the functioning of the health service to prevent the spread of the epidemic and to help patients. This has required the involvement of not only doctors and nurses, but also pharmacists. Pharmacists are the most accessible sources of professional healthcare advice. Exploitation of the full potential of pharmacists for counseling patients in prevention, care and treatment of skin affected by the described disorders could aid the limited resources of overloaded healthcare systems in the era of COVID-19.
The goal of this work is to review current skin manifestations as consequences of the COVID-19 disease itself, but also as consequences of the preventative measures taken to avoid the infection from the pharmacist's perspective. The emphasis is on the position and role of pharmacist in prevention and management of skin disorders related to COVID-19 pandemic.

Keywords: *COVID-19, skin disorders, maskne, the role of pharmacist*

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KOŽA I PANDEMIJA VIRUSA COVID-19 IZ PERSPEKTIVE FARMACEUTA

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Korona virus COVID-*19 izaziva bolest* SARS-CoV-2 koju, u najtežem obliku, prate teška upala pluća, akutni respiratorni distres sindrom, septički šok i multiorganska insuficijencija. Iako češće prisutan u blažoj formi, COVID-19 utiče na mnoge organe uključujući kožu, dovodeći do poremećaja u metabolizmu, čime je često zahvaćen i lipidom kože. Kožne manifestacije su brojne i mogu biti posledica same bolesti, ali i preventivnih mera koje se preduzimaju da se infekcija spreči. Varijanta akni, takozvane „maskne“, (kovanica nastala tokom pandemije), veoma je česta u opštoj populaciji i povezana je sa zaštitnom opremom (maske). Primena pojačanih higijenskih mera (gelova za dezinfekciju i često pranje ruku) povećala je učestalost pridruženih poremećaja na koži. Različiti egzantemi pripisuju se, u poslednje vreme, samoj virusnoj infekciji, a prijavljuju se i nove manifestacije erupcija na koži, koje su u vezi sa virusom COVID-19. Takođe, prijavljuju se dermatološke neželjene reakcije na lekove, koji se koriste u lečenju bolesti koju ovaj virus izaziva.
Pandemija virusa COVID-19 uticala je na sve sfere života. Najveći izazov je prilagoditi funkcionisanje zdravstvenog sistema, kako bi se sprečilo širenje bolesti i pomoglo pacijentima. Ovo zahteva učešće svih zdravstvenih radnika, uključujući farmaceute. Farmaceut je najdostupniji zdravstveni profesionalac. Iskorišćenje punog potencijala farmaceuta u savetovanju pacijenata radi prevencije, nege i tretmana kože zahvaćenom opisanim poremećajima moglo bi pomoći ograničenim resursima preopterećenih zdravstvenih sistema u eri COVID-19 virusa.
Cilj ovog rada je sagledavanje uloge farmaceuta u prevenciji i tretmanu poremećaja kože koji su posledica pandemije COVID-19 virusa i preventivnih mera koje se preduzimaju da se infekcija spreči.

Ključne reči: *COVID-19, maskne, poremećaji kože, uloga farmaceuta*

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APPLICATION OF CELL CULTURES IN PHARMACY

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Cell cultures have a great application in various fields in pharmacy. The *in vitro* studies on cell cultures are indispensable in preclinical trials of drugs and medical devices but also in drug design and production. There are different cell models used for these purposes and the choice of an adequate model depends on the type of an agent being tested or produced as well as its potential application. Different cell models can be used such as classical 2D and more complex 3D cell models that mimic *in vivo* tissue microenvironment. Primary cell cultures as well as continuous cell cultures in a monoculture and co-culture systems give us an opportunity to analyze different effects of biologically active substances on one or more cell types as well as their interactions. Besides the application of cell cultures in testing of biologically active substances and biomaterials, cell cultures can be used for drug design and production since they are used as expression systems for the production of recombinant proteins using recombinant DNA technology. Recombinant proteins produced in this way may be used for preparation of drugs, vaccines and dermocosmetics. There are various cell models used for testing of cosmetic products and preparations intended for topical application, which is of great importance in the field of cosmetology due to very restricted use of *in vivo* models for these purposes. Great application of cell cultures is in the field of tissue engineering and regenerative medicine. For these purposes, mostly adult stem cells are used, alone or in combination with growth factors for cell therapy and in combination with biomaterials for *in vitro* artificial tissue and organ development which is of great importance for tissue and organ transplantation as well as obtaining adequate *in vitro* models that simulates corresponding *in vivo* conditions for drug testing.

Keywords: *cell cultures, in vitro, preclinical testing, biologically active substances, drug design, drug production*

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PRIMENA ĆELIJSKIH KULTURA U FARMACIJI

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Ćelijske kulture imaju veliku primenu u raznim oblastima farmacije. *In vitro* ispitivanja na ćelijskim kulturama nezamenljiva su u pretkliničkim ispitivanjima lekova i medicinskih sredstava, ali i u dizajnu i proizvodnji lekova. Postoje različiti modeli ćelija koji se koriste u ove svrhe, a izbor adekvatnog modela zavisi od vrste agensa koji se testira ili proizvodi, kao i od njegove potencijalne primene. Mogu se koristiti različiti modeli ćelija, kao što su klasični 2D i složeniji 3D ćelijski modeli, koji oponašaju mikrookruženje tkiva *in vivo*. Primarne ćelijske kulture, kao i kontinuirane ćelijske kulture u monokulturi i sistemi kokultura daju nam priliku da analiziramo različite efekte biološki aktivnih supstanci na jednom tipu ili više tipova ćelija, kao i da proučimo njihove interakcije. Pored primene ćelijskih kultura u ispitivanju biološki aktivnih supstanci i biomaterijala, ćelijske kulture mogu se koristiti za dizajn i proizvodnju lekova, budući da se koriste kao ekspresioni sistemi za proizvodnju rekombinantnih proteina, upotrebom tehnologije rekombinantne DNK. Ovako proizvedeni rekombinantni proteini mogu se koristiti za pripremu lekova, vakcina i kozmetičkih proizvoda. Postoje različiti ćelijski modeli koji se koriste za testiranje kozmetičkih proizvoda i preparata namenjenih za lokalnu primenu, što je od velikog značaja u oblasti kozmetologije, zbog veoma ograničene upotrebe *in vivo* modela u ove svrhe. Velika primena ćelijskih kultura u oblasti je tkivnog inženjerstva i regenerativne medicine. U ove svrhe, uglavnom se koriste adultne matične ćelije, same ili u kombinaciji sa faktorima rasta za ćelijsku terapiju i u kombinaciji sa biomaterijalima za *in vitro* kreiranje veštačkih tkiva i organa, što je od velikog značaja za transplantaciju tkiva i organa, kao i za dobijanje adekvatnih *in vitro* modela, koji simuliraju odgovarajuće *in vivo* uslove za potrebe testiranja lekova.

Ključne reči: *ćelijske kulture, in vitro, pretkliničko testiranje, biološki aktivne supstance, dizajniranje lekova, proizvodnja lekova*

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ETHICAL RULES, ETHICAL PRINCIPLES AND CODE OF ETHICS FOR SERBIAN PHARMACISTS: ANALYSIS OF CASES FROM PRACTICE

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Modern pharmaceutical practice in the pharmacy as a health institution implies care for the well-being of the patient, brings with it new types of professional expectations and obligations, which can produce serious conflicts and ethical dilemmas. The pharmacist is obliged to build an adequate ethical relationship with the user of the health service, and this especially refers to some questions that the pharmacist asks the patient during the communication process, as well as questions related to professional secrecy.

Ethical analysis of cases from the pharmaceutical practice was performed. The relationship between pharmacists and health care users is based not only on legal rules, but also on the rules of health ethics, which rely on each other and complement each other.

It is necessary to develop awareness of the difference between legal and ethical and to develop a sense of collective ethics that serves as a basis for determining right and wrong. It is necessary to integrate professional ethics into the collective ethics of pharmacy and to develop moral awareness and sensitivity to ethical problems in practice, i.e., learn how to recognize ethical dilemmas and how to solve them in real working conditions. For this reason, it is necessary to be aware of the existence of ethical rules and ethical principles that pharmacists must adhere to when interacting with the patient, as well as to possess knowledge of professional codes of ethics.

The practical application of ethical codes and principles is not always simple and successful, so pharmacists must sometimes review their personal value systems to ensure that their professional communication meets the needs of health care users, and that the outcomes of pharmaceutical health care are focused on maintaining and improving the quality of life of the patient.

Keywords: *ethical rules, ethical principles, Code of ethics for pharmacists, ethical analysis, application in practice*

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ETIČKA NAČELA, ETIČKI PRINCIPI I ETIČKI KODEKS FARMACEUTA SRBIJE: ANALIZA SLUČAJEVA IZ PRAKSE

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Savremena farmaceutska praksa u apoteci, kao i u zdravstvenoj ustanovi podrazumeva brigu za dobrobit pacijenta, što nosi sa sobom nove vrste profesionalnih očekivanja i obaveza, koje mogu proizvesti ozbiljne konflikte i etičke dileme. Farmaceut je dužan da izgradi adekvatan etički odnos sa korisnikom zdravstvene usluge, a ovo se naročito odnosi na neka pitanja koja farmaceut postavlja pacijentu tokom procesa komunikacije, kao i pitanja vezana za očuvanje profesionalne tajne.

Izvršena je etička analiza slučajeva iz farmaceutske prakse. Odnos između farmaceuta i korisnika zdravstvene usluge ne odvija se samo prema pravnim pravilima, nego i prema pravilima zdravstvene etike, koja se oslanjaju jedna na druge i međusobno dopunjuju.

Potrebno je razviti svest o postojanju razlike između zakonskog i etičkog i stvoriti osećaj kolektivne etike, koja služi kao osnova za određivanje ispravnog i pogrešnog. Neophodno je profesionalnu etiku integrisati u kolektivnu etiku apoteke i razviti moralnu svest i osetljivost na etičke probleme u praksi, tj. naučiti kako prepoznati etičke dileme i kako ih rešiti u realnim radnim uslovima. Iz tog razloga, neophodna je svesnost o postojanju etičkih načela i etičkih principa, kojih se farmaceuti moraju pridržavati u interakciji sa pacijentom i nepohodno je i poznavanje profesionalnih etičkih kodeksa.

Praktična primena etičkih kodeksa i principa nije uvek jednostavna i uspešna, pa farmaceuti moraju ponekad da preispitaju i svoje lične sisteme vrednosti kako bi bili sigurni da njihova profesionalna komunikacija zadovoljava potrebe korisnika zdravstvene usluge, te da su ishodi farmaceutske zdravstvene delatnosti usmereni na održanje i unapređenje kvaliteta života pacijenta.

Ključne reči: *etička načela, etički principi, etički kodeks farmaceuta, etička analiza, praktična primena*

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GALENIC PRODUCTION OF MEDICINES AND A POSSIBILITY OF ADAPTATION TO TODAY'S CHALLENGES

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Galen laboratories are designed to produce small batches of drugs according to the regulations of pharmacopoeias and master formulas with internal quality control, with the aim of more efficient and quick supply of patients with drugs that are not available as industrially produced ready-made drugs. Registered medicines do not always satisfy the needs of all patients, which highlights the importance of the knowledge and skills of pharmacists when preparing galenic medicines, general purpose preparations and magisterial medicines. The need for the production of galenic and magisterial medicines arises as a result of a limited selection of doses and strengths of medicinal substances in registered medicines or the absence of appropriate pharmaceutical forms, but also the absence of suitable combinations of two or more medicinal substances in the same form. Apart from these reasons, there is a great need for the development of formulations that exist in the production program of large pharmaceutical companies, because they offer patients these preparations on much more favorable terms with at least the same product quality. For the health system of every country, it is of great importance to create galenic and magisterial preparations as a substitute for certain registered medicines, to solve the problem of shortages, when possible, or to provide patients with the necessary medicines that cannot be produced in the pharmaceutical industry. Of particular importance is their social importance in emergency states emergency situations.

Keywords: *galenic drug, galenic laboratory, magisterial medicines, registered drug*

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GALENSKA IZRADA LEKOVA I MOGUĆNOST PRILAGOĐAVANJA IZAZOVIMA DANAŠNJICE

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Galenske laboratorije su osmišljene da proizvode male serije lekova po propisima farmakopeja i magistralnih formula sa internom kontrolom kvaliteta, a u cilju efikasnijeg i bržeg snabdevanja pacijenata lekovima koji nisu dostupni kao industrijski proizvedeni gotovi lekovi.
Registrovani lekovi ne zadovoljavaju uvek potrebe svih bolesnika, čime se ističe značaj znanja i veština farmaceuta prilikom izrade galenskih lekova, preparate opšte namene i magistralnih lekova. Potreba za izradom galenskih i magistralnih lekova nastaje kao rezultat ograničenog izbora doza i jačina lekovitih supstanci u registrovanim lekovima ili nepostojanja odgovarajućih farmaceutskih oblika, ali i nepostojanja odgovarajućih kombinacija dve ili više lekovitih supstanci u istom obliku. Osim ovih razloga, velika je potreba i za izradom formulacija koje postoje u proizvodnom programu velikih farmaceutskih kompanija, jer nude pacijentima ove preparate po mnogo povoljnijim uslovima uz najmanje isti kvalitet.
Za zdravstveni sistem svake zemlje od velikog je značaja da se izradom galenskih i magistralnih preparata, kao zamenom za određene registrovane lekove, reši problem nestašica, kada je to moguće, ili obezbede potrebni lekovi za bolesnike koji se ne mogu proizvoditi u farmaceutskoj industriji, a poseban značaj i šire društvenu važnost pokazuju u vanrednim stanjima i vanrednim situacijama.

Ključne reči: *galenski lek, galenska laboratorija, magistralni lek, registrovani lek.*

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FROM TRADITIONAL MEDICINE TO MODERN PHYTOTHERAPY

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The use of medicinal plants for the prevention and treatment of diseases and injuries in local communities around the world dates back to the dawn of mankind. Even today, they are used as the primary form of health care for approximately 80% of the world's population. Archeological studies have discovered that the plants have been used as drugs for about 60,000 years. Medicinal plants were originally used in their natural form, in whole or in part, and taken as such and as herbal teas. Their healing properties, but also their toxicity, became known gradually and developed over time. Over the centuries, this knowledge grew into folk medicine systems such as traditional Chinese medicine (TCM), Ayurveda, Kampo, traditional Arabic and Islamic medicine (TAIM) and traditional European medicine (TEM). The common denominator for all these systems is that they were based on experience. At the beginning of the nineteenth century, with the rapid development of analytical methods and phytochemistry, it was proven that chemical compounds in plants determined their healing properties. The development of phytochemistry has conditioned the development of modern phytotherapy. Today, phytotherapy combines centuries-old knowledge about the healing properties of the plants with the latest achievements in chemical, biological and clinical research. Modern phytotherapy is a scientifically proven medical practice, which is using plants and plant preparations for the treatment and prophylaxis of diseases or injuries according to recognized standards of quality, safety and efficacy.

Keywords: *traditional medicine, medicinal plants, modern phytotherapy, phytochemistry*

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OD TRADICIONALNE MEDICINE DO SAVREMENE FITOTERAPIJE

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Upotreba lekovitih biljnih vrsta za prevenciju i lečenje bolesti i povreda u lokalnim zajednicama širom sveta datira još od praskozorja čovečanstva. Lekovito bilje se i danas koristi kao primarni oblik zdravstvene zaštite kod približno 80% svetske populacije. Arheološka istraživanja otkrila su da su biljne vrste korišćene u lekovite svrhe oko 60.000 godina. Lekovite biljne vrste prvobitno su korišćene u svom prirodnom obliku, u celini ili njihovi delovi i uzimane ili kao takve ili kao čajevi. Njihova lekovitost, ali i toksičnost, upoznavane su postepeno i vremenom se to znanje razvijalo. Kroz vekove je ovo znanje stvorilo sisteme narodne medicine, kao što su tradicionalna kineska medicina (TCM), ajurveda, Kampo, tradicionalna arapska i islamska medicina (TAIM) i tradicionalna evropska medicina (TEM). Zajednički imenitelj za sve ove sisteme je zasnovanost na iskustvu. Početkom devetnaestog veka, brzim razvojem analitičkih metoda i fitohemije, dokazano je to da hemijska jedinjenja u biljkama određuju njihovu lekovitost. Razvoj fitohemije uslovio je razvoj savremene fitoterapije. Danas, fitoterapija spaja vekovna saznanja o lekovitosti biljnih vrsta sa najnovijim dostignućima hemijskih, bioloških i kliničkih istraživanja. Savremena fitoterapija naučno je dokazana medicinska praksa, koja koristi biljne vrste i biljne preparate za lečenje i profilaksu bolesti ili povreda, prema priznatim standardima kvaliteta, bezbednosti i efikasnosti.

Ključne reči: *tradicionalna medicina, lekovite biljne vrste, savremena fitoterapija, fitohemija.*

Zahvalnica: *Autor se zahvaljuje Ministarstvu prosvete, nauke i tehnološkog razvoja Republike Srbije (broj: 451-03-68/2022-14/200113) i Internom projektu Medicinskog fakulteta Univerziteta u Nišu, Srbija. (br. 68).*

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HERBAL MEDICINAL PRODUCTS WITH CLINICALLY PROVEN EFFICACY

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The use of plants for therapeutic purposes is as old as mankind. Phytotherapy (a treatment system based on the application of herbal medicinal products) nowadays belongs not only to pharmacotherapy and conventional medicine, but also to traditional (folk) medicine, and complementary and alternative medicine. Rational phytotherapy encompasses the treatment, alleviation, and prevention of diseases and health problems with herbal medicines (herbal medicinal products of scientifically and clinically proven therapeutic efficacy—evidence-based herbal medicines). The Committee on Herbal Medicinal Products of the European Medicines Agency publishes EU monographs on herbal medicinal substances, which comprise preclinical and clinical data on herbal medicinal products with well-established use, as well as data on traditional use. The number of herbal medicinal substances with clinically proved efficacy and safety (that is one more very important issue) is slowly but constantly growing. To market medicines with an active component of plant origin, both Serbia and the European Union offer three procedures for product registration—two for herbal medicines and one for traditional herbal medicines. The Agency for Medicines and Medical Devices of Serbia maintains the Herbal medicines and Traditional herbal medicines registers and controls the contents of the patient information leaflet for the medicines. An integral part of WHO Drug Global for the classification of products and substances is the HATC (Herbal ATC) system that classifies herbal medicines. Clinically proven efficacy of herbal medicinal products is the base for their rational application and rational phytotherapy. The patient information leaflet for the registered herbal medicine and traditional herbal medicine contains all relevant information (which, among other things, lists all the information on contraindications, precautions, known and confirmed adverse effects, and interactions). The application of registered herbal medicines constitutes a modern phytotherapeutic approach and a part of pharmacotherapy.

Keywords: *rational phytotherapy, evidence-based herbal medicines, the active component of plant origin, registers, HATC, patient information leaflet*

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BILJNI LEKOVITI PROIZVODI KLINIČKI DOKAZANE EFIKASNOSTI

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Upotreba biljaka u terapeutske svrhe stara je koliko i čovečanstvo. Fitoterapija (sistem lečenja zasnovan na primeni biljnih lekova) danas pripada ne samo farmakoterapiji i konvencionalnoj medicini, već i tradicionalnoj (narodnoj) medicini, te komplementarnoj i alternativnoj medicini. Racionalna fitoterapija obuhvata lečenje, ublažavanje i prevenciju bolesti i zdravstvenih tegoba biljnim lekovima (biljni lekovi naučno i klinički dokazane terapeutske efikasnosti – biljni lekovi zasnovani na dokazima).

Komitet za biljne lekovite proizvode Evropske agencije za lekove objavljuje monografije EU o biljnim lekovitim supstancama, koje obuhvataju pretkliničke i kliničke podatke o biljnim lekovitim proizvodima sa dobro potvrđenom upotrebom, kao i podatke o tradicionalnoj upotrebi. Broj biljnih lekovitih supstanci sa klinički dokazanom efikasnošću i bezbednošću (što je još jedno veoma važno pitanje) polako, ali stalno raste. Za plasiranje lekova sa aktivnom komponentom biljnog porekla i Srbija i Evropska unija nude tri procedure za registraciju proizvoda – dve za biljne lekove i jednu za tradicionalne biljne lekove. Agencija za lekove i medicinska sredstva Srbije vodi registre biljnih lekova i tradicionalnih biljnih lekova i kontroliše sadržaj uputstava za pacijente. Sastavni deo SZO *Drug Global* za klasifikaciju proizvoda i supstanci je *HATC* (*Herbal ATC*) sistem koji klasifikuje biljne lekove. Klinički dokazana efikasnost biljnih lekova je osnova za njihovu racionalnu primenu i racionalnu fitoterapiju. Uputstvo za pacijenta registrovanih biljnih i tradicionalnih biljnih lekova sadrži sve relevantne informacije (u kojima su, između ostalog, navedeni svi podaci o kontraindikacijama, merama opreza, poznatim i potvrđenim štetnim efektima i interakcijama).

Primena registrovanih biljnih lekova i tradicionalnih biljnih lekova predstavlja savremeni fitoterapeutski pristup i deo je farmakoterapije.

Ključne reči: *Racionalna fitoterapija, biljni lekovi zasnovani na dokazima, aktivna komponenta biljnog porekla, registri, HATC, uputstvo za pacijenta*

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FUNCTIONAL FOODS – CURRENT TRENDS AND CHALLENGES

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Functional food consists of biologically and physiologically active compounds and has beneficial health effects on humans in addition to its nutritional properties. Definitions of functional food have changed over the years, as has its division, and have varied depending on the regulatory body. Functional food is the concept that has been developed in response to chronic non-communicable disease mass morbidity, primarily in the countries that have used a diet rich in saturated fats and refined sugars. The awareness of healthy eating is very high in the 21st century and people are interested in preventing or slowing down the development of diseases before they become irreversible.

Functional food includes a wide range of products with different ingredients (nutrients and bioactive compounds) which affect many physiological functions of the organism and which are important in improving health and preventing the risk of developing diseases. This food is minimally processed, can be enriched, and when consumed regularly can have potentially beneficial effects on human health. These effects include a number of biological activities such as antioxidant, anti-inflammatory, immunomodulatory, osteoprotective, antihypertensive, prebiotic and many others. Some examples of functional foods are nuts, whole grains, garlic, oatmeal, eggs enriched with ω-3 fatty acids, yogurts with probiotic cultures, but also lactose-free milk and gluten-free bread.

Epidemiological studies have shown a positive correlation between the effect on health and the intake of foods rich in bioactive compounds, such as phenolic compounds, which include flavonoids, stilbenes, lignans, tannins, carotenoids, and many more. It is believed that the intake of these compounds can reduce the risk of diverse diseases, including Alzheimer's, cancer, cardiovascular, cataracts, diabetes and others.

The properties of functional foods and bioactive compounds during storage, as well as the digestion process itself and the presence of other nutrients can significantly limit bioactivity and expected benefits. Therefore, high bioavailability, maintaining the biological characteristics of bioactive compounds in food and ensuring safety are among the greatest challenges for researchers. Further research on this food is important and necessary.

Keywords: *functional food, bioactive compounds, nutrition, prevention, non-communicable diseases*

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FUNKCIONALNA HRANA – NOVINE I IZAZOVI

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Funkcionalna hrana se sastoji iz biološki i fiziološki aktivnih jedinjenja i pored nutritivnih osobina obezbeđuje povoljne zdravstvene efekte kod čoveka. Definicije funkcionalne hrane su se menjale tokom godina, kao i njena podela, i različite su u zavisnosti od zakonodavnog tela koje ih reguliše. Funkcionalna hrana predstavlja koncept koji se razvio kao posledica masovnog oboljevanja od hroničnih nezaraznih bolesti, prvenstveno u zemljama koje su koristile ishranu bogatu zasićenim mastima i rafinisanim šećerima. Svest o zdravoj ishrani je veoma velika u 21. veku i ljudi su zainteresovani da preveniraju ili uspore razvoj bolesti pre nego što one postanu ireverzibilne.

Funkcionalna hrana obuhvata širok spektar proizvoda sa različitim sastojcima (nutrijentima i bioaktivnim jedinjenjima), koje utiču na brojne fiziološke funkcije organizma i koji su značajni u zdravlju i sprečavaju rizik od razvoja bolesti. Ova hrana je minimalno prerađena, može biti obogaćena i kada se konzumira redovno može imati potencijalne povoljne efekte na ljudsko zdravlje. Ovi efekti uključuju brojne biološke aktivnosti kao što su antioksidativna, antiinflamatorna, imunomodulatorna, osteoprotektivna, antihipertenzivna, prebiotska i mnoge druge. Neki od primera funkcionalne hrane su orašasti plodovi, žitarice od celog zrna, beli luk, ovsena kaša, jaja obogaćena ω-3 masnim kiselinama, jogurt sa probiotskim kulturama, ali i mleko bez laktoze i hleb bez glutena.

Epidemiološka istraživanja su pokazala pozitivnu korelaciju između efekta na zdravlje i unosa hrane bogate bioaktivnim jedinjenjima, kao što su fenolna jedinjenja u koja se ubrajaju flavonoidi, stilbeni, lignani, tanini, karotenoidi i druga. Smatra se da unos ovih jedinjenja može smanjiti rizik od raznih bolesti, uključujući Alchajmerovu bolest, rak, kardiovaskularne bolesti, kataraktu, dijabetes i druge.

Osobine funkcionalne hrane i bioaktivnih jedinjenja tokom čuvanja, kao i sam proces varenja i prisustvo drugih hranljivih materija, mogu značajno da ograniče aktivnost i očekivane koristi. Zato su velika bioraspoloživost, održanje bioloških karakteristika bioaktivnih jedinjenja u hrani i obezbeđivanje sigurnosti jedni od najvećih izazova za istraživače. Dalja istraživanja ove hrane su značajna i potrebna.

Ključne reči: *funkcionalna hrana, bioaktivna jedinjenja, ishrana, prevencija, nezarazne bolesti.*

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NEW NATURAL ANTI-INFLAMMATORY AGENTS

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The incidence of diseases with inflammatory etiopathology is constantly increasing. Inflammation is a complex biological response of the vascular tissue caused by various harmful stimuli. Suppression of inflammation can help in delaying, preventing and controlling various chronic diseases such as cardio- and cerebrovascular ones, diseases of the joints, blood, lungs, liver, intestines, periodontitis, etc. Conventional anti-inflammatory drugs are used in the treatment of various forms of inflammation, but they also carry with them the risk of potential side effects, so in recent years the development of new anti-inflammatory drugs from natural sources has been intensively considered. Previous *in vivo* and *in vitro* studies have shown that anti-inflammatory effects of plants are most often achieved by inhibiting the expression of nuclear factor-κB, proinflammatory cytokines (e.g. tumor necrosis factor-α, interleukin-1β, interleukin-6), chemokines, intercellular adhesion molecules, proinflammatory mediators (e.g., inducible nitric oxide synthase, cyclooxygenase, lipoxygenase), etc. In recent years, in clinical trials, the modulation of inflammation using herbal products has been proven in patients with arthritis, gingivitis, stomatitis, dermatitis, colitis, asthma, cardiovascular disorders, diabetes, due to their effective phytocompounds such as various phenols, flavonoids, alkaloids, phenolic acids and polysaccharides, etc. Besides the well-known *Boswellia serrata* Roxb., *Salix* spp., *Curcuma longa* L., *Harpagophytum procumbens* (Burch.) DC. ex Meisn., *Chamomilla recutita* L., plant species with prominent anti-inflammatory effects in these studies are also *Zingiber officinale* Roscoe, *Borago officinalis* L., *Andrographis paniculata* (Burm.f.) Nees, *Oenothera biennis* L., *Rosa canina* L., *Quercus brantii* Lindl., *Tripterygium wilfordii* Hook. f., etc., while isolated phytocompounds such as curcumin, quercetin, resveratrol, epigallocatechin-3-gallate, bromelain and capasaicin have been shown to be effective agents. Research and development of natural products is breaking new ground in the prophylaxis and treatment of inflammatory diseases, so the significant therapeutic potential of such products should be used with proven efficacy and safety.

Keywords: *inflammation, medicinal plant species, natural compounds, clinical trials*

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NOVI PRIRODNI ANTIINFLAMATORNI AGENSI

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Incidencija bolesti sa inflamatornom etiopatologijom je u stalnom porastu. Inflamacija predstavlja složeni biološki odgovor vaskularnog tkiva koji nastaje usled različitih štetnih nadražaja. Suzbijanje inflamacije može pomoći u odlaganju, sprečavanju i kontroli raznih hroničnih bolesti kao što su kardio i cerebrovaskularne, bolesti zglobova, krvi, pluća, jetre, creva, parodontopatija, itd. Konvencionalni antiinflamatorni lekovi se koriste u tretmanu raznih formi inflamacija, ali nose sa sobom i rizik od potencijalnih neželjenih efekata, stoga se zadnjih godina intenzivno razmatra razvoj novih antiinflamatornih lekova iz prirodnih izvora. U dosadašnjim *in vivo* i *in vitro* studijama pokazano je da se antiinflamatorni efekti biljaka najčešće ostvaruju inhibicijom ekspresije nuklearnog faktora-κB, proinflamatornih citokina (npr. faktor nekroze tumora-α, interleukin-1β, interleukin-6), hemokina, intercelularnih adhezionih molekula, proinflamatornih medijatora (npr. inducibilna sintaza azot oksida, ciklookcigenaza, lipooksigenaza) itd. Poslednjih godina u kliničkim ispitivanjima modulacija inflamacije upotrebom biljnih proizvoda dokazana je kod pacijenata sa artritisom, gingivitisom, stomatitisom, dermatitisom, kolitisom, astmom, kardiovaskularnim poremećajima, dijabetesom, zahvaljujući svojim efikasnim fitojedinjenjima poput raznih fenola, flavonoida, alkaloida, polisaharida, masnih kiselina, terpenoida i dr. Biljne vrste sa istaknutim antiinflamatornim efektima u ovim istraživanjima su pored dobro poznatih *Boswellia serrata* Roxb., *Salix* spp., *Curcuma longa* L., *Harpagophytum procumbens* (Burch.) DC. ex Meisn., *Chamomilla recutita* L., zatim *Zingiber officinale* Roscoe, *Borago officinalis* L., *Andrographis paniculata* (Burm.f.) Nees, *Oenothera biennis* L., *Rosa canina* L., *Quercus brantii* Lindl., *Tripterygium wilfordii* Hook.f., i dr., a kao efikasni agensi pokazala su se i izolovana fitojedinjenja poput kurkumina, kvercetina, rezveratrola, epigalokatehin-3-galata, bromelina, kapasaicina. Istraživanja i razvoj lekovitih prirodnih proizvoida otvaraju novi put u profilaksi i terapiji inflamatornih bolesti, stoga treba iskoristiti njihov značajan terapijski potencijal uz dokazanu efikasnost i bezbednost.

Ključne reči: *inflamacija, lekovite biljne vrste, prirodna jedinjenja, kliničke studije*

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FROM FOOD TO HERBAL MEDICINAL PRODUCTS

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Ancient eating habits have always been health-oriented. Many plant species used for centuries today are of interest to scientific research in the field of pharmacy and medicine, due to the high content of bioactive compounds and the beneficial effect on human health. Plants and isolated active metabolites have played an important role in the development of new drugs and the discovery of innovative mechanisms of action. During the last century, modern science, as well as medical practice, have given too much importance to the use of synthetic drugs, while traditional medicine and therapy with medicinal herbs have been visibly neglected. In recent decades, the use of herbal medicinal products, herbal, and traditional herbal medicines, as well as herbal teas or dietary supplements, is constantly increasing. Herbal medicinal products are used both in the prevention and treatment of many diseases, as relatively safe and harmless therapeutic agents compared to synthetic drugs. The trend of returning to natural resources in nutrition and therapy is growing in all countries of the world and puts medicinal herbs in the focus of the scientific and professional public. The World Health Organization has recognized about 20,000 medicinal plants in the world, of which a higher percentage are those that have been used in the diet since ancient times. The use of plants with proven pharmacological properties in the form of the herbal medicinal product and dietary supplement, but also in a regular balanced diet could significantly contribute to the human health care system and reduce the incidence of many chronic diseases. An example is berries, which are the subject of modern scientific research precisely because of their nutritional value, and conducted preclinical and clinical studies confirm the pharmacological effects of these plant species and their pharmaceutical products. The principle "*Let food be your medicine and medicine be your food*", which was advocated by Hippocrates several centuries ago, is also today's current topic.

Keywords: *Herbal medicinal products, Herbal dietary supplements, Nutrition, Drug*

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OD HRANE DO BILJNIH LEKOVITIH PROIZVODA

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Drevne navike u ishrani oduvek su bile orjentisane ka zdravlju. Mnoge biljne vrste korišćene vekovima danas su predmet interesovanja naučnih istraživanja u oblasti farmacije i medicine, zbog visokog sadržaja bioaktivnih jedinjenja i povoljnog uticaja na zdravlje ljudi. Biljke i izolovani aktivni metaboliti imali su važnu ulogu u razvoju novih lekova i otkriću inovativnih mehanizama delovanja. Tokom prošlog veka savremena nauka kao i lekarska praksa veliki značaj dala je upotrebi sintetskih lekova, dok je tradicionalna medicina i lečenje lekovitim biljem bilo vidno zanemareno. Poslednjih decenija aktuelnost upotrebe biljnih lekovitih proizvoda, biljnih i tradicionalnih biljnih lekova, kao i čajeva i biljnih dijetetskih suplemenata, u stalnom je porastu. Biljni lekoviti proizvodi koriste se kako u prevenciji, tako i u terapiji mnogih bolesti, kao relativno bezbedna i neškodljiva terapijska sredstva u poređenju sa sintetskim lekovima. Trend povratka prirodnim resursima u ishrani i lečenju raste u svim zemljama sveta i stavlja lekovito bilje u fokus naučne i stručne javnosti. Svetska zdravstvena organizacija je u svetu prepoznala oko 20.000 lekovitih biljaka od kojih je veći procenat onih koje se od davnina koriste u ishrani. Upotreba biljaka sa potvrđenim farmakološkim svojstvima u formi biljnih lekovitih proizvoda i dodataka ishrani, ali i u redovnoj izbalansiranoj ishrani mogla bi znatno doprineti sistemu zdravstvene zaštite ljudi i smanjiti incidencu razvoja mnogih hroničnih bolesti. Kao primer može se navesti bobičasto voće koje je upravo zbog svojih nutritivnih karakteristika predmet savremenih naučnih istraživanja, a sprovedene pretkliničke i kliničke studije potvrđuju farmakološke efekte ovih biljnih vrsta i njihovih farmaceutskih proizvoda. Načelo „*Neka hrana bude tvoj lek i lek neka bude tvoja hrana*“, koje je pre više vekova zastupao Hipokrat aktuelna je tema današnjice.

Ključne reči: *Biljni lekoviti proizvodi, Biljni dijetetski suplementi, Ishrana, Lek*

Zahvalnica: *Ministarstvo prosvete, nauke i tehnološkog razvoja Republike Srbije (Br. 451-03-68/2022-14/200003 i 451-03-68/2022-14/200113) i Interni projekat Medicinskog fakulteta Univerziteta u Nišu, Srbija, br. 68.*

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NOVEL PSYCHOACTIVE SUBSTANCES: HEALTH AND ANALYTICAL CHALENGES

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The abuse of psychoactive substances has long been a major problem. In recent decades, novel psychoactive substances have emerged, which is a cause for concern. The term "new" does not refer to newly synthesized substances, but to substances that have recently appeared on the market. The main problem is that they are not illegal, so regulatory authorities in countries around the world are struggling to add the substances to the lists of illegal substances as soon as they appear in order to stop their distribution and consumption. When the manufacturer minimally changes the structure of a substance, a newly created psychoactive substance is legal. Thus, the number of these substances is constantly increasing, while their consumption is widespread throughout the world. New psychoactive substances are produced in illegal laboratories (clandestine labs). The synthesis products are not adequately purified mixtures of unknown substances. Due to the DarkNet and numerous head shops, it is extremely difficult to monitor distribution and sales. Physicians do not have sufficient experience in treating NPS overdoses. The constant change in composition makes overdose symptoms unpredictable. We also do not have relevant information on potential chronic toxicity, as well as carcinogenicity and genotoxicity, due to the short duration of observation and use. Detection and determination of new psychoactive substances in seizures and biological samples is a major challenge for analysts who are continuously working to develop and improve analytical methods. Because of all these problems, the collaboration of experts from many fields is required: physicians, pharmacists, chemists, lawyers, and criminologists. Today, they are involved in the Early Warning Advisory on New Psychoactive Substances established by the United Nations. The aim of this system is to monitor, share information, and educate about the risks, harmfulness, and emergence of new NPS.

Keywords: *NPS, analytics, toxicology, abuse*

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NOVE PSIHOAKTIVNE SUPSTANCE: ZDRAVSTVENI I ANALITIČKI IZAZOVI

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Problem zloupotrebe psihoaktivnih supstanci postoji od davnina, ali u poslednjim decenijama pojavile su se nove psihoaktivne supstance, koje predstavljaju razlog za zabrinutost. Termin "nove" se ne odnosi na novosintetisane supstance, već na supstance koje su odskoro na tržištu. Ove supstance imaju različite nazive: "legal highs", "bath salts", "designer drugs", "new uregulated drugs", "research chemicals", "herbal highs", "herbal incense", "plant food", klubske droge. Najveći problem predstavlja činjenica da ove droge nisu zabranjene, ali pravni sistemi država širom sveta se bore da ove supstance uključe u spiskove ilegalnih supstanci odmah po izlasku na tržište, kako bi se onemogućila njihova distribucija i primena. Ukoliko proizvođač unese i najmanju promenu u strukturu neke supstance, dobija se nova psihoaktivna supstanca koja je legalna, te njihov broj raste iz godine u godinu, a upotreba je raširena u svim delovima sveta. Nove psihoaktivne supstance se proizvode u ilegalnim laboratorijama, pri čemu se dobijaju smeše nepoznatog sastava i čistoće. Praćenje puteva distribucije i prodaje ovih supstanci je otežano zbog razvoja *DarkNet*-a i *Headshop*-ova. Klinička slika i efekti prilikom predoziranja ovim supstancama su nepredvidivi, zbog nedostatka iskustva kliničara i stalne promene sastava ovih supstanci. Takođe, imajući u vidu kratak period upotrebe, nisu poznate posledice i ozbiljnost hronične primene, eventualna karcinogenost i genotoksičnost. Detekcija i određivanje novih psihoaktivnih supstanci u zaplenama i biološkim uzorcima predstavljaju veliki izazov za analitičare, koji kontinuirano rade na razvoju i unapređenju analitičkih metoda. Zbog svih nabrojanih problema, postoji potreba za saradnjom stručnjaka iz brojnih oblasti: lekara, farmaceuta, hemičara, pravnika, kriminologa. Oni su danas uključeni u Sistem ranog upozoravanja na Nove psihoaktivne supstance, organizovanog od strane Ujedinjenih nacija. Cilj ovog Sistema su monitoring, razmena informacija i edukacija o rizicima, štetnosti i pojavi novih NPS.

Ključne reči: *NPS, analitika, toksikologija, zloupotreba*

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DRUG DEVELOPMENT BASED ON THE INHIBITION OF MEDICALLY IMPORTANT ENZYMES

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Enzyme inhibition is one way to regulate enzyme activity, both under natural and experimental conditions. Most medicines work by inhibiting a specific enzyme. Some of the medically important enzymes are xanthine oxidase (XO), deoxyribonuclease I (DNase I), dipeptidyl peptidase-4 (DPP-4) and 5-lipoxygenase (5-LO). XO catalyzes the oxidative hydroxylation of hypoxanthine and xanthine to uric acid in purine catabolism. XO inhibitors have significant applications in the treatment of gout and other hyperuricemia-associated conditions. Allopurinol and febuxostat are relatively effective XO inhibitors, approved by the FDA for the treatment of gout, but have limited therapeutic use due to side effects. One of the approved, structurally innovative, XO inhibitors is topiroxostat. DNase I degrades DNA giving primarily 5'-oligonucleotides as final products. Playing a fundamental role in DNA degradation during apoptosis, DNase I might be involved in the development of many diseases (cardiovascular, neurodegenerative, autoimmune...) caused by excessive cell death. DNase I inhibitors represent an attractive potential target for the design of alternative strategies for the treatment of such pathological conditions. DPP-4 is a target macromolecule in the treatment of diabetes. This enzyme breaks down incretin hormones (glucagon-like peptide-1 and gastric inhibitory polypeptide) which, by increasing insulin release and decreasing glucagon release, lower blood glucose levels. Numerous structurally diverse DPP-4 inhibitors have been found, and some have been approved for the treatment of diabetes (sitagliptin, vildagliptin, saxagliptin...). 5-LO participates in the production of leukotrienes, arachidonic acid metabolites which directly affect the development of inflammatory reactions associated with numerous pathophysiological conditions, including asthma, allergies, cardiovascular and autoimmune disorders. 5-LO is therefore considered a potential target against inflammatory diseases. Zileuton is currently the only 5-LO inhibitor approved by the FDA for the treatment of asthma, while several inhibitors are in the clinical trial phase. All the above indicates the importance of discovering and developing new effective inhibitors of the described enzymes.

Keywords: *enzyme inhibition, xanthine oxidase, deoxyribonuclease I, dipeptidyl peptidase-4, 5-lipoxygenase*

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RAZVOJ LEKOVA NA BAZI INHIBICIJE MEDICINSKI ZNAČAJNIH ENZIMA

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Inhibicija enzima je jedan od načina kojim se reguliše aktivnost enzima, kako u prirodnim, tako i u eksperimentalnim uslovima. Većina lekova funkcioniše inhibiranjem specifičnog enzima. Neki od medicinski značajnih enzima su ksantin oksidaza (KO), dezoksiribonukleaza I (DNaza I), dipeptidil peptidaza-4 (DPP-4) i 5-lipoksigenaza (5-LO). KO učestvuje u metabolizmu purina katalizujući oksidativnu hidroksilaciju hipoksantina i ksantina do mokraćne kiseline. Inhibitori KO imaju značajnu primenu u prevenciji i terapiji gihta i drugih stanja povezanih sa hiperurikemijom. Alopurinol i febuksostat su relativno efikasni inhibitori KO, odobreni od strane FDA za lečenje gihta. Međutim, usled neželjenih efekata njihova terapijska primena je ograničena. Jedan od odobrenih, strukturno inovativnih, inhibitora KO je topiroksostat. DNaza I razlaže DNK pri čemu kao finalni proizvodi prvenstveno nastaju 5'-oligonukleotidi. DNaza I je jedna od glavnih nukleaza odgovornih za degradaciju DNK tokom apoptoze, pa može imati ključnu ulogu u razvoju mnogih bolesti (kardiovaskularnih, neurodegenerativnih, autoimunih...) uzrokovanih prekomernom smrću ćelija. Inhibitori DNaze I predstavljaju atraktivnu potencijalnu metu za dizajn alternativnih strategija za prevenciju i/ili terapiju ovakvih patoloških stanja. DPP-4 je ciljni makromolekul u terapiji dijabetesa. Ovaj enzim razgrađuje inkretin hormone (glukagonu sličan peptid-1 i gastrični inhibitorni polipeptid) koji, povećavajući oslobađanje insulina i smanjujući oslobađanje glukagona, smanjuju nivo glukoze u krvi. Pronađeni su brojni strukturno različiti inhibitori DPP-4 od kojih su neki i odobreni za primenu u terapiji dijabetesa (sitagliptin, vildagliptin, saksagliptin...). 5-LO učestvuje u proizvodnji leukotriena, metabolita arahidonske kiseline, pod čijim direktnim uticajem dolazi do razvoja reakcije inflamacije koja je povezana sa brojnim patofiziološkim stanjima, poput astme, alergije, kardiovaskularnih i autoimunih poremećaja. Stoga se 5-LO smatra potencijalnim targetom u borbi protiv inflamatornih bolesti. Zileuton je trenutno jedini inhibitor 5-LO odobren od strane FDA za lečenje astme, dok je nekoliko inhibitora u fazi kliničkog ispitivanja. Sve navedeno ukazuje na značaj otkrivanja i razvoja novih efikasnih inhibitora opisanih enzima.

Ključne reči: *Inhibicija enzima, Ksantin oksidaza, Dezoksiribonukleaza I, Dipeptidil peptidaza-4, 5-Lipoksigenaza*

Zahvalnica: *Ovaj rad je podržan od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije (broj granta: 451-03-68/2022-14/200113).*

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APPLICATION, IMPORTANCE AND ANALYSIS OF VITAMINS IN MODERN PHARMACY AND COSMETOLOGY

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Vitamins are micronutrients necessary for many chemical reactions. They are important compounds in maintaining the health and proper functioning of the human body. Dietary supplements are an area of the pharmaceutical industry in intensive growth. The reasons for that are the loss of consumer confidence in processed food products, the aging population, as well as the growing trend in health care and disease prevention. Awareness of the use of vitamin supplements has increased especially due to the Covid-19 pandemic. In recent years, the market has been crowded with many multivitamin products whose role is to compensate for the lack of vitamins in the daily diet or increase their intake in special conditions (diseases, pregnancy, breastfeeding, intensive training). In the field of regulation, dietary supplements are between food and drugs, so products of very different quality can appear on the market. In recent years, the use of vitamins in cosmetics has become widespread. They are used as antioxidants to protect skin from damage by UV radiation, maintain skin moisture and health, prevent skin aging and as anti-inflammatory agents. Formulations containing a combination of several vitamins are especially attractive to customers.

For the quality control of these products, it is important to develop and introduce modern, highly selective instrumental analytical methods for the simultaneous determination of vitamins. In our work, the content of liposoluble and hydrosoluble vitamins was determined by the liquid chromatography technique (HPLC) in pharmaceutical and cosmetic products, infant formulas, as well as in plant extracts used in the production of cosmetic preparations. Solid-phase extraction (SPE) or saponification method was used to prepare the samples. HPLC methods in combination with the SPE extraction technique have been developed for the analysis of vitamins E, A, D, beta-carotene, B1, B2 and pantothenic acid in commercial products. The analyses of pharmaceutical and cosmetic preparations for the content of vitamins have confirmed the appropriate quality of the products represented in our pharmacies.

Keywords: *vitamins, HPLC analysis, dietary supplements, pharmaceuticals, cosmetics*

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PRIMENA, ZNAČAJ I ANALITIKA VITAMINA U SAVREMENOJ FARMACIJI I KOZMETOLOGIJI

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Vitamini, kao mikronutrienti neophodni za odigravanje mnogih hemijskih reakcija, predstavljaju značajnu komponentu u održavanju zdravlja i pravilnog funkcionisanja ljudskog organizma. Dijetetski suplementi čine oblast farmaceutske industrije koja je u intenzivnom usponu. Razlozi za to su gubitak poverenja potrošača u savremene, prerađene prehrambene proizvode, sve starija populacija, kao i rastući trend brige o zdravlju i prevenciji bolesti. Svest o upotrebi vitaminskih suplemenata je naročito porasla usled pandemije *Covid-19*. Poslednjih godina tržište je preplavljeno raznovrsnim multivitaminskim preparatima, čija je uloga da nadoknade nedostatak vitamina u dnevnoj ishrani ili povećaju njihov unos u posebnim stanjima organizma (bolesti, trudnoća, dojenje, intenzivni treninzi). Dijetetski suplementi su u oblasti regulative između hrane i lekova, pa se na tržištu mogu za istu vrstu suplemenata pojaviti proizvodi vrlo različitog kvaliteta. Poslednjih godina je raširena upotreba vitamina i u kozmetici, a koriste se kao antioksidansi, za zaštitu kože od oštećenja UV zracima, za održavanje vlažnosti i zdravlja kože, za prevenciju starenja kože (*anti-age* preparati) i kao antiinflamatorna sredstva. U kozmetičkoj industriji posebno su aktuelne formulacije koje sadrže kombinaciju više različitih vitamina.

Za kontrolu kvaliteta ovih proizvoda važan je razvoj i uvođenje savremenih, visoko selektivnih instrumentalnih analitičkih metoda za simultano određivanje vitamina. U našem radu, sadržaj liposolubilnih i hidrosolubilnih vitamina je određivan tehnikom tečne hromatografije (HPLC) u farmaceutskim i kozmetičkim proizvodima, infant formulama, kao i biljnim ekstraktima koji su korišćeni u izradi kozmetičkih preparata. Za pripremu uzoraka je primenjena ekstrakcija na čvrstoj fazi (*SPE*) ili metoda saponifikacije. Razvijene su nove i poboljšane postojeće *HPLC* metode u kombinaciji sa *SPE* ekstrakcionom tehnikom za analizu vitamina E, A, D, beta-karotena, B1, B2 i pantotenske kiseline u komercijalnim proizvodima. Ispitivanja farmaceutskih i kozmetičkih preparata na sadržaj vitamina su pokazala odgovarajući kvalitet proizvoda zastupljenih u našim apotekama.

Ključne reči: *vitamini, HPLC analiza, dijetetski suplementi, farmaceutski proizvodi, kozmetički proizvodi*

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MODERN USE AND BIOLOGICAL ACTIVITY OF PLANTS FROM APIACEAE FAMILY

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The Apiaceae family is represented with approximately 2,850 species grouped into 480 taxa. Because of the abundance of essential oil, the species from this family are widely used for many purposes: in nutrition (carrot - *Daucus carota* L., celery - *Apium graveolens* L., parsnip - *Pastinaca sativa* L., parsley - *Petroselinum crispum* (Mill.) Fuss), as spices (dill - *Anethum graveolens* L., lovage - *Levisticum officinale* Koch), drugs (caraway - *Carum carvi* L., aniseed - *Pimpinella anisum* L., coriander - *Coriandrum sativum* L., fennel - *Foeniculum vulgare* Mill.) or poisons (hemlock - *Conium maculatum* L., cowbane - *Cicuta virosa* L.). Contemporary researches indicate that essential oils and extracts obtained from plants that belong to the Apiaceae family show antimicrobial, antioxidant, and cytotoxic activity. The significant content of phenols and flavonoids is recorded even in the species from the territory of Serbia: *Cachrys cristata* DC. - spiny basil, *Eryngium serbicum* Pančić - Serbian eryngo, *Heracleum sphondylium* L. - cow parsnip, *Opopanax hispidus* (Friv.) Griseb., *Peucedanum officinale* L. - hog's fennel and *Tordylium maximum* L. - hartwort. It is confirmed that there is a correlation between the plant composition and biological activity.
Numerous studies confirm that secondary metabolites of plants from the Apiaceae family manifest significant biological activities. In order to use their full potential for the development of new pharmaceutical, cosmetic and nutritional formulations, it is necessary to analyse in more detail their efficiency and safety.

Keywords: *Apiaceae, chemical composition, antimicrobial activity, antioxidant activity*

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SAVREMENA UPOTREBA I BIOLOŠKA AKTIVNOST PREDSTAVNIKA FAMILIJE APIACEAE

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Familija *Apiaceae* zastupljena je sa približno 2850 vrsta grupisanih u 420 rodova. Zbog bogatstva etarskim uljem vrste koje pripadaju ovoj familiji koriste se u širokom opsegu: kao hrana (šargarepa - *Daucus carota* L., celer - *Apium graveolens* L., paškanat - *Pastinaca sativa* L., peršun - *Petroselinum crispum* (Mill.) Fuss), začini (mirođija - *Anethum graveolens* L., selen - *Levisticum officinale* Koch), lekovi (kim - *Carum carvi* L., anis - *Pimpinella anisum* L., korijander - *Coriandrum sativum* L., morač - *Foeniculum vulgare* Mill.) ili otrovi (velika kukuta - *Conium maculatum* L., barska kukuta - *Cicuta virosa* L.). Savremena istraživanja ukazuju da etarska ulja i ekstrakti dobijeni iz biljaka koje pripadaju familiji *Apiaceae* pokazuju antimikrobnu, antioksidativnu i citotoksičnu aktivnost. Značajan sadržaj ukupnih fenola i flavonoida zabeležen je i kod vrsta koje rastu na teritoriji Srbije: *Cachrys cristata* DC. - krestasti kahris, *Eryngium serbicum* Pančić- srpski kotrljan, *Heracleum sphondylium* L. - mečja šapa, *Opopanax hispidus* (Friv.) Griseb., *Peucedanum officinale* L. - siljevina i *Tordylium maximum* L. - vrtovilje. Dokazano je da postoji korelacija između hemijskog sastava i njihove biološke aktivnosti.

Brojna istraživanja ukazuju da sekundarni metaboliti biljaka iz familije *Apiaceae* ispoljavaju značajne biološke aktivnosti. Kako bi se iskoristio njihov potencijal za razvoj novih farmaceutskih, kozmetičkih i nutritivnih formulacija, neophodno je detaljnije ispitati njihovu efikasnost i bezbednost.

Ključne reči: *Apiaceae, Hemijski sastav, Antimikrobna aktivnost, Antioksidativna aktivnost.*

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PHARMACEUTICAL HEALTH SERVICES IN PHARMACIES – HOW TO ACHIEVE OPTIMAL OUTCOMES OF THERAPY WITH A FOCUS ON THE INDIVIDUAL NEEDS OF PATIENTS

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The aging population, the negative consequences of accelerated technological progress, new threats to human health, high patient expectations and demands for greater savings in health budgets are contributing to great pressure on health systems. This requires changing health systems and adapting to new needs. One of the solutions for relieving such a stressful health care system is the introduction and development of certain health care services both vertically and horizontally through the health care system. This is especially true for parts of the system that are insufficiently recognized and integrated as places that can highly meet the health care needs of the population. Public pharmacies are certainly one of those places where the integration processes (legal, market, social) have begun, which have enabled the pharmaceutical health care service to become more visible, and more and more purposeful for the users. The aim of this paper is to show the possibility of applying the services of pharmacy in the conditions of public pharmacies, as well as the role of the pharmacist in providing these services. However, significant capacity in terms of new advanced pharmaceutical services available and standardized in a large number of countries such as: therapy review, drug delivery service, chronic disease management therapy (diabetes, hypertension, asthma), pharmacy vaccination services, withdrawal from smoking, screening and testing remained unused. These services require not only a change in the traditional role of pharmacists in the development and dispensing of drugs, but also, through the concept of pharmaceutical health care, transformation into a pharmacist who, with new knowledge and skills, can optimize drug use, promote health and participate in disease prevention activities.

Keywords: *pharmacist, pharmaceutical care, community pharmacy, pharmaceutical services, medicines use review*

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USLUGE FARMACEUTSKE ZDRAVSTVENE ZAŠTITE U APOTEKAMA – KAKO OSTVARITI OPTIMALNE ISHODE TERAPIJE SA FOKUSOM NA INDIVIDUALNE POTREBE PACIJENATA

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Starenje populacije, negativne posledice ubrzanog tehnološkog napretka, nove pretnje po zdravlje ljudi, velika očekivanja pacijenata i zahtevi za veće uštede u budžetima za zdravstvo doprinose velikom pritisku na zdravstvene sisteme. To zahteva menjanje zdravstvenih sistema i prilagođavanje novim potrebama. Jedno od rešenja za rasterećenje ovako napregnutog zdravstvenog sistema jeste uvođenje i razvoj određenih zdravstvenih usluga kako vertikalno, tako i horizontalno, kroz sistem zdravstvene zaštite. Posebno se to odnosi na delove sistema koji su nedovoljno prepoznati i integrisani kao mesta koja mogu u visokom stepenu zadovoljiti potrebe za zdravstvenom zaštitom stanovništva. Apoteke primarne zdravstvene zaštite su svakako jedno od takvih mesta u kojima su započeti procesi integracije (pravne, tržišne, društvene) koji su omogućili da usluga farmaceutske zdravstvene zaštite postane vidljivija, a korisnicima svrsishodnija. Cilj ovog rada je da pokaže mogućnost primene usluga farmacije u apotekama primarne zdravstvene zaštite, kao i ulogu farmaceuta u pružanju tih usluga. Međutim, značajan kapacitet u pogledu novih naprednih farmaceutskih usluga koje su dostupne i standardizovane u velikom broju zemalja poput: pregleda terapije, usluga uvođenja novog leka u terapiju, upravljanje terapijom za hronične bolesti (dijabetes, hipertenzija, astma), usluga vakcinacije u apotekama, odvikavanje od pušenja, skrining i testiranja, ostao je neiskorišćen. Ove usluge zahtevaju ne samo promenu tradicionalne uloge farmaceuta koja se odnosi na izradu i izdavanje leka, već i preko koncepta farmaceutske zdravstvene zaštite, transformaciju u farmaceuta koji će uz pomoć novih znanja i veština moći da optimizuje upotrebu lekova, promoviše zdravlje i učestvuje u aktivnostima za prevenciju bolesti.

Ključne reči: *farmaceut, farmaceutska zdravstvena zaštita, apoteka, farmaceutske usluge, individualni pregled terapije*

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PLACE OF COMMUNITY PHARMACY IN CONDUCTING PROFESSIONAL STUDENT PRACTICE

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The intensive changes that have taken place in the last few decades in modern pharmaceutical practice are also reflected in the education of pharmacists. Integrated academic studies in Pharmacy should provide the acquisition of knowledge, skills and abilities required to achieve the function of "a seven-star health professional". Accordingly, learning based on experience in a real work environment is a very important and indispensable form of teaching in the education of pharmacy students. This type of learning gives students the opportunity to be involved in real professional activities (in an environment that offers enough opportunities for learning), development of critical thinking and problem-solving skills, improving communication skills and teamwork. A professional student practice is a form of teaching activity that relies on practical work with students in order to generate competent pharmacists. In the implementation of professional student practice, in addition to teachers from the faculty, there are also the mentors from practice who conduct supervision, support and assessment of progress. In this way, learning based on experience in community pharmacy as a real work environment is enabled and represents an irreplaceable part of the education of every future pharmacist. The mentors from practice in community pharmacies enable students to apply, improve and enhance the knowledge and skills that the student has acquired while studying, but also to acquire new knowledge and responsibilities. Accordingly, the community pharmacy has an important place in the implementation of professional student practice and ensuring the quality of the teaching process in a real work environment.

Keywords: *community pharmacy, mentor, professional student practice*

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MESTO JAVNE APOTEKE U SPROVOĐENJU STRUČNE STUDENTSKE PRAKSE

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Intenzivne promene koje se u poslednjih nekoliko decenija dešavaju u savremenoj farmaceutskoj praksi odražavaju se i na obrazovanje farmaceuta. Integrisane akademske studije farmacije treba da obezbede sticanje znanja, veština i sposobnosti koje su potrebne za dostizanje funkcije "zdravstvenog profesionalca sa sedam zvezdica". U skladu sa tim, učenje zasnovano na iskustvu u realnom radnom okruženju predstavlja vrlo važan i neizostavan vid nastave u obrazovanju studenata farmacije. Ovakav vid učenja studentima pruža mogućnost da budu uključeni u realne profesionalne aktivnosti (u okruženju koje nudi dovoljno mogućnosti za učenje), razvoj kritičkog načina razmišljanja i sposobnosti za rešavanje problema, unapređenje veština komunikacije i timski rad. Stručna studentska praksa predstavlja oblik nastavne aktivnosti koji se oslanja na praktični rad sa studentima u cilju generisanja kompetentnih farmaceuta. U sprovođenju stručne studentske prakse, pored nastavnika sa fakulteta, učestvuju i mentori iz prakse koji sprovode nadzor, podršku i procenu napredovanja. Na ovaj način omogućeno je učenje zasnovano na iskustvu u javnoj apoteci kao realnom radnom okruženju i predstavlja nezamenljiv deo obrazovanja svakog budućeg farmaceuta. Mentori iz prakse u javnim apotekama omogućavaju studentima primenu, usavršavanje i unapređenje znanja i veština koje je student stekao tokom studiranja, ali i sticanje novih znanja i odgovornosti. U skladu sa tim, javna apoteka ima važno mesto u sprovođenju stručne studentske prakse i obezbeđenju kvaliteta nastavnog procesa u realnom radnom okruženju.

Ključne reči: *javna apoteka, mentor, stručna studentska praksa*

POSTER PRESENTATION

POSTER PREZENTACIJE

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CHEMICAL CHARACTERIZATION OF WATER EXTRACTS OF *VERBASCUM* SPECIES

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Verbascum species are known for numerous biological activities, such as anti-inflammatory, antimicrobial, and antioxidant effects, they act as immunostimulants and cytotoxic agents, and have beneficial effects on wound healing. A large number of activities is a consequence of the rich phytochemical composition.

Our study aimed to determine the secondary metabolites of water extracts of *Verbascum niveum* and *Verbascum speciosum*. The plant material was collected in the vicinity of Bosilegrad, and the extracts were prepared using the percolation method. Reversed phase HPLC coupled to diode array detector (DAD) was used for identification and quantification. Identification of all components was performed using standards, and chromatograms were recorded under the same conditions. According to our results, all extracts are rich in iridoids (the catalpol content was higher than the aucubin content), while the phenylethanoid glycoside verbascoside was detected in a measurable quantity only in the leaf extract of *V. niveum*. The flavonoid luteolin-7-*O*-glucoside was detected in the leaf extracts of both species, while a smaller amount of apigenin-7-*O*-glucoside was detected in the flower extract of *V. niveum*. All extracts contain significant amounts of *p*-hydroxybenzoic acid and gallic acid; flower extracts of both species also contain significant amounts of protocatechuic acid.

HPLC analysis showed that the extracts of both flowers and leaves of both tested *Verbascum* species contain a large number of secondary metabolites, so further studies of pharmacological activities are justified.

Keywords: *V. niveum, V. speciosum, HPLC, secondary metabolites*

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HEMIJSKA KARAKTERIZACIJA VODENIH EKSTRAKATA VRSTA *VERBASCUM*

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Vrste iz roda *Verbascum* poznate su po brojnim biološkim aktivnostima, poput: antiinflamatornog, antimikrobnog i antioksidativnog efekta, deluju kao imunostimulansi i citotoksični agensi, a ispoljavaju povoljne efekte i na zarastanje rana. Ovako veliki broj aktivnosti posledica je bogatog fitohemijskog sastava.

Cilj našeg ispitivanja bio je određivanje sekundarnih metabolita vodenih ekstrakata vrsta *Verbascum niveum* i *Verbascum speciou*s. Biljni materijal je prikupljen u okolini Bosilegrada, a ekstrakti su pripremljeni metodom perkolacije. Za identifikaciju i kvantifikaciju korišćena je *HPLC* reverzne faze spojena sa detektorom s nizom dioda (*DAD*). Identifikacija svih jedinjenja je izvršena korišćenjem standarda, a hromatogrami su snimani pod istim uslovima. Prema našim rezultatima, ekstrakti obe vrste su bogati iridoidima (sadržaj katalpola je bio veći od sadržaja aukubina), dok je feniletanoidni glikozid verbaskozid u merljivoj količini detektovan samo u ekstraktu lista vrste *V. niveum*. U ekstraktima listova obe vrste detektovan je flavonoid luteolin-7-*O*-glikozid, dok je u ekstraktu cvetova *V. niveum* detektovana manja količina apigenin-7-*O*-glukozida. Svi ekstrakti sadrže značajne količine galne kiseline i *p*-hidroksibenzoeve kiseline, a ekstrakti cvetova obe vrste i značajne količine protokatehinske kiseline.

HPLC analiza pokazala je da ekstrakti i cvetova i listova obe ispitivane *Verbascum* vrste sadrže veliki broj sekundarnih metabolita pa su dalja ispitivanja farmakoloških aktivnosti opravdana.

Ključne reči: *V. niveum, V. speciosum, HPLC, sekundarni metaboliti*

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DRUG POISONING PATTERN IN SOUTHEAST SERBIA - TWO YEARS EVALUATION

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WHO reports estimate drug poisoning as one of the most common causes of increased morbidity and mortality rates worldwide. Epidemiological data on this important health issue are scarce in southeast Serbia, so the study aimed to identify patterns of drug intoxication in this area. This cross-sectional study was conducted in Niš, the center of southeast Serbia, which has a population of nearly 2 million inhabitants. The data (gender and age of patients, identified substances in samples from the Clinical Centre Niš) were extracted from records available at the Institute of Forensic Medicine. The monitored period was from March 2020 to March 2022. Results were evaluated using Excel 2010. Drug poisonings were reported in 323 cases (74.25%), which is consistent with results published in 2018 by the National Centre for Poisoning Control of the Military Medical Academy in Belgrade (69.20%). A maximum number of cases was observed in the age groups 12–19 (25%) followed by 36–43 (15.80%). Female poisoning predominance (57.58%) was observed in all groups. Multiple substance poisoning was reported in 78.64% of cases. Sedatives (30.63%) were the predominant drug class, followed by antiepileptics (19.97%), analgesics (13.63%) and antidepressants (11.20%). Intoxications with atypical antipsychotic drug aripiprazole and new antiepileptic drugs topiramate and levetiracetam were reported for the first time in this laboratory. A high prevalence of pregabalin intoxications was also observed (12.38%). These results emphasize the importance of awareness about young women's mental health. Prescribing sedatives should always be carefully considered, as this class of drugs is the most common in poisonings. Clinicians and toxicologists must be up to date with newly registered drugs, to be able to detect and treat possible poisonings.

Keywords: *poisoning, toxicology, drugs, evaluation, Serbia*

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TROVANJA LEKOVIMA NA JUGOISTOKU SRBIJE – DVOGODIŠNJA EVALUACIJA

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Svetska zdravstvena organizacija navodi da je trovanje lekovima jedan od najčešćih razloga povećanog mortaliteta i morbiditeta širom sveta. Ne postoje aktuelni epidemiološki podaci o ovom važnom pitanju na jugoistoku Srbije, te je cilj ove studije bilo utvrđivanje obrazaca trovanja lekovima na ovom području. Studija preseka je sprovedena u Nisu, centru jugoistočne Srbije, gde živi oko dva miliona stanovnika. Korišćeni su podaci Zavoda za sudsku medicinu, koji se odnose na pol i godište pacijenata, kao i dokazane supstance u uzorcima poslatim iz Kliničkog centra Niš, u periodu od marta 2020. do marta 2022. godine. Rezultati su obrađeni u programu Excel 2010. Trovanja lekovima su dokazana u 323 slučaja (74,25%), što je u skladu sa podacima godišnjaka Nacionalnog centra za kontrolu trovanja Vojnomedicinske akademije u Beogradu iz 2018. godine (69,20%). Najveći broj trovanja je zabeležen u populacijama 12 – 19 godina (25%) i 36 – 43 godine (15,80%). Zabeležena su predominantno trovanja u ženskoj populaciji (57,58%) u svim starosnim grupama. Multi trovanja su dokazana u 78,64% slučajeva. U najvećem broju slučajeva je dokazano prisustvo sedativa (30,63%), a zatim antiepileptika (19,97%), analgetika (13,63%) i antidepresiva (11,20%). Trovanja atipičnim antipsihotikom aripiprazolom i antiepilepticima nove generacije levetiracetamom i topiramatom po prvi put su zabeležena na ovom području. Primećena je visoka prevalenca trovanja pregabalinom (12,38%). Prikazani rezultati ukazuju na potrebu za povećanjem svesti o značaju mentalnog zdravlja mladih osoba ženskog pola. Propisivanje sedativa treba uvek pažljivo razmotriti, s obzirom da se oni najčešće koriste u cilju trovanja. Lekari i toksikolozi uvek treba da budu u toku sa novim registrovanim lekovima, kako bi mogli da potvrde trovanje i primene adekvatne mere lečenja.

Ključne reči: *trovanje, lekovi, toksikologija, evaluacija, Srbija*

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THE INFLUENCE OF EXTRACTION SOLVENT ON UV PROTECTIVE POTENTIAL OF GREEN TEA LEAF EXTRACT

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In recent years, there has been an increasing trend of using herbal raw materials in the cosmetic and pharmaceutical industry. Accordingly, natural raw materials are being tested as potential UV absorbers in sunscreens. As required by law, it is necessary to quantify their ability to protect against the sun and determine the SPF (Sun protection factor). The aim of this study was to investigate the influence of the extraction solvent on the SPF value of green tea leaf extracts, prepared by the ultrasound assisted extraction. Water, 50% ethanol, aqueous solution of 30%, 50% and 70% glycerol, as well as a mixture of water, glycerol and ethanol (1:1:1) were used as extraction solvents. The extraction was carried out in an ultrasonic bath (1 hour, 30°C, extract ratio 1:10). The SPF was determined using *in vitro* Mansur's spectrophotometric method, as an alternative to commonly used *in vivo* method. The results showed that the extract obtained by extraction using a mixture of water, glycerol and ethanol had the highest measured SPF value (12.45), while the extract obtained by extraction using water had the lowest SPF (9.04). The SPF of water-glycerol extracts was the highest in the case when the extraction solvent was 50% glycerol (SPF=10.44). The results show that green tea can be used as a raw material for the production of extracts that have the ability to absorb UV radiation, and that through the extraction optimization process, using a mixture of solvents as an extraction solvent, plant extracts with a higher UV protection potential can be obtained.

Keywords: *Green tea leaf extract, SPF, UV protection, Ultrasound assisted extraction*

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UTICAJ SREDSTVA ZA EKSTRAKCIJU NA UV ZAŠTITNI POTENCIJAL EKSTRAKTA LISTA ZELENOG ČAJA

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Poslednjih godina, u kozmetičkoj i farmaceutskoj industriji je prisutan trend intenzivne primene sirovina biljnog porekla. U skladu s tim, vrši se ispitivanje prirodnih sirovina kao potencijalnih apsorbera UV zračenja u cilju primene u kozmetičkim proizvodima za zaštitu od sunčevog zračenja. Kako zakonska regulativa nalaže, potrebno je kvantifikovati sposobnost njihove zaštite od sunca i odrediti SPF (*Sun protection factor*). Cilj ovog rada bio je da se ispita uticaj sredstva za ekstrakciju na SPF vrednost ekstrakata lista zelenog čaja, izrađenih metodom ultrazvučne ekstrakcije. Kao sredstva za ekstrakciju korišćeni su voda, 50% etanol, vodeni rastvor glicerola 30%, 50% i 70%, kao i smeša vode, glicerola i etanola (1:1:1). Ekstrakcija je vršena pomoću ultrazvučnog kupatila u trajanju od jednog sata na temperaturi 30°C, a odnos droge i sredstva za ekstrakciju bio je 1:10. Određivanje SPF vrednosti vršeno je primenom *in vitro* Mansurove spektrofotometrijske metode, koja je alternativna *in vivo* metodama koje se obično primenjuju za određivanje SPF. Rezultati su pokazali da najveću izmerenu SPF vrednost ima ekstrakt dobijen ektrakcijom pomoću smeše vode, glicerola i etanola (1:1:1) (SPF = 12,45), a da najmanju SPF vrednost ima ekstrakt dobijen ekstrakcijom pomoću vode (SPF = 9,04). SPF vrednost vodeno-glicerolnih ekstrakata bila je najveća u slučaju kada je sredstvo za ekstrakciju bio 50% glicerol (SPF=10,44). Rezultati pokazuju da zeleni čaj može da se koristi kao sirovina za izradu ekstrakata koji imaju sposobnost apsorpcije UV zračenja, a da se kroz proces optimizacije ekstrakcije, primenom smeše rastvarača kao sredstva za ekstrakciju, mogu dobiti biljni ekstrakti većeg UV zaštitnog potencijala.

Ključne reči: *Ekstrakt lista zelenog čaja, SPF vrednost, UV zaštita, ultrazvulčna ekstrakcija*

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MULTITARGET DRUG - ADVANTAGES AND CHALLENGES

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Insufficient understanding of the multifactorial basis of many chronic diseases may be the cause of insufficient efficacy of their treatment. The concept "one drug - one target" is not always effective enough. Biological systems resist small changes well with compensatory mechanisms. Due to the multifactorial nature of neurodegenerative, infectious, metabolic and cardiovascular diseases and cancers, their treatment requires the modulation of multiple biological targets in order to restore the physiological balance, which can be accomplished by combining several drugs with a specific target (polypharmacy, more complicated dosing regimen), a combination of fixed doses of different drugs in the same formulation (with limitations due to pharmacokinetic differences, and possible interactions), or the use of *multitarget* drugs in one chemical entity that act on several biological targets (receptors, enzymes and macromolecular interactions), giving additive and synergistic effects (polypharmacology, suitable in terms of bioavailability, pharmacokinetics, drug-drug interactions and simpler therapeutic regimen).

The rational design of multitarget compounds is not a simple task, considering that it involves the selection of the right combination of targets, that the development of the chemotype is more difficult the more different the targets are, that their localization in cellular and tissue compartments also has to be taken into account, that it involves balancing the activity on individual biomolecules and excluding activity on unwanted biomolecules, with the complexity of the task increasing as the number of targets that need to be balanced increases, all the while efforts to maintain the drug-like characteristics are made.

The identification of such agents was mostly a result of chance, while their design is now an aspiration of medicinal chemistry, which, despite the numerous challenges, carries great potential for future therapeutic innovations.

Keywords: *multitarget drug, polypharmacology, combination therapy, multifactorial diseases*

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MULTITARGET LEK – PREDNOSTI I IZAZOVI

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Nedovoljno razumevanje multifaktorijalne osnove mnogih hroničnih oboljenja može biti uzrok nedovoljne uspešnosti terapije ovakvih indikacija. Koncept "jedan lek – jedna meta" nije uvek dovoljno efikasan. Kompenzatornim mehanizmima biološki sistemi se dobro opiru manjim promenama.

Terapija neurodegenerativnih, infektivnih, metaboličkih, kardiovaskularnih oboljenja i karcinoma, usled multifaktorijalne prirode, disregulacije više signalnih puteva i fizioloških procesa, zahteva modulaciju više bioloških meta kako bi fiziološki balans bio obnovljen i kako bi se postigle višestruke promene u patološkoj kaskadi. Ovo može biti ostvareno kombinovanjem više lekova sa specifičnom metom (polifarmacija, komplikovaniji režim doziranja), kombinacijom fiksnih doza različitih lekova u istoj formulaciji (uz ograničenja usled farmakokinetičkih razlika agenasa, i mogućih interakcija), ili primenom *multitarget* lekova u jednom hemijskom entitetu koji deluju na više bioloških meta (receptori, enzimi i makromolekulske interakcije), dajući aditivne i sinergistične efekte (polifarmakologija, pogodno sa aspekta bioraspoloživosti, farmakokinetike, lek-lek interakcija i terapijskog režima, koji sada biva jednostavniji, uz poboljšanu komplijansu).

Racionalni dizajn *multitarget* jedinjenja nije jednostavan zadatak, počev od selektovanja prave kombinacije meta, sa težim razvojem hemotipa što su mete različitije, uzimajući u obzir i lokalizovanost meta u ćelijskim i tkivnim kompartmentima, preko balansiranja aktivnosti na pojedinačnim biomolekulima, isključujući aktivnost na neželjenim biomolekulima, uz uvećanje složenosti zadatka sa povećanjem broja meta koje je potrebno izbalansirati, istovremeno pokušavajući da se *drug-like* karakteristike zadrže.

Identifikacija ovakvih agenasa je uglavnom bila rezultat slučajnosti, dok je njihov dizajn sada težnja medicinske hemije, koji, pored brojnih izazova, nosi veliki potencijal za buduće terapijske inovacije.

Ključne reči: *multitarget lek, polifarmakologija, kombinovana terapija, multifaktorijalna oboljenja*

Zahvalnica: *Zahvaljujemo se Ministarstvu prosvete, nauke i tehnološkog razvoja Republike Srbije na podršci projektu pod evidencionim brojem 451-03-68/2022-14/200113.*

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THE INFLUENCE OF THERAPEUTIC MODALITIES ON DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Rheumatoid arthritis (RA) is a chronic, autoimmune and systemic disease that can manifest itself at any age. A wide range of drugs allows an individual approach to each patient during the treatment of this disease. Determining and monitoring the disease activity index DAS28 (disease activity score in 28 joints) is of great importance for making a clinical decision on starting or changing treatment in patients with RA. The aim of the study is to evaluate the impact of therapeutic modalities on disease activity in patients with RA. A cross-sectional retrospective study was conducted, which included 109 patients suffering from RA treated during 2019 and 2020.The results of the conducted research indicate a low or moderate disease activity in more than half of the patients (51.37%), while the other patients, in spite of treatment, show high disease activity. Low disease activity is most effectively achieved with a therapeutic modality based on the application of a combination of glucocorticoids and biological drugs. The combination of glucocorticoids and more than one disease-modifying drug has been shown to be effective in a group of patients with moderate disease activity. Additionally, the PLUM regression analysis performed showed that disease activity significantly correlated with the values of erythrocyte sedimentation and C-reactive protein ($p < 0.05$) as a marker of inflammation. The combined administration of glucocorticoids with disease-modifying or biological drugs is the basis for achieving low activity and/or disease remission in RA patients.

Keywords: *Rheumatoid arthritis, DAS28, disease activity, SE, CRP, therapeutic modalities*

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UTICAJ TERAPIJSKIH MODALITETA NA AKTIVNOST BOLESTI KOD OBOLELIH OD REUMATOIDNOG ARTRITISA

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Reumatoidni artritis (RA) predstavlja hroničnu, autoimunu i sistemsku bolest koja se može ispoljiti u svim životnim dobima. Širok spektar lekova omogućava individualni pristup svakom pacijentu tokom lečenja ove bolesti. Određivanje i praćenje indeksa aktivnosti bolesti DAS28 (*engl. disease activity score in 28 joints*) je od velike važnosti za donošenje kliničke odluke o započinjanju ili promeni terapije kod pacijenata koji boluju od RA. Cilj rada je procena uticaja terapijskih modaliteta na aktivnost bolesti kod obolelih od RA. Sprovedena je retrospektivna studija preseka kojom je obuhvaćeno 109 pacijenata koji boluju od RA lečenih tokom 2019. i 2020. godine. Rezultati sprovedenog istraživanja ukazuju na nisku ili umereno aktivnu bolest kod više od polovine pacijenata (51,37%), dok ostali pacijenti, uprkos terapiji, pokazuju visoku aktivnost bolesti. Niska aktivnost bolesti je najefikasnije postignuta terapijskim modalitetom zasnovanim na primeni kombinacije glukokortikoida i bioloških lekova. Kombinacija glukokortikoida i više od jednog leka koji modifikuje bolest pokazala se efikasnom u grupi pacijenata kod kojih je prisutna umerena aktivnost bolesti. Dodatno, sprovedena *PLUM* regresiona analiza pokazala je da je aktivnost bolesti značajno korelirala sa vrednostima sedimentacije eritrocita i C-reaktivnog proteina ($p < 0,05$) kao markera zapaljenja. Kombinovana primena glukokortikoida sa biološkim ili lekovima koji modifikuju bolest predstavlja osnov za postizanje niske aktivnosti i/ili remisije bolesti kod pacijenata sa RA.

Ključne reči: *Reumatoidni artritis, DAS28, aktivnost bolesti, SE, CRP, terapijski modaliteti*

Zahvalnica: *Autori se zahvaljuju Ministarstvu prosvete, nauke i tehnološkog razvoja Republike Srbije (Br: 451-03-68/2022-14/200113), autori se takođe zahvaljuju Klinici za reumatologiju Vojnomedicinske akademije*

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GALENIC MEDICINES FROM THE ANTISEPTIC GROUP IN THE COVID PANDEMIC

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Topical chemotherapeutics are compounds that kill or stop the growth of various microorganisms. They differ according to their selective toxicity and are divided into: disinfectants (used on objects), antiseptics (used on living tissues) and preservatives used in food and pharmaceutical industry. Diluted ethanol works by denaturing proteins in the cell membrane of microorganisms. Diluted hydrogen works by oxidizing the lipid membranes in the cells of microorganisms. Galenic medicines which are made in the registered Galenic laboratory of the Pharmacy Institution in Niš in accordance with all valid legal regulations and are used in the COVID pandemic as antiseptics are: Diluted ethanol and Diluted hydrogen peroxide. They belong to the pharmacopoeial group Liquid preparations for application to the skin (*Praeparationes liquidae ad usum dermicum*), i.e. Solutions for application to the skin. The starting raw materials are of the quality for pharmaceutical use and the production is carried out in an area registered for the production of galenic medicines, in accordance with the official formulations, using validated equipment and procedures that ensure the required quality of the preparation. Interphase process control is carried out during production, and final product control is carried out before releasing a batch of medicine. The production is performed in accordance with the work orders which define each stage of the preparation process, with recording the responsible persons for each of the phases. The stability study was conducted in accordance with the ICH Q1A and ICH Q1E guidelines and the WHO stability guide. A long-term stability study was conducted where the samples were stored at a temperature of 25°C ±2°C and humidity of 60%RH ±5%, as determined for the international climate zone II. The test results are presented graphically. The equations of the true dependence of the content on time are y=-0.0325x+70.23 for diluted ethanol and y=-0.0052x+3.1337 for diluted hydrogen peroxide.

Based on the obtained results, the indicated galenic medicines are stable, of suitable quality and effective as antiseptics in the COVID pandemic.

Keywords: *Antiseptics, Galenic medicines, Covid, ICH, WHO*

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GALENSKI LEKOVI IZ GRUPE ANTISEPTIKA U COVID PANDEMIJI

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Lokalni hemoterapeutici su jedinjenja koja ubijaju ili zaustavljaju rast različitih mikroorganizama. Razlikuju se prema selektivnoj toksičnosti i dele se na: dezinficijense (koriste se na objektima), antiseptike (koriste se na živa tkiva) i konzervanse (koriste se u prehrambenoj i farmaceutskoj industriji). Diluirani etanol deluje tako što denaturiše proteine u ćelijskoj membrani mikroorganizama. Diluirani hidrogen deluje tako što oksidiše lipidne membrane u ćelijama mikroorganizama. Galenski lekovi koji se izrađuju u registrovanoj Galenskoj laboratoriji Apotekarske ustanove Niš u skladu sa svim važećim zakonskim propisima i koji se koriste u COVID pandemiji kao antiseptici su: Diluirani etanol i Diluirani hidrogen-peroksid. Oni pripadaju farmakopejskoj grupi tečnih preparata za primenu na koži (*Praeparationes liquidae ad usum dermicum*) i to kao rastvori za primenu na koži. Polazne sirovine su kvaliteta za farmaceutsku primenu, izrada se vrši u prostoru registrovanom za izradu galenskih lekova, prema oficinalnim formulacijama, korišćenjem validirane opreme i postupaka koji obezbeđuju traženi kvalitet preparata. U toku izrade vrši se međufazna procesna kontrola, a pre puštanja serije leka u promet, kontrola završnog proizvoda. Izradu prate radni nalozi koji definišu svaku etapu procesa izrade preparata uz evidentiranje odgovornih lica za svaku od faza. Studija stabilnosti je rađena prema smernicama ICH Q1A i ICH Q1E i vodiča za stabilnost WHO. Ispitivana je dugotrajna studija stabilnosti gde se uzorci čuvaju na temperaturi od 25°C ± 2°C i vlažnosti 60% RH ± 5% koji su definisani za internacionalnu klimatsku zonu II. Rezultati ispitivanja prikazani su grafički. Jednačine prave zavisnosti sadržaja od vremena su za diluirani etanol y = -0,0325x + 70,23 i za diluirani hidrogen-peroksid y = -0,0052x + 3,1337.

Dobijeni rezultati pokazuju da su naznačeni galenski lekovi stabilni, odgovarajućeg kvaliteta i efikasni kao antiseptici u COVID pandemiji.

Ključne reči: *Antiseptici, Galenski lekovi, Covid, ICH, WHO*

Zahvalnica: *Zahvaljujemo se na podršci i saradnji u toku izrade rada Apotekarskoj ustanovi Niš, Udruženju farmaceuta FNP koji je sastavni deo SFUS-a i Medicinskom fakultetu u Nišu, Odseku za farmaciju.*

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GALENIC MEDICINES FOR COUGH THERAPY IN THE COVID PANDEMIC

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Cough is one of the most common symptoms of the COVID-19 infection, where herbal medicines are of great importance. Plantain syrup contains plantain extract as an active ingredient and it is used for dry cough as a mucus drug and as a mild expectorant. Primrose syrup contains primrose extract, thyme tincture and menthol complex as an active principle. It is used as an antiseptic (the effect comes from thyme tincture and menthol) and an expectorant (due to the action of saponins found in the primrose root). Thyme syrup contains thyme tincture and anise essential oil as active ingredients, which act as an expectorant, an antitussive and an antispasmodic due to the presence of the essential oil and flavonoids. The active principle in marshmallow syrup is mucopolysaccharide mucus which forms a protective layer on the surface of the mucous membrane and soothes the inflammation and irritation of the mucous membrane of the mouth and throat. Galenic medicines, which are used in cough therapy, belong to the pharmacopoeial group Liquid preparations for oral use – Syrups (*Preparationes liquidae peroraliae*) are made in a registered Galenic laboratory, in accordance with all valid legal regulations and guidelines related to the production of this type of medicine. The starting raw materials are of the quality for pharmaceutical use and the production is carried out in an area registered for the production of galenic medicines, in accordance with the official formulations, using validated equipment and procedures that ensure the required quality of the preparation. Interphase process control is carried out during production, and final product control is carried out before releasing a batch of medicine into circulation. Each manufactured batch is tested in accordance with pharmacopoeial requirements, and in order to determine the expiration dates of the manufactured galenic drugs, a long-term stability study was conducted under the conditions defined for the international climate zone II, according to the ICH Q1Ai and ICH Q1E guidelines.
Based on the obtained results, the indicated galenic medicines are stable, of suitable quality and effective in the treatment of cough in the COVID pandemic.

Keywords: *Galenic medicines, Cough, Covid 19, ICH*

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GALENSKI LEKOVI ZA TERAPIJU KAŠLJA U COVID PANDEMIJI

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Kašalj je jedan od najčešćih simptoma obolelih od COVID-19 infekcije gde biljni lekovi imaju veliki značaj. Sirup bokvice kao aktivni princip sadrži ekstrakt bokvice, koristi se kod suvog kašlja kao sluzna droga i kao blagi ekspektorans. Sirup jagorčevine, složen kao aktivni princip, sadrži ekstrakt jagorčevine, tinkturu timijana i mentol. Koristi se kao antiseptik (dejstvo potiče od tinkture timijana i od mentola) i ekspektorans (zbog delovanja saponina koji se nalaze u korenu jagorčevine). Sirup timijana kao aktivne principe sadrži tinkturu timijana i etarsko ulje anisa, koji zbog prisustva etarskog ulja i flavonoida deluju kao ekspektorans, antitusik i spazmolitik. U sirupu belog sleza aktivni principi su mukopolisaharidne sluzi koje formiraju zaštitni sloj na površini sluzokože i smiruju upalu i iritaciju sluzokože usta i grla. Galenski lekovi koji se koriste u terapiji kašlja pripadaju farmakopejskoj grupi Tečni preparati za oralnu upotrebu – sirupi (*Preparationes liquidae peroraliae*) izrađuju se u registrovanoj galenskoj laboratoriji, u skladu sa svim važećim zakonskim propisima i smernicama koji se odnose na izradu ove vrste lekova. Polazne sirovine su kvaliteta za farmaceutsku primenu, izrada se vrši u prostoru registrovanom za izradu galenskih lekova, prema oficinalnim formulacijama, korišćenjem validirane opreme i postupaka koji obezbeđuju traženi kvalitet preparata. U toku izrade vrši se međufazna procesna kontrola, a pre puštanja serije leka u promet kontrola završnog proizvoda. Svaka izrađena serija ispituje se u skladu sa farmakopejskim zahtevima, a u cilju utvrđivanja roka upotrebe izrađenih galenskih lekova ispitivana je dugotrajna studija stabilnosti u uslovima koji su definisani za internacionalnu klimatsku zonu II, prema smernicama ICH Q1Ai ICH Q1E.
Na osnovu dobijenih rezultata zaključujemo da su naznačeni galenski lekovi stabilni, odgovarajućeg kvaliteta i efikasni u terapiji kašlja u COVID pandemiji.

Ključne reči: *galenski lekovi, kašalj, Covid 19, ICH*

Zahvalnica: *Zahvaljujemo se na podršci i saradnji u toku izrade rada Apotekarskoj ustanovi Niš, Udruženju farmaceuta FNP koji je sastavni deo SFUS-a i Medicinskom fakultetu u Nišu, Odseku za farmaciju.*

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GALENIC MEDICINES FROM THE VASOCONSTRICTORS GROUP IN THE COVID PANDEMIC

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Nasal congestion is a common symptom of the COVID-19 infection. Sympathomimetics are used as nasal decongestants and with their alpha-adrenergic effects they cause vasoconstriction, redistribution of local blood flow and a reduction of edema of the nasal mucosa, which improves nasal ventilation, drainage and reduces nasal congestion. They are poorly resorbed from the nasal mucosa and have no pronounced systemic effects. Medicinal rhinitis occurs when vasoconstriction is followed by vasodilatation with even more severe congestion, hyperactivity and resistance to decongestant therapy. Therefore, if possible, the use should be limited to 3 to 5 or a maximum of 7 consecutive days, but only when necessary. Ephedrine hydrochloride is the least likely to cause congestion and it is the drug of choice in the pediatric population. Galenic medicines, which are used as vasoconstrictors in the Covid pandemic, belong to the pharmacopoeial group Nasal preparations (*Nasalia*), i.e. nasal drops and liquid nasal sprays, and are made in the registered Galenic laboratory of the Niš Pharmacy Institution in accordance with all applicable legal regulations are: Ephedrine hydrochloride, nasal drops 0.25%, 0.5%, 1% and 2%; Ephedrine-hydrochloride, hydrophilic gel for the nose, complex; Naphazoline hydrochloride, nasal drops 0.05% and 0.1%; Naphazoline-hydrochloride, nasal drops, spray 0.1% and Xylometazoline-hydrochloride, nasal drops, spray 0.1%. A long-term stability study was conducted under the conditions defined for the international climatic zone II, according to the guidelines of ICH Q1A and ICH Q1E and the WHO stability guide. The results are presented graphically. The equations of the true dependence of the content on time are: y= 0.0003x+0.247 for 0.25% Ephedrine-hydrochloride; y=0.0003x+0.4919 for 0.5% Ephedrine-hydrochloride; y=0.0001x+0.9901 for 1% Ephedrine-hydrochloride; y=-0.00009x+1.9541 for 2% Ephedrine-hydrochloride; y=0.0005x+0.04972 for 0.05% Naphazoline-hydrochloride; y=0.0002x+0.0978 for 0.1% Naphazoline-hydrochloride; y= 0.0002x+0.1054 for 0.1% Xylometazoline hydrochloride.

Based on the obtained results, the indicated galenic medicines are stable, of suitable quality and effective as vasoconstrictors in the COVID pandemic.

Keywords: *Nasal decongestants, Galenic medicnes, Covid, ICH, WHO*

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GALENSKI LEKOVI IZ GRUPE VAZOKONSTRIKTORA U COVID PANDEMIJI

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Nazalna kongestija je čest simptom infekcije COVID-19. Simpatomimetici se koriste kao nazalni dekongestivi, svojim alfa-adrenergičnim efektima izazivaju vazokonstrikciju, redistribuciju lokalnog protoka krvi, smanjuju edem nazalne mukoze, čime se poboljšava nazalna ventilacija, drenaža i smanjuje zapušenosti nosa. Slabo se resorbuju sa nazalne sluzokože i nemaju izražene sistemske efekte. Medikamentozni rinitis nastaje kad nakon vazokonstrikcije nastaje vazodilatacija sa još težom kongestijom, hipereaktivnost i rezistencija na terapiju dekongestivima. Zbog toga upotrebu treba ograničiti na tri do pet, najduže sedam uzastopnih dana, ako je moguće samo kada je to neophodno. Efedrin-hidrohlorid poseduje najmanji potencijal da dovede do kongestije i predstavlja lek izbora u pedijatrijskoj populaciji. Galenski lekovi, koji se koriste kao vazokonstriktori u Covid pandemiji, pripadaju farmakopejskoj grupi preparata za nos (*Nasalia*) i to kapi za nos i tečni sprejevi za nos, a izrađuju se u registrovanoj Galenskoj laboratoriji Apotekarske ustanove Niš u skladu sa svim važećim zakonskim propisima. To su: Efedrin-hidrohlorid, kapi za nos 0,25%, 0,5%, 1% i 2%; Efedrin-hidrohlorid, hidrofilni gel za nos, složeni; Nafazolin-hidrohlorid, kapi za nos 0,05% i 0,1% ; Nafazolin-hidrohlorid, kapi za nos, sprej 0,1% i Ksilometazolin-hidrohlorid, kapi za nos, sprej 0,1%. Ispitivana je dugotrajna studija stabilnosti u uslovima koji su definisani za internacionalnu klimatsku zonu II, prema smernicama ICH Q1A i ICH Q1E I vodiča za stabilnost WHO. Rezultati su prikazani grafički. Jednačine prave zavisnosti sadržaja od vremena su za: Efedrin-hidrohlorid 0,25% y = 0,0003x + 0,247; Efedrin-hidrohlorid 0,5% y = 0,0003x + 0,4919; Efedrin-hidrohlorid 1% y = 0,0001x + 0,9901; Efedrin-hidrohlorid 2% y = -0,00009x + 1,9541; Nafazolin-hidrohlorid 0,05% y = 0,0005x + 0,04972; Nafazolin-hidrohlorid 0,1% y = 0,0002x + 0,0978; Ksilometazolin-hidrohlorid 0,1% y = 0,0002x + 0,1054.
Na osnovu dobijenih rezultata zaključujemo da su naznačeni galenski lekovi stabilni, odgovarajućeg kvaliteta i efikasni kao vazokonstriktori u COVID pandemiji.

Ključne reči: *nazalni dekongestivi, galenski lekovi, Covid, ICH, WHO*

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GALENIC MEDICINES FOR THERAPY OF FEBRILE CONDITIONS IN THE COVID PANDEMIC

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Antipyretics are used as pain relievers and in conditions of elevated body temperature. Paracetamol is a non-selective inhibitor of cyclooxygenase and it acts by inhibiting the isomeric form of COX-1, designated as COX-3, which is found only in the hypothalamus, where the thermoregulatory center is located. Paracetamol binds to the peroxide active site in the enzyme, which is different from the salicylate binding site. Caffeine as an analgesic adjuvant acts in all segments of pain transmission and modulation. Diazepam is a benzodiazepine used to prevent febrile convulsions. Galenic medicines, which are used for the treatment of febrile conditions in the Covid pandemic, belong to the pharmacopoeial groups Oral powders (*Pulveres perorales*) and Rectal preparations (*Rectalia*), i.e. suppositories and rectal solutions, and are made in the registered Galenic laboratory of the Niš Pharmacy Institution in accordance with all valid legal regulations include: Paracetamol and caffeine, oral powder; Paracetamol suppositories for children 60 mg; 120 mg and 250 mg; Diazepam, solution for rectal administration 5 mg/2.5 ml; Diazepam, suppositories 5 mg and 10 mg. The starting raw materials are of the quality for pharmaceutical use and the production is carried out in an area registered for the production of galenic medicines, in accordance with the official formulations, using validated equipment and procedures that ensure the required quality of the preparation. A long-term stability study was conducted under the conditions defined for the international climate zone II, according to the guidelines of ICH Q1A and ICH Q1E and the WHO stability guide. The results are presented graphically. The equations of the true dependence of the content on time are: in Paracetamol and caffeine oral powder $y=0.6026x+477.93$ for paracetamol and $y=-0.0877x+62.21$ for caffeine; $y=-0.0162x+116.83$ for 120 mg Paracetamol suppositories; $y=-0.0023x+5.16$ for 5 mg Diazepam suppositories; and $y=-0.0042x+4.98$ for 5 mg/2.5 ml Diazepam solution for rectal administration.
Based on the obtained results, the indicated galenic medicines are stable, appropriate quality and effective in the treatment of febrile conditions in the COVID pandemic.

Keywords: *Antipyretics, Galenic medicines, Covid, ICH, WHO*

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GALENSKI LEKOVI ZA TERAPIJU FEBRILNIH STANJA U COVID PANDEMIJI

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Antipiretici se koriste u terapiji bola i u stanjima povišene telesne temperature. Paracetamol je neselektivan inhibitor ciklooksigenaze, deluje inhibicijom izomernog oblika COX-1, označenog kao COX-3, koji se nalazi samo u hipotalamusu, gde je i termoregulacioni centar. Paracetamol se vezuje za peroksidno aktivno mesto u enzimu, koje se razlikuje od mesta vezivanja salicilata. Kofein kao analgezijski adjuvans deluje u svim segmentima transmisije i modulacije bola. Diazepam je benzodiazapin koji se koristi u prevenciji febrilnih konvulzija. Galenski lekovi koji se koriste za terapiju febrilnih stanja u Covid pandemiji pripadaju farmakopejskim grupama Oralnih praškova (*Pulveres perorales*) i Rektalnih preparata (*Rectalia*) i to supozitorija i rektalnih rastvora, a izrađuju se u registrovanoj Galenskoj laboratoriji Apotekarske ustanove Niš u skladu sa svim važećim zakonskim propisima su: Paracetamol i kofein, oralni prašak; Paracetamol supozitorije za decu 60 mg; 120 mg i 250 mg; Diazepam, rastvor za rektalnu primenu 5 mg/2,5ml; Diazepam, supozitorije 5 mg i 10 mg. Polazne sirovine su kvaliteta za farmaceutsku primenu, izrada se vrši u prostoru registrovanom za izradu galenskih lekova, prema oficinalnim formulacijama, korišćenjem validirane opreme i postupaka koji obezbeđuju kvalitet preparata. Ispitivana je dugotrajna studija stabilnosti u uslovima koji su definisani za internacionalnu klimatsku zonu II, prema smernicama ICH Q1A i ICH Q1E i vodiča za stabilnost WHO. Rezultati su prikazani grafički. Jednačine prave zavisnosti sadržaja od vremena su za: Paracetamol I kofein, oralni prašak: $y = 0,6026x + 477,93$ paracetamol i $y = -0,0877x + 62,21$ kofein; Paracetamol supozitorije 120 mg $y = -0,0162x + 116,83$; Diazepam,supozitorije 5 mg $y = -0,0023x+5,16$ i Diazepam, rastvor za rektalnu primenu 5 mg/2,5 ml $y = -0,0042x + 4,98$.
Na osnovu dobijenih rezultata zaključujemo da su naznačeni galenski lekovi stabilni, odgovarajućeg kvaliteta i efikasni u terapiji febrilnih stanja u COVID pandemiji.

Ključne reči: *antipiretici, galenski lekovi, Covid, ICH, WHO*

Zahvalnica: *Zahvaljujemo se na podršci i saradnji u toku izrade rada Apotekarskoj ustanovi Niš, Udruženju farmaceuta FNP koji je sastavni deo SFUS-a i Medicinskom fakultetu u Nišu, Odseku za farmaciju.*

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POTENTIAL INFLUENCE OF INTERLEUKIN 6 GENE POLYMORPHISM ON GRAFT FUNCTION AND TACROLIMUS DOSE-ADJUSTED CONCENTRATION IN KIDNEY TRANSPLANT PATIENTS

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Interleukin-6 (IL-6) plays a significant role in the initiation and progression of chronic graft rejection after kidney transplantation (Tx). Its expression is determined by the -174G>C gene polymorphism. Furthermore, it has been indicated that IL-6 may exert an influence on tacrolimus (Tac) metabolism. Tacrolimus dose-adjusted trough concentration (C_0/D) within the first post-transplantation year represents a surrogate marker of Tac metabolism rate. The aim of the study was to investigate the influence of IL-6-174G>C gene polymorphism on graft function, defined as estimated glomerular filtration rate (eGFR), during the five-year period after Tx. Additionally, the aim was to compare Tac C_0/D in relation to the genotype of the examined polymorphism during the first post-transplantation year. The study included 94 kidney transplant patients on tacrolimus-based immunosuppression. Interleukin-6 genotyping was performed by using the PCR-RFLP method. The results showed that carriers of the -174GG genotype had lower eGFR values compared to patients with -174CC genotype (median=47.7 mL/min/1.73m^2 vs. median=61.02 mL/min/1.73m^2; p=0.013) between the 13th and 24th month post-transplantation. There was no difference in eGFR among patients with different genotypes between months 6 and 12, during the third, fourth and fifth year post-transplantation. A difference has been observed in Tac C_0/D between 6 and 12 months comparing patients with the -174GG genotype and -174C allele carriers (median=1.4 ng/mL/mg vs. median=1.73 ng/mL/mg; p=0.044), whereby there was no difference in C_0/D in the early period (around the 3rd month). Interleukin-6 genotyping may be useful in assessing the risk of developing chronic graft dysfunction in kidney transplant patients. Additionally, the examined IL-6 gene polymorphism may contribute to the variability of Tac C_0/D among patients.

Keywords: *kidney transplantation, tacrolimus, interleukin 6, gene polymorphism*

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POTENCIJALNI UTICAJ POLIMORFIZMA GENA ZA INTERLEUKIN 6 NA FUNKCIJU GRAFTA I KONCENTRACIJU KORIGOVANU DOZOM TAKROLIMUSA KOD PACIJENATA SA TRANSPLANTIRANIM BUBREGOM

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Interleukin-6 (IL-6) ima značajnu ulogu u inicijaciji i progresiji hroničnog odbacivanja grafta nakon transplantacije bubrega (Tx). Njegova ekspresija određena je -174G>C genskim polimorfizmom. Dodatno, pokazano je da IL-6 može ispoljiti uticaj na metabolizam takrolimusa (Tac). Minimalna koncentracija korigovana dozom (C_0/D) Tac unutar prve post-transplantacione godine predstavlja surogat marker brzine metabolizma Tac. Cilj istraživanja je bio ispitati uticaj IL-6-174G>C genskog polimorfizma na funkciju grafta, definisanu kao procenjena brzina glomerularne filtracije (eGFR), u petogodišnjem periodu nakon Tx. Pored toga, cilj je bio poređenje Tac C_0/D u odnosu na genotip ispitivanog polimorfizma tokom prve post-transplantacione godine. Studija je obuhvatila 94 pacijenta sa transplantiranim bubregom na takrolimus-baziranoj imunosupresiji. Interleukin-6 genotipizacija je sprovedena PCR-RFLP metodom. Rezultati istraživanja su pokazali da su nosioci -174GG genotipa imali niže eGFR vrednosti u odnosu na pacijente sa -174CC genotipom (medijana = 47,7 mL/min/1,73m^2 vs. medijana = 61,02 mL/min/1,73m^2; p = 0,013) između 13. i 24. post-transplantacionog meseca. Nije bilo razlike u eGFR među pacijentima sa različitim genotipom između 6. i 12. meseca, tokom treće, četvrte i pete post-transplantacione godine. Takođe, pokazana je razlika u C_0/D Tac u periodu između 6. i 12. meseca među pacijentima sa -174GG genotipom i nosiocima -174C alela (medijana = 1,4 ng/mL/mg vs. medijana = 1,73 ng/mL/mg; p = 0,044), pri čemu nije bilo razlike u C_0/D u ranom post-transplantacionom periodu (oko trećeg meseca). Genotipizacija IL-6 može imati značaja u proceni rizika za razvoj hronične disfunkcije grafta kod pacijenata sa transplantiranim bubregom. Dodatno, ispitivani IL-6 genski polimorfizam može doprineti varijabilnosti C_0/D Tac među pacijentima.

Ključne reči: *transplantacija bubrega, takrolimus, interleukin 6, genski polimorfizam*

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HYDROLATE OF OREGANO AS A POTENTIAL ANTIMICROBIAL AND ANTI-INFLAMMATORY AGENT

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Hydrolates, aqueous solutions also known as hydrosols, floral or aromatic waters, are obtained as by-products during the isolation of essential oils. Although they have a different composition compared to the corresponding essential oils, hydrolates have organoleptic properties and a biological activity which makes them useful potential raw materials in many industries.
This research aimed to investigate the antimicrobial and anti-inflammatory activity of the hydrolate obtained by hydrodistillation of the aerial part of *Origanum vulgare* L. (Lamiaceae). The effect of pure hydrolate and its diluted solutions (50%, 25%, and 12.5%) was tested with a microdilution test on five bacterial strains (*Escherichia coli, Pseudomonas aeruginosa, Staphilococcus aureus, Enterococcus faebacterium* and *Cutibacterium acnes*) and the yeast *Candida albicans*. The results are presented as minimum inhibitory concentrations (MIC in v/v%). The MIC values were 100 (v/v%) for all tested bacterial strains, while the hydrosol did not show activity against *Candida albicans*. *In vitro* anti-inflammatory activity was tested for the pure hydrolate using bovine serum albumin (BSA assay). *O. vulgare* hydrolate exhibited a significant anti-inflammatory effect with an inhibition percentage of BSA denaturation of 71.2±0.006 %, which is less the than standard value for diclofenac (95.6±0.001%).
The established antimicrobial and anti-inflammatory activity of *Origanum vulgare* hydrolat can be of great importance for its potential application in medicine, veterinary medicine, and the pharmaceutical industry.

Keywords: *hydrolates, Origanum vulgare, antimicrobial effect, anti-inflammatory effect*

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HIDROLAT ORIGANA KAO POTENCIJALNI ANTIMIKROBNI I ANTIINFLAMATORNI AGENS

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Hidrolati, vodeni rastvodi koji su poznati još i kao hidrosoli, cvetne ili aromatične vode, dobijaju se kao nusproizvodi pri izolovanju etarskih ulja. Iako su različitog sastava u odnosu na odgovarajuća etarska ulja, hidrolati imaju organoleptička svojstva i biološku aktivnost koja ih čini korisnim potencijanim sirovinama u mnogim industrijama.
Ovo istraživanje je imalo za cilj da ispita antimikrobnu i antiinflamatornu aktivnost hidrolata dobijenog hidrodestilacijom nadzemnog dela *Origanum vulgare* L. (Lamiaceae). Uticaj čistog hidrolata i njegovih razblaženih rastvora (50%, 25% i 12,5%) je testiran mikrodilucionim testom na pet sojeva bakterija (*Escherichia coli, Pseudomonas aeruginosa, Staphilococcus aureus, Enterococcus faebacterium* i *Cutibacterium acnes*) i gljivu *Candida albicans*. Rezultati su izraženi kao minimalne inhibitorne koncentracije (MIC u v/v%). Vrednosti MIC su bile 100 (v/v%) za sve testirane bakterijske sojeve, a hidrolat nije ispoljio aktivnost protiv *Candida albicans. In vitro* antiinflamatorna aktivnost je testirana za čist hidrolat korišćenjem goveđeg serumskog albumina (BSA test). Hidrolat *O. vulgare* je ispoljio značajno antiinflamatorno dejstvo sa procentom inhibicije denaturacije BSA od 71,2 ± 0,006 %, što je manje od standardne vrednosti za diklofenak (95,6 ± 0,001%).
Utvrđena antimikrobna i antiinflamatorna aktivnost *Origanum vulgare* hidrolata može biti od velikog značaja za njegovu potencijalnu primenu u medicini, veterini i farmaceutskoj industriji.

Ključne reči: *hidrolat, Origanum vulgare, antimikrobno dejstvo, antiinflamatorno dejstvo*

Zahvalnica: *Ovo istraživanje podržali su Ministarstvo prosvete i nauke Republike Srbije (br. 451-03-68/2022-14/200113) i Interni naučni projekat Medicinskog fakulteta Univerziteta u Nišu br. 15.*

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PHARMACOTHERAPY REVIEW IN GERIATRIC PATIENTS WITH CHRONIC RENAL DISEASE

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In order to detect potentially inappropriate medication (PIM), several tools have been developed. One of the widely used explicit criteria are screening tools of older person's prescriptions/screening tool to alert physicians to correct treatment (STOPP/START) developed in 2008 and reviewed in 2014. PIM-Check is a modern software for PIM identification in prescribed pharmacotherapy. The study aimed to investigate the existence of PIM in pharmacotherapy of complex renal patients by two different approaches, with quantification and qualification. Data from 100 patients older than 65 with chronic renal insufficiency was collected retrospectively from their medical charts. STOPP/START criteria were applied to analyze patients' pharmacotherapy using the PIM-Check program for comparative data analysis. Statistical analysis was performed using SPSS statistical software (version 20). The most common STOPP criteria were the use of benzodiazepines. The number of drugs in therapy showed the greatest influence on their occurrence (median value 8). START criteria identified a deficiency in statin as a secondary cardiovascular protection. The occurrence of STOPP/START criteria (1,43/1,66 per patient) was most affected by the number of comorbidities and the number of drugs in therapy. With the PIM-Check program, the need for preventive vaccination was identified in the largest percentage, followed by a requirement to adjust the dose and the duration of therapy. In the line with the reported results, the development of a structured approach to pharmacotherapy in geriatric population is currently a necessity in Serbia. Thus, the screening tool for PIM adapted for clinical use could improve future pharmacotherapy decisions.

Keywords: *Geriatric pharmacotherapy, Potentially inappropriate medication, STOP/START criteria, Pharmacotherapy decisions*

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PREGLED FARMAKOTERAPIJE GERIJATRIJSKIH PACIJENATA SA HRONIČNOM BUBREŽNOM INSUFICIJENCIJOM

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U cilju uočavanja potencijalno neadekvatno propisanih lekova (PIM, engl. Potentially Inappropriate Medication) razvijeno je nekoliko smernica. Jedan od najčešće primenjivanih kriterijuma jesu smernice razvijene 2008. godine, a revidirane 2014. kojima se prati terapija starijih osoba, odnosno alati koji upozoravaju lekare na pravilno lečenje (STOPP/START). Sa druge strane, PIM-Check je savremeni program za identifikaciju PIM u farmakoterapiji. Cilj studije je istraživanje postojanja potencijalno neadekvatno propisanih lekova u terapiji pacijenata sa bubrežnom insuficijencijom sa kvantitativnog i kvalitativnog aspekta. Podaci su prikupljeni retrospektivno iz medicinske dokumentacije 100 pacijenata starijih od 65 godina sa hroničnom bubrežnom insuficijencijom. STOPP/START kriterijumi su primenjeni za analizu farmakoterapije pacijenata uz korišćenje PIM-Check programa za uporednu analizu podataka. Statistička analiza je izvršena pomoću programa SPSS (verzija 20). Najčešće prisutan STOPP kriterijum je bio primena benzodiazepina. Broj lekova u terapiji pokazao je najveći uticaj na njihovu pojavu (medijana 8). Primenom START kriterijuma identifikovan je nedostatak statina kao sekundarne kardiovaskularne prevencije. Na broj identifikovanih STOPP/START kriterijuma (1,43/1,66 po pacijentu) je najviše uticao broj komorbiditeta i lekova prisutnih u terapiji. PIM-Check programom je u najvećem procentu identifikovana potreba za preventivnom vakcinacijom, praćena zahtevom za prilagođavanjem doze i dužine trajanja terapije. U saglasnosti sa dobijenim rezultatima, u Srbiji je neophodan sveobuhvatniji pristup farmakoterapiji starijih pacijenata. S obzirom na to, smernice sa alatom za identifikaciju PIM, prilagođene kliničkoj upotrebi, mogle bi unaprediti donošenje odluka o farmakoterapiji u budućnosti.

Ključne reči: *gerijatrijska farmakoterapija, potencijalno neadekvatno propisani lekovi, STOPP/START kriterijumi, farmakoterapijske odluke*

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CHEMICAL COMPOSITION AND ANTIMICROBIAL ACTIVITY OF FRACTIONATED *GENTIANA ASCLEPIADEA* L. EXTRACT

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The underground parts of *Gentiana asclepiadea* L. (Gentianaceae) show promising antimicrobial activity against gastrointestinal pathogens, which is consistent with their traditional use. One of the most sensitive among the tested strains was *Enterococcus faecalis*. Antimicrobial activity can be improved by extract fractionation, but there is no data on the correlation with the chemical composition. This study aimed to determine the chemical composition of the water-ethanol extract of *G. asclepiadea* underground parts and its fractions (petrolether, ethyl acetate, butanol, and water) and to evaluate the connection with the anti-*Enterococcus faecalis* activity. The chemical analysis comprised of the quantification of swertiamarine, gentiopicroside, isovitexin, isoorientin, and isogentisin using HPLC-DAD and the total phenolics using the Folin-Ciocalteu method. The correlation between the chemical composition and the anti-*Enterococcus faecalis* activity was estimated by a Pearson correlation analysis. Fractionation significantly affected the phytochemical profile of the samples. Gentiopicroside content was in the range from 4.60±0.18 to 120.38±8.43 mg/g and was a dominant component of all samples except for the petrolether fraction where isogentisin was dominant (4.87±0.15 mg/g). In the case of the ethyl acetate fraction, which showed the best anti-*Enterococcus faecalis* activity, the content of most compounds was higher compared to the extract, except for svertiamarin and isovitexin, whose content was lower. There was no significant correlation ($p > 0.05$) between the anti-*Enterococcus faecalis* activity and the content of any monitored compound. The absence of correlations implies that the synergism among different compounds or undetermined minor compounds could be responsible for the activity. Further research is required to address these assumptions.

Keywords: *willow gentian, Enterococcus faecalis, bioassay-guided fractionation, phytochemical profile*

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HEMIJSKI SASTAV I ANTIMIKROBNA AKTIVNOST FRAKCIONISANOG EKSTRAKTA VRSTE *GENTIANA ASCLEPIADEA* L.

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Podzemni delovi vrste *Gentiana asclepiadea* L. (Gentianaceae) pokazuju obećavajuću antimikrobnu aktivnost prema gastrointestinalnim patogenima što je u skladu sa njihovom tradicionalnom primenom. Među ispitivanim sojevima, jedan od najosetljivijih bio je *Enterococcus faecalis*. Antimikrobna aktivnost može biti poboljšana frakcionisanjem ekstrakta, ali nema podataka o korelaciji aktivnosti sa hemijskim sastavom. Cilj ovog istraživanja bio je analizirati hemijski sastav vodeno-etanolnog ekstrakta podzemnih delova vrste *G. asclepiadea* i njegovih frakcija (petrol-etarska, etil-acetatna, butanolna i vodena) i ispitati korelaciju sa anti-*Enterococcus faecalis* aktivnošću. Hemijska analiza je obuhvatala kvantifikaciju svercijamarina, genciopikrozida, izoviteksina, izoorijentina i izogentizina korišćenjem tečne hromatografije visokih performansi, kao i kvantifikaciju ukupnih polifenola upotrebom Folin-Ciocalteu metode. Korelacija između hemijskog sastava i anti-*Enterococcus faecalis* aktivnosti je određena Pirsonovim testom korelacije. Frakcionisanje je znatno uticalo na fitohemijski profil uzoraka. Genciopikrozid, sa sadržajem koji je varirao u rasponu od 4,60 ± 0,18 do 120,38 ± 8,43 mg/g, bio je dominantan u svim uzorcima, osim u petrol-etarskoj frakciji, gde je sa sadržajem od 4,87 ± 0,15 mg/g bio dominantan izogentizin. U etil-acetatnoj frakciji, koja je pokazala najbolju anti-*Enterococcus faecalis* aktivnost, sadržaj većine jedinjenja bio je veći u odnosu na ekstrakt, osim svercijamarina i izoviteksina, čiji je sadržaj bio niži. Nije utvrđena statistički značajna korelacija između anti-*Enterococcus faecalis* aktivnosti i sadržaja nijednog praćenog jedinjenja ($p > 0,05$). Odsustvo korelacije ukazuje da bi za aktivnost mogao biti odgovoran sinergizam različitih jedinjenja ili jedinjenje koje nije kvantifikovano. Potrebno je sprovesti dalja istraživanja da bi se ispitala ova pretpostavka.

Ključne reči: *trava od žutice, Enterococcus faecalis, frakcionisanje vođeno biološkim testom, fitohemijski profil*

Zahvalnica: *Ovo istraživanje je finansirano od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije, broj projekatata 451-03-68/2022-14/200113 i 451-03-68/2022-14/200003.*

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WILD APPLE FRUIT AND SUNFLOWER OIL IN SKIN CARE PRODUCTS

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Wild apple fruit represents a good source of the bioactive hydration substances (polyphenols). Sunflower oil can be used to extract these active substances, but also as a good emollient for the skin. The application of products with oil extract of wild apple fruit shows beneficial hydrating effects on the skin. The aim of this study was the preparation of wild apple fruit extract (*Malus sylvestris fructus* (L.) Mill., Rosaceae), originated from Serbia, using sunflower oil, as well as the preparation of creams with the extract, the investigation of the amount of polyphenols in the creams, and *in vivo* investigation of efficacy of the creams after skin application. Liquid oil extract (ES) was prepared in the drug:extract ratio 1:5 (m:m) with sunflower oil as a solvent and digestion as the extraction method. ES was then incorporated into o/w type creams, which were stabilized by biodegradable (cream ESCB) and conventional (ESCC) mixed emulsifiers. The polyphenol content (phenols, flavonoids, tannins, anthocyanins) was determined by the *HPLC* analysis, while *in vivo* efficacy included the investigation of the hydration potential of the creams, the trans-epidermal water loss-TEWL and the skin pH 6 hours after the application of the cream onto healthy volunteers' skin. The obtained results indicated a good polyphenol content in the examined creams (the content was better in ESCB (54.86mg/100g ESCB) compared to ESCC (36.07mg/100g ESCC)). The *in vivo* investigation showed beneficial effects on the skin after the application of the creams (a significant increase in skin's hydration was recorded after the application of ESCB (ΔEC was 13.3±16.77) compared to ESCC (ΔEC was 10.12±5.86)), while TEWL and skin pH values remained unchanged. Wild apple fruit as a valuable source of polyphenols in combination with sunflower oil showed beneficial hydration effects on human skin, and therefore it can be used in skin care products.

Keywords: *Wild apple fruit, Sunflower oil, Polyphenols, Skin hydration, Skin care product*

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PLOD DIVLJE JABUKE I SUNCOKRETOVO ULJE U PROIZVODIMA ZA NEGU KOŽE

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Plod divlje jabuke predstavlja dobar izvor bioaktivnih hidratacionih supstanci (polifenoli). Suncokretovo ulje se može koristiti za ekstrakciju ovih aktivnih supstanci, ali i kao dobar emolijens za kožu. Primena proizvoda sa uljanim ekstraktom ploda divlje jabuke pokazuje povoljne hidratacione efekte na koži. Cilj rada bio je priprema ekstrakta ploda divlje jabuke (*Malus sylvestris fructus* (L.) Mill., Rosaceae), poreklom iz Srbije, sa suncokretovim uljem, izrada kremova sa ekstraktom, ispitivanje sadržaja polifenola u kremovima, kao i *in vivo* ispitivanje efikasnosti kremova nakon primene na koži. Tečni uljani ekstrakt (ES) je pripremljen u droga:ekstrakt odnosu 1:5 (m:m) sa suncokretovim uljem kao ekstragensom i primenom digestije kao ekstrakcione metode. ES je zatim inkorporiran u kremove u/v tipa, koji su stabilizovani biodegradabilnim (krem ESKB) i konvencionalnim (ESKK) mešanim emulgatorima. Sadržaj polifenola (fenola, flavonoida, tanina, antocijana) je određen *HPLC* analizom, a *in vivo* efikasnost je podrazumevala ispitivanje hidratacionog potencijala kremova, transepidermalnog gubitka vode-TEGV i pH kože nakon 6 sati primene kremova na koži zdravih dobrovoljaca. Dobijeni rezultati su ukazali na dobar sadržaj polifenola u ispitivanim kremovima (sadržaj je bio bolji u ESKB (54,86 mg/100 g ESKB) u odnosu na ESKK (36,07 mg/100 g ESKK)). *In vivo* ispitivanje je pokazalo povoljne efekte na koži nakon primene kremova (zabeleženo je značajnije povećanje hidratacije kože nakon primene ESKB (ΔEC je bila 13,3 ± 16,77) u odnosu na ESKK (ΔEC je bila 10,12 ± 5,86)), dok su vrednosti TEGV i pH kože ostale nepromenjene. Plod divlje jabuke, kao značajan izvor polifenola, u kombinaciji sa suncokretovim uljem pokazao je povoljne hidratacione efekte na humanoj koži, pa se može koristiti u proizvodima namenjenim za negu kože.

Ključne reči: *plod divlje jabuke, suncokretovo ulje, polifenoli, hidratacija kože, proizvodi za negu kože*

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BILBERRY EFFECT ON THE BASAL MEMBRANE OF THE RAT KIDNEY

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Bilberry, a very delicious fruit and a functional food, has been in the focus of much research lately. It was documented to have many health-promoting effects and, due to its antioxidant activity, it could be used in the prevention of diseases caused by oxidative stress. The aim of our study was to examine whether bilberry-fed rats had the function and structure of their kidneys and its basal membrane impaired by comparing it with a control group of rats given only saline. The study was conducted with two groups of rats: control (C) group and B group which was treated with bilberry. Kidney function was evaluated and histopathological studies were carried out. Bilberry did not cause any significant changes in the serum urea and creatinine levels when compared to the control group. Also, the histological analysis revealed that the B group of rats had normal kidney structure. Based on our results the bilberry diet in dosage of 100 mg/kg daily is safe for rat kidneys and does not cause them any structural or functional damage, considering that the kidney tissue basal membrane of treated rats stayed intact and that the serum parameters were unaltered.

Key words: *rat, bilberry, oxidative stress*

Acknowledgement: *451-03-68/2022-14/200113*

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EFEKAT BOROVNICE NA BAZALNU MEMBRANU BUBREGA PACOVA

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Jako uskusno voće i funkcionalna hrana, borovnica, u poslednje vreme se nalazi u fokusu istraživanja. Dokumentovano je da ima mnogo efekata na zdravlje i da se može koristiti kao prevencija protiv bolesti uzrokovanih oksidativnim stresom zbog svoje antioksidativne aktivnosti. Cilj našeg istraživanja bio je da ispitamo da li je kod pacova hranjenih borovnicom oštećena funkcija i struktura bubrega i bazalne membrane, upoređivanjem sa kontrolnom grupom pacova koji su dobijali samo fiziološki rastvor. Istraživanje je sprovedeno na dve grupe pacova: kontrolnoj (C) grupi i B grupi, tretiranoj borovnicom. Procenjena je funkcija bubrega, kao i histopatološke studije. Borovnica nije izazvala značajne promene u serumu uree i kreatinina u poređenju sa kontrolnom grupom. Takođe, histološkom analizom utvrđeno je da B grupa pacova ima normalnu strukturu bubrega. Na osnovu naših rezultata utvrdili smo da je ishrana borovnicom u dozi od 100 mg/kg dnevno bezbedna za bubrege pacova i ne izaziva nikakva strukturna ili funkcionalna oštećenja. Bazalna membrane bubrega pacova je ostala netaknuta.

***Ključne reči**: pacov, borovnica, oksidativni stres*

***Zahvalnica**: 451-03-68/2022-14/200113*

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ANTIMICROBIAL ACTIVITY OF SPIRONOLACTONE EMULSION AGAINST *STAPHYLOCOCCUS AUREUS* AND *PSEUDOMONAS AERUGINOSA*

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Introduction: Spironolactone (SP), a well-known synthetic steroidal diuretic drug, is being used as an off-label treatment for acne, alopecia and hirsutism. Recently, there has been a growing interest in topical SP formulations in order to minimize the systemic side effects associated with the oral drug administration. Our previous study confirmed safety of topical 5% SP preparations. In this regard, we aimed to investigate the potential activity of SP emulsion against two bacterial strains that can cause skin infections.

Materials and methods: We tested 5% SP topical emulsion stabilized with alkyl polyglucoside (APG) sugar emulsifier *Cetearyl glucoside & cetearyl alcohol*. For antimicrobial bioassay, two bacterial strains were used: *Staphylococcus aureus* (ATCC 6538) and *Pseudomonas aeruginosa* (ATCC 9027), since they cause numerous skin infections. Minimum inhibitory concentration (MIC) was determined by a microwell dilution method according to the recommendations of the National Committee for Clinical Laboratory Standards. Tigecycline and chloramphenicol were used as positive, while placebo sample (emulsion without SP) was used as negative control.

Results and discussion: 5% SP emulsion showed certain antimicrobial potential against both tested bacterial strains. The MIC values were 6.25mg/g for *Pseudomonas aeruginosa* and 12.5mg/g for *Staphylococcus aureus*. The placebo sample showed minor activity against the tested microbial strains. On the other hand, commercial antimicrobial drugs tigecycline and chloramphenicol exhibited obviously higher antimicrobial activity than SP emulsion, as expected.

Conclusion: SP emulsion showed satisfactory antimicrobial activity against the tested bacterial strains. This opens the possibility of using topical SP preparations for the treatment of infected skin, especially considering the increase in bacterial resistance to commonly used antibiotics.

Keywords: *spironolactone, antimicrobial activity, alkyl polyglucoside emulsifier, skin infection*

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ANTIMIKROBNA AKTIVNOST EMULZIJE SA SPIRONOLAKTONOM PREMA *STAPHYLOCOCCUS AUREUS* I *PSEUDOMONAS AERUGINOSA*

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Uvod. Spironolakton (SP), poznati sintetski sterodini diuretik, koristi se u vidu "off-label" terapije akni, alopecije i hirzutizma. U poslednje vreme raste interesovanje za lokalnom primenom SP u cilju smanjivanja sistemskih neželjenih efekata povezanih sa oralnom primenom leka. Naša prethodna studija je potvrdila bezbednost primene emulzija za primenu na koži sa 5% SP. S tim u vezi, želeli smo da ispitamo potencijalnu aktivnost emulzije sa SP prema dva bakterijska soja koja mogu izazvati kožne infekcije.

Materijali i metode. Cilj rada bio je da se ispita antimikrobna aktivnost emulzije za lokalnu primenu na koži sa 5% SP stabilizovane šećernim alkil-poliglukozidnim emulgatorom *Cetearil glukozid & cetearil alcohol*. U tu svrhu korišćena su dva bakterijska soja: *Staphylococcus aureus* (ATCC 6538) i *Pseudomonas aeruginosa* (ATCC 9027), budući da izazivaju brojne kožne infekcije. Za određivanje minimalne inhibitorne koncentracije (MIK) korišćena je mikrodiluciona metoda u skladu sa preporukama Nacionalnog komiteta za standarde kliničkih laboratorija. Tigeciklin i hloramfenikol su služili kao pozitivna, dok je placebo uzorak (emulzija bez SP) bio negativna kontrola.

Rezultati i diskusija. Emulzija sa 5% SP je pokazala određeni antimikrobni potencijal prema oba testirana bakterijska soja. Vrednosti MIK su bile 6,25 mg/g za *Pseudomonas aeruginosa* i 12,5 mg/g za *Staphylococcus aureus*. Placebo uzorak je pokazao slabiju aktivnost prema ispitivanim bakterijskim sojevima. Sa druge strane, komercijalni antibiotski lekovi tigeciklin i hloramfenikol pokazali su očigledno veću antimikrobnu aktivnost od emulzije sa SP, kako se i očekivalo.

Zaključak. Emulzija sa SP je pokazala zadovoljavajuću antimikrobnu aktivnost prema ispitivanim bakterijskim sojevima. Ovo otvara mogućnost primene lokalnih preparata SP za lečenje inficirane kože, posebno imajući u vidu rastuću rezistenciju bakterija na najčešće korišćene antibiotike.

Ključne reči: *spironolakton, antimikrobna aktivnost, alkil-poliglukozidni emulgator, kožna infekcija*

Zahvalnica: *Ovaj rad je podržan od strane Ministarstva prosvete, nauke i tehnološkog razvoja Rebuplike Srbije (451-03-9/2021-14/200113) i internog naučnog projekta (br. 15) Medicinskog fakulteta Univerziteta u Nišu.*

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CHEMICAL COMPOSITION AND ANTIOXIDANT ACTIVITY OF ANISE (*PIMPINELLA ANISUM* L.) FRUCTUS ESSENTIAL OIL HYDRODISTILLATION FRACTIONS

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The aim of this study was to examine the effect of hydrodistillation time on anethole content (as well as other constituents of essential oil) and antioxidant activity of collected essential oils' fractions from anisi fructus for five hydrodistillation periods: I (0-15 min), II (15-30 min), III (30-60 min), IV(60-90 min) and V (90-120 min). Plant material (*Anisi fructus*) was collected in North Macedonia and essential oil was obtained by Clevenger-type hydrodistillation (CHD). The qualitative and quantitative composition of collected essential oil fractions was determined by a combination of gas chromatography with mass spectrometry (GC/MS) and flame ionization detection (GC/FID). The efficiency of different fractions of essential oil to scavenge 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals was evaluated using a spectrophotometry method. Essential oil yield increased with the length of the CHD time and reached a maximum at 120 min (2.26%). The content of monoterpenes and oxygenated monoterpenes decreased, while the content of aromatic compounds increased with the time of CHD. The content of (*E*)-anethole increased (I-60.0%, II-67.1%, III-72.0%, IV-77.2%, V-81.3%), while the content of fenchone decreased (I-22.9%, II-21.1%, III-18.1%, IV-13.8%, V-10.3%) with the time of CHD. Results indicated that all obtained essential oils exhibited remarkable antioxidant activity (IC50 range was 71.63-14.80 mg/ml – I-V, respectively). The obtained antioxidant potential most probably should be addressed to aromatic compounds, first of all to anethole. This study proved that CHD time affects the composition and antioxidant activity of anise essential oil, and also provides the possibility of "leading the process" until the highest anethole contribution is achieved.

Keywords: *Pimpinella anisum* L., *anise, essential oil, hydrodistillation fractions, antioxidant activity*

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HEMIJSKI SASTAV I ANTIOKSIDATIVNA AKTIVNOST FRAKCIJA ETARSKOG ULJA PLODA ANISA (*PIMPINELLA ANISUM* L.) DOBIJENIH HIDRODESTILACIJOM

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Cilj ovog istraživanja bio je da se ispita uticaj vremena hidrodestilacije na sadržaj anetola (kao i drugih sastojaka etarskog ulja) i antioksidativna aktivnost sakupljenih frakcija etarskog ulja iz ploda anisa u pet perioda hidrodestilacije: I (0-15 min), II (15-30 min), III (30-60 min), IV (60-90 min) i V (90-120 min). Biljni materijal (*Anisi fructus*) je sakupljen u Severnoj Makedoniji, a etarsko ulje je dobijeno hidrodestilacijom po Klevengeru (CHD). Kombinacijom gasne hromatografije sa masenom spektrometrijom (GC/MS) i plameno jonizujućim detektorom (GC/FID) određen je kvalitativni i kvantitativni sastav sakupljenih frakcija etarskog ulja. Efikasnost različitih frakcija etarskog ulja u uklanjanju 2,2-difenil-1-pikrilhidrazil (DPPH) radikala je procenjena metodom spektrofotometrije. Prinos etarskog ulja se povećavao sa dužinom CHD vremena i dostigao maksimum za vreme od 120 min (2,26%). Sadržaj monoterpena i oksigenisanih monoterpena opada, dok se sadržaj aromatičnih jedinjenja povećava sa vremenom CHD. Sadržaj (*E*)-anetola raste (I-60,0%, II-67,1%, III-72,0%, IV-77,2%, V-81,3%), dok sadržaj fenhona opada (I-22,9%, II- 21,1%, III-18,1%, IV-13,8%, V-10,3%) sa vremenom CHD. Rezultati su pokazali da su sva dobijena etarska ulja pokazala izuzetnu antioksidativnu aktivnost (raspon IC50 bio je 71,63-14,80 mg/ml – I-V, respektivno). Za antioksidativni potencijal najverovatnije su odgovorna aromatična jedinjenja, pre svega anetol. Ova studija je dokazala da vreme CHD utiče na sastav i antioksidativnu aktivnost etarskog ulja anisa, a takođe pruža mogućnost „vođenja procesa“ dok se ne postigne najveći prinos anetola.

Keywords: *Pimpinella anisum L., anis, etarsko ulje, hidrodestilacija, frakcije,antioksidativna aktivnost*

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THIRD DEGREE BURNS TREATMENT: THEORETICAL APPROACH

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Here we discuss novel and emerging pharmaceutical agents and dressings for the treatment of third-degree burns. The severity of burns can be stratified in several ways, and the classification given by the American Burn Association is most often applied. When treating third-degree burns, analgesic therapy is initially introduced, and depending on the extent of the injury, liquid replacement is usually performed according to the "Parkland formula". Initial debridement by a surgeon may be necessary in certain cases. In our institution, the initial triple dressing (vaseline, saline solution, dry gauze) is used. However, there are other ways to manage this kind of injury. For reducing the risk of bleeding during surgical management, a thrombin spray or epinephrine are currently in use. Wound dressings can be divided into biological, semi-biological, conventional and synthetic. Dressings based on chitosan biopolymers and cellulose-based hydrogels have been shown to be successful in healing and preventing bacterial infection. The use of antimicrobial topical agents (bacitracin, mupirocin, etc.) and dressings containing silver is widespread in burn patients. The potential benefits of new active substances are still being investigated with the aim of treating the metabolic imbalance that can occur after severe burns. These include recombinant human growth hormone, insulin, oxandrolone, metformin, propranolol, Szeto-Schiller peptide etc. The research results indicate that the use of epidermal growth factor, fibroblast growth factor and granulocyte and macrophage colony stimulation factor can promote wound healing. Using epidermal growth factor, fibroblast growth factor and granulocyte-macrophage colony- stimulating factor could promote better wound healing. We believe that it is necessary to know modern ways of treating burns, as well as drugs that can be used in clinical practice, but it is also necessary to pay attention to those that are yet to be used.

Keywords: *burns, wound, agents, management, healing, dressings*

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TERAPIJA OPEKOTINA TREĆEG STEPENA: TEORIJSKI PRISTUP

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U ovom radu razmatramo nove načine zbrinjavanja opekotina trećeg stepena. Težina opekotina može se stratifikovati na više načina, a najčešće se primenjuje klasifikacija koju je dalo Američko udruženje za opekotine. Prilikom zbrinjavanja opekotina trećeg stepena inicijalno se uvodi analgetska terapija, a zavisno od opsežnosti povrede vrši se nadoknada tečnosti, najčešće prema "Parklandovoj formuli". Inicijalni debridman od strane hirurga može biti neophodan u određenim slučajevima. U svakodnevnoj kliničkoj praksi praktikuje se inicijalno previjanje trostrukim prevojem (vazelin, fiziološki rastvor, suva gaza). Međutim, postoje i drugi načini zbrinjavanja ovakvog tipa povreda. Radi smanjenja rizika od krvarenja tokom hirurškog zbrinjavanja, trenutno su u upotrebi trombinski sprej i epinefrin. Zavoji za rane mogu se podeliti u biološke, polubiološke, konvencionalne i sintetičke. Zavoji na bazi biopolimera hitozana i hidrogelova baziranih na celulozi pokazali su se uspešnim u zaceljivanju i sprečavanju bakterijske infekcije. Upotreba antimikrobnih topikalnih agenasa (bacitracin, mupirocin i sl.) i zavoja koji sadrže srebro je rasprostranjena kod pacijenata sa opekotinama. Potencijalna korist novih aktivnih supstanci se tek ispituje, sa ciljem zbrinjavanja metaboličkog disbalansa koji može nastupiti nakon teških opekotina. Neke od njih su rekombinantni humani hormon rasta, insulin, oksandrolon, metformin, propranolol i Szeto-Schiller peptid. Rezultati istraživanja upućuju da korišćenje: epidermalog faktora rasta, faktora rasta fibroblasta i faktora stimulacije kolonija granulocita i makrofaga može pospešiti zaceljivanje rana. Mišljenja smo da je neophodno poznavanje savremenih načina tretiranja opekotina, kao i lekova koji se mogu koristiti u kliničkoj praksi, ali je potrebno obratiti pažnju i na one koji će se tek naći u upotrebi.

Ključne reči: *opekotine, rane, supstance, zaceljivanje, zbrinjavanje, zavoji*

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ADVERSE EFFECTS OF IMMUNOSUPPRESSIVE DRUGS IN RENAL TRANSPLANT RECIPIENTS

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After renal transplantation, patients face a life-long regimen of immunosuppressive drugs. Their adverse effects can affect the patients' quality of life, leading to nonadherence and impaired graft survival. The objective was to evaluate the frequency and differences of adverse effects within renal transplant recipients in relation to the calcineurin inhibitor regimen (tacrolimus (TAC) or cyclosporine A (CsA) based). This research was conducted on 67 stable renal transplant recipients (average age 44.33±11.45 years), who received prednisone, enteric-coated mycophenolate sodium, and TAC or CsA. The patients were treated in the Clinic of Nephrology, University Clinical Centre of Nis, Serbia. An evaluation of adverse effects was performed by a scoring system developed by Meaney et al. from the University of Buffalo. Adverse effects were grouped according to the nature of symptoms: gastrointestinal (GIT), esthetic (EST), central nervous system (CNS) and osteomuscular (OST). The most common adverse effects were GIT (78.6%), followed by CNS (69.5%) and EST (57.8%). Patients treated with TAC experienced a significantly higher GIT ratio than CsA (0.18±0.15 vs 0.09±0.11; p=0.045). There was no difference between patients treated with TAC and CsA for the EST, CNS, OST, and cumulative adverse effect ratios. For individual adverse effects, the reported incidence of vomiting is higher in patients treated with TAC, while gingival hyperplasia is more common in patients treated with CsA. Careful prescribing of immunosuppressive drugs and prospective clinical monitoring of adverse effects may improve patient adherence, quality of life and graft outcomes.

Keywords: *Immunosuppressive drugs, tacrolimus, cyclosporine A, adverse effects, renal transplantation*

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NEŽELJENI EFEKTI IMUNOSUPRESIVNIH LEKOVA KOD PACIJENATA SA TRANSPLANTIRANIM BUBREGOM

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Nakon transplantacije bubrega pacijenti se suočavaju sa doživotnom primenom imunosupresivnih lekova. Neželjeni efekti imunosupresivne terapije mogu značajno da smanje adherencu pacijenata, utiču na kvalitet života i preživljavanje grafta. Cilj našeg istraživanja bila je procena učestalosti i razlika u ispoljenim neželjenim efektima kod pacijenata sa transplantiranim bubregom na terapiji kalcineurinskim inhibitorom (režim zasnovan na takrolimusu (TAC) ili ciklosporinu A (CsA)). Istraživanje je obuhvatilo 67 pacijenata sa transplantiranim bubregom (prosečne starosti 44,33 ± 11,45 godina) na terapiji prednizonom, natrijumovom soli mikofenolne kiseline i TAC ili CsA. Pacijenti su lečeni na Klinici za nefrologiju Univerzitetskog kliničkog centra Niš, Srbija. Procena neželjenih efekata izvršena je pomoću sistema za ocenjivanje neželjenih efekata koji su razvili Meaney i saradnici sa Univerziteta Bufalo. Neželjeni efekti su grupisani prema prirodi simptoma na: gastrointestinalne (GIT), estetske (EST), osteomuskularne (OST) i neurološke (CNS). Najčešći neželjeni efekti bili su GIT (78,6%), CNS (69,5%) i EST (57,8%). Pacijenti lečeni TAC imali su izraženije GIT neželjene efekte u poređenju sa pacijentima na terapiji CsA (0,18 ± 0,15 naspram 0,09 ± 0,11; p = 0,045). Nije bilo razlike u EST, CNS, OST i kumulativnom skoru između pacijenata na terapiji TAC i CsA. U pogledu individualnih neželjenih efekata, incidenca povraćanja bila je veća kod pacijenata lečenih TAC, dok je hiperplazija gingive bila češća kod pacijenata lečenih CsA. Pažljivo propisivanje imunosupresivnih lekova i kontinuirano praćenje neželjenih efekata mogu poboljšati adherencu pacijenata, njihov kvalitet života i ishode lečenja.

Ključne reči: *imunosupresivni lekovi, takrolimus, ciklosporin A, neželjeni efekti, transplantacija bubrega*

Zahvalnica: *Rad je rezultat istraživanja koje je finansiralo Ministarstvo prosvete, nauke i tehnološkog razvoja Srbije (451-03-68/2022-14/200113)*

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EDUCATION ON THE ROLE OF NEW INFORMATION TECHNOLOGIES IN MARKETING IN PHARMACY

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New information technologies in pharmacy can be used in marketing through advertising, marketing products and services, and connecting with other health professionals. This paper aims to highlight the importance of pharmacist education and the importance and advantages of modern methods. A project includes a workshop for health professionals to raise digital literacy to a higher level.

The workshop was conducted three times for three months and included pharmacists from Serbia, Montenegro, Croatia, and Bosnia and Herzegovina. A total of 30 pharmacists attended it. In addition to basic pharmacy studies, the educator completed the School of Personal Development for Masters in Pharmacy education with respected colleague Arijana Meštrović, then the digital marketing course at the Ludus Academy, and the Virtual Assistant course at the Nikolina Andrić Academy.

The workshop contains the following modules: 1. Basics of working in WordPress - website as the primary communication channel; 2. Content and copywriting for health professionals; 3. Work in Mailchimp – newsletter; 4. Work at Thinkifink - a program for online workshops; 5. Social Networks - Running an IG page, Facebook page – FacebookAds; LinkedIn; 5. Creation of an e-book; 6. Working in Canva – program on design; 7. Program Shopify. Recordings of lectures that participants could listen to indefinitely, written materialand 1-on-1 consultations at the end of the modules were used. During the evaluation of the workshop's effectiveness, it was observed that the most significant number of colleagues started successfully writing professional texts on pharmaceutical platforms, 50%. 10% of colleagues created their e-books, 10% of colleagues successfully conducted their online workshop, and all of them mastered the use of social medianetwork to promote their services.

The most apparent benefit is marketing through advertising and marketing of products and services and connecting with other health professionals. Participants learned techniques for writing professional texts for pharmaceutical platforms and mastered the use of social networks and e-book writing. In future activities, we should devise ways and empower colleagues to master better WordPress and Shopify, which can be very significant in marketing their pharmacies.

Keywords: *education, workshop, digital, profession, improvement*

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EDUKACIJA O PRIMENI NOVIH INFORMACIONIH TEHNOLOGIJA U MARKETINGU U FARMACIJI

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Nove informacione tehnologije u farmaciji se mogu koristiti u oblasti marketinga kroz oglašavanje i plasiranje proizvoda i usluga kao i za povezivanje sa drugim zdravstvenim profesionalacima. Cilj ovog rada bio je da se ukaže na značaj edukacije farmaceuta i značaj i prednosti savremenih metoda koje se koriste. Projekat koji podrazumeva radionicu za zdravstvene profesionalce sa svrhom podizanja digitalne pismenosti na viši nivo.
Radionica je sprovedena tri puta u trajanju od tri meseca i obuhvatala je farmaceute iz Srbije, Crne Gore, Hrvatske i Bosne i Hercegovine. Pohađala su je ukupno 30 farmaceuta. Edukator, pored završenih osnovnih studija farmacije je završio edukaciju Škola osobnog razvoja za magistre farmacije kod uvažene koleginice Arijane Meštrović, potom kurs digitalnog marketinga na Ludus akademiji i kurs za Virtualnog asistenta na Akademiji Nikoline Andrić.
Radionica sadrži sledeće module: 1. Osnove rada u *WordPress* – sajt kao primarni kanal komunikacije; 2. Content i *copywriting* za zdravstvene profesionalce; 3. Rad u *Mailchimpu* – *newsletter*; 4. Rad u Thinkifinku – program za online radionice; 5. Društvene mreže – Vođenje IG stranice; *Facebook* stranica – *FacebookAds*; *LinkedIn*; 5.Izrada e-book-a; 6. Rad u Canvi – program o dizajnu; 7. Program *Shopify*. Korišćeni su snimci predavanja koje su polaznici mogli slušati neograničeno, pisani materiali, kao i konsultacije jedan na jedan na kraju odslušanih modula. U toku procene efikasnosti radionice uočeno je da je najveći broj kolega počeo uspešno pisati stručne tekstove na farmaceutskim platformama, 50%, sopstveni e-book je izradilo 10% kolega, sopstvenu onlajn radionicu je uspešno sprovelo 10% kolega, a svi su savladali korišćenje društvenih mreža u cilju promocija svojih usluga.
Najočigledniji benefit je u oblasti marketinga kroz oglašavanje i plasiranje proizvoda i usluga, kao i povezivanje sa drugim zdravstvenim profesionalacima. Učesnici su naučili tehnike pisanja stručnih tekstova za farmaceutske platforme i savladali korišćenje društvenih mreža i pisanje *e-booka*. U budućim aktivnostima treba osmisliti načine i osnažiti kolege da bolje savladaju *WordPress* i *Shopify*, što može biti veoma značajno u marketingu sopstvenih apoteka.

Ključne reči: *edukacija, radionica, digital, profesija, unapređivanje*

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THE SIGNIFICANCE OF DETERMINING THE SEVERITY OF LOWER URINARY TRACT SYMPTOMS IN THE MALE POPULATION IN THE REPUBLIC OF SERBIA

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A reliable diagnostic tool used to measure the severity of symptoms of lower urinary tract disorders is the International Prostate Symptom Score questionnaire (IPSS), developed by the American Urological Association in 1992. The IPSS is available online in 53 different language variants. Twenty-seven language versions of the questionnaire have been validated in 22 published studies. The aim of the work is to examine the prevalence of lower urinary tract symptoms in men in the Republic of Serbia. The research was conducted between May and June 2022, on a sample of 207 males. The respondents were a randomly selected group over the age of 18. After the obtained results, data processing was started in the SPSS program. Most of the respondents were over 56 years old (32.4%), and according to their level of education, most of the respondents had a university education (40.1%) and high school (36.7%). To the question "How often in the last month did they get up at night to urinate?", the largest percentage of respondents answered that they never got up (26.6%). Other answers were from 1 to 5 and more, respectively 18.8%; 17.4%; 16.4%; 12.6%; 8.2%. Half of the respondents (51.2%) had intermittent urination in the last month, and 49.3% of the respondents could not delay urination in the last month. The prevalence of lower urinary tract symptoms is high in the studied population. It is necessary to increase the awareness of the general population about the importance of lower urinary tract symptoms.

Keywords: *urinary tract, IPSS, urologist, urinary diseases*

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ZNAČAJ ODREĐIVANJA TEŽINE SIMPTOMA DONJIH URINARNIH PUTEVA U MUŠKOJ POPULACIJI U REPUBLICI SRBIJI

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Pouzdan dijagnostički alat koji se koristi za merenje težine simptoma poremećaja donjeg urinarnog trakta je upitnik Internacionalni prostatični simptom skor (IPSS). Razvijen je od strane Američke urološke asocijacije 1992. godine. IPSS je dostupan na internetu u 53 različite jezičke varijante. Dvadeset sedam jezičkih varijanti upitnika je validirano u 22 objavljene studije. Cilj rada bio je ispitati prevalencu simptoma donjeg urinarnog trakta kod muškaraca u Republici Srbiji. Istraživanje je sprovedeno tokom maja i juna, na uzorku od 207 muškaraca. Ispitanici su bili nasumično odabrana grupa muškaraca starosti preko 18 godina. Nakon dobijenih rezultata pristupilo se obradi podataka u programu SPSS. Najviše je bilo ispitanika starijih od 56 godina (32,4%), a prema nivou obrazovanja, najviše je bilo ispitanika sa fakultetskim (40,1%) i srednjim obrazovanjem (36,7%). Na pitanje „Koliko su često u poslednjih mesec dana ustajali noću radi mokrenja?“ najveći procenat ispitanika odgovorio negativno (26,6%). Ostali odgovori bili su od jedanput do pet i više, redom 18,8%; 17,4%; 16,4%; 12,6%; 8,2%. Kod polovine ispitanika (51,2%) bilo je prisutno isprekidano mokrenje poslednjih mesec dana, a 49,3% ispitanika u poslednjih mesec dana nije moglo da odloži mokrenje. Prevalenca simptoma donjih urinarnih puteva je visoka u ispitanoj populaciji. Potrebno je povećati i svest opšte populacije o značaju simptoma donjih urinarnih puteva.

Ključne reči: *urinarni trakt, IPSS, urolog, urinarna oboljenja*

Zahvalnica*: Rad je podržan od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije (Br: 451-03-68/2022-14/200161)*

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CASE STUDY: UNIVARIATE TIME SERIES ANALYSIS AND FORECASTING OF PHARMACEUTICAL PRODUCTS' SALES DATA AT SMALL SCALE

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This work aimed to validate different methods and approaches related to sales univariate time series data of preparation, analysis and forecasting, with the goal to facilitate recommending sales and marketing strategies based on trend/seasonality effects and forecasting sales of eight different groups of pharmaceutical products with diverse characteristics, such as stationarity, seasonality, the volume of residuals and sales data variance. Aggregate sales data related to different classes of pharmaceutical products in hourly time periods were used, namely: anti-inflammatory and anti-rheumatic products (M01AB, M01AE), analgesics and antipyretics (N02BA, N02BE), psycholeptics drugs (N05B, N05C), drugs for obstructive airway diseases (R03) and antihistamines for systemic use (R06). Effectiveness of three forecasting methods, namely: ARIMA, Prophet and Long-Short Term Memory (LSTM) neural networks was investigated. Methods were complemented with two optimization and validation approaches, relevant for short-term (so - called rolling forecast scenario) and long-term forecasting. For the rolling forecasts, the best results were achieved by using the ARIMA-based method, with RMSE forecasting errors ranging from RMSE=7.98 for N05C to RMSE=71.56 for M01AB. As for long-term forecasting, the most performed algorithms were LSTM-based architectures, namely stacked LSTM and bi-directional models. Time-series analyses and forecasts have guided useful conclusions and recommendations. Daily, weekly and annual seasonality analyses were proven useful for identifying the proposed periods for special sales and marketing campaigns. Forecasts have proven better than Naïve methods and in acceptable intervals for long-term planning. The forecasts could be significantly improved by also considering other features, such as weather data, price data and different date/time features.

Keywords: *pharmaceutical products, sales forecasting, neural networks, time-series analysis*

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STUDIJA SLUČAJA: ANALIZA UNIVARIJANTNE VREMENSKE SERIJE I PREDVIĐANJE PODATAKA O PRODAJI FARMACEUTSKIH PROIZVODA U MALOM RAZMERU

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Ovaj rad je imao za cilj validaciju različitih metoda i pristupa koji se odnose na pripremu, analizu i prognozu podataka univarijantnih vremenskih serija prodaje, sa ciljem da omogući preporuku prodajnih i marketinških strategija zasnovanih na efektima trenda/sezonalnosti i predviđanje prodaje osam različitih grupa farmaceutskih proizvoda sa različitim karakteristikama, kao što su stacionarnost, sezonalnost, obim reziduala i varijacija podataka o prodaji. Korišćeni su zbirni podaci o prodaji koji se odnose na različite klase farmaceutskih proizvoda u časovnim periodima, i to: antiinflamatorni i antireumatski proizvodi (M01AB, M01AE), analgetici i antipiretici (N02BA, N02BE), psiholeptici (N05B, N05C), lekovi za opstruktivne bolesti disajnih puteva (R03) i antihistaminici za sistemsku primenu (R06). Ispitivana je efikasnost tri metode predviđanja, a to su: ARIMA, *Prophet* i *Long-Short Term Memory* (LSTM) neuronske mreže. Metode su dopunjene sa dva pristupa optimizacije i validacije, relevantna za kratkoročno (tzv. scenario rotirajućih prognoza) i dugoročno predviđanje. Za rotirajuće prognoze, najbolji rezultati su postignuti korišćenjem ARIMA metode, sa greškom u rasponu od RMSE = 7,98 za N05C do RMSE = 71,56 za M01AB. Kod dugoročnog predviđanja, najefikasniji algoritmi su bile arhitekture zasnovane na LSTM mrežama, odnosno višeslojni i bidirekcioni LSTM modeli. Analize i prognoze vremenskih serija dovele su do korisnih zaključaka i preporuka. Dnevna, nedeljna i godišnja analiza sezonalnosti pokazala se korisnom za identifikaciju predloženih perioda za prodajne i marketinške kampanje. Prognoze su se pokazale boljim od naivnih metoda i nalaze se u prihvatljivim intervalima za dugoročno planiranje. Prognoze bi se mogle poboljšati uzimanjem u obzir drugih karakteristika, kao što su vremenski podaci i podaci o cenama.

Ključnereči: *predviđanje prodaje, neuronske mreže, analiza vremenskih serija*

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SPASMOLYTIC POTENTIAL OF LEMON (*CITRUS LIMON* (L.) OSBECK) ESSENTIAL OIL ON ISOLATED RAT DISTAL COLON

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Citrus limon (L.) Osbeck is a member of the Rutaceae family, and apart from its everyday usage as foodstuff, it has been used in the traditional medicine of many nations and has numerous potential beneficial roles. The essential oil of this fruit has a stress-relieving potential, cytotoxic and analgesic effects, and causes an increase in lipolysis and results in the suppression of body weight gain. All gastrointestinal disorders involve, to a certain extent, the disturbance of intestinal motility. Due to the vast number of beneficial properties of lemon, as well as due to its presence in everyday food, the present study aimed to evaluate the effects of *C. limon* essential oil, isolated from flavedo (obtained from Pharmanais, Srbija) on spontaneous rat distal colon contractions. Cumulative concentrations of the essential oil (0.01-50 μg/mL) were added to a tissue bath containing isolated Wistar rat distal colon strips. The changes in the contraction patterns were followed by an isometric transducer (TSZ-04-E, Experimetria Ltd., Budapest, Hungary) and the results were monitored in a compatible software (SPEL Advanced ISOSYS Data Acquisition System). The results of the present study indicate that the application of the tested lemon essential oil in a cumulative manner produces a concentration-dependent decrease in spontaneous distal colon contractions. The most prominent spasmolytic action was obtained when the highest concentration of the essential oil was added. Our future studies should involve the examination of the active constituents of lemon essential oil and their impact on contraction patterns of the distal colon.

Keywords: *Citrus limon, Essential oil, Distal colon, Contractions.*

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SPAZMOLITIČKI EFEKAT ETARSKOG ULJA LIMUNA (*CITRUS LIMON* (L.) OSBECK) NA IZOLOVANI DISTALNI SEGMENT DEBELOG CREVA PACOVA

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Citrus limon (L.) Osbeck pripada porodici Rutaceae, a osim u svakodnevnoj upotrebi kao hrana, koristi se i u tradicionalnoj medicini mnogih naroda i ima brojne blagotvorne zdravstvene efekte. Etarsko ulje plodova ima potencijal za ublažavanje stresa, citotoksično i analgetičko dejstvo, izaziva lipolizu, što za rezultat ima suzbijanje povećanja telesne mase. Svi gastrointestinalni poremećaji uključuju, u određenoj meri, poremećaj motiliteta creva. Zbog velikog broja korisnih svojstava limuna, kao i zbog njegovog prisustva u svakodnevnoj ishrani, ova studija je imala za cilj da proceni efekte etarskog ulja *C. limon*, izolovanog iz flaveda (pribavljeno od Pharmanais, Srbija) na spontane kontrakcije distalnog dela debelog creva pacova. Kumulativne koncentracije etarskog ulja (0,01 – 50 μg/mL) dodavane su u kupatilo za izolovane organe koje sadrži izolovane segmente distalnog kolona *Wistar* pacova. Promene u kontrakcijama praćene su preko izometrijskog pretvarača (TSZ-04-E, Ekperimetria Ltd., Budimpešta, Mađarska) i rezultati su praćeni u kompatibilnom softveru (SPEL Advanced ISOSIS Data Acquisition System). Rezultati ove studije ukazuju da kumulativna primena ispitivanog etarskog ulja limuna dovodi do smanjenja spontanih kontrakcija distalnog kolona u zavisnosti od koncentracije. Najizraženije spazmolitičko dejstvo je postignuto kada je dodata najviša koncentracija etarskog ulja. Naše buduće studije bi trebalo da uključe ispitivanje aktivnih sastojka etarskog ulja limuna i njihovog uticaja na obrasce kontrakcija distalnog segmenta debelog creva.

Ključne reči: *Citrus limon, etarsko ulje, distalni kolon, kontrakcije.*

Zahvalnica: *Ovo istraživanje je finansirano od strane projekta Ministarstva prosvete, nauke i tehnološkog razvoja (451-03-68/2022-14/200113).*

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EVALUATION OF THE IMPACT OF LEMON BALM (*MELISSA OFFICINALIS* L.) ESSENTIAL OIL ON NEUROTRANSMITTER METABOLIZING ENZYMES ACTIVITY

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Lemon balm (*Melissa officinalis* L.) is a well-known ethnomedicinal herb with a wide profile of beneficial properties; however, its application, especially its essential oil, was found to possess the most prominent impact on central nervous system (CNS) functioning. Neurotransmitters are the core of brain functioning, and their disbalance is behind every disease affecting CNS. Their synthesis and metabolism are dependent on the enzymes whose activity is finely regulated by brain cells. This study aimed to evaluate the inhibitory potential of the essential oil of *M. officinalis* herb, obtained from commercial sources (Siempreviva, Niš, Serbia), on GABA transaminase, total monoamine oxidase, and glutamic acid decarboxylase (GAD) in mouse brain homogenate using standard biochemical methods. The activity of GABA transaminase was decreased when the ascending concentrations of the essential oil were added to the homogenate and reached an IC_{50} of 97.5 μg/mL, while at the same time vigabatrin reached IC_{50} at a concentration of 64 μmol/mL. Total monoamine oxidase was inhibited only 36.6% by 1 mg/ml of the essential oil, while the standard inhibitor iproniazide inhibited this enzyme activity by 50% at a concentration of 40.7 μmol/L. Finally, the essential oil tested at 1 mg/mL diminished GAD activity by around 60%, while a standard competitive inhibitor 3-mercaptopropionic acid reached IC_{50} at 43 μmol/L. The results of this study revealed that *M. officinalis* essential oil exhibits most prominently GABA transaminase inhibitory activity.

Keywords: *Lemon balm, GABA transaminase, Monoamine oxidase, Glutamic acid decarboxylase.*

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ISPITIVANJE UTICAJA ETARSKOG ULJA MATIČNJAKA (*MELISSA OFFICINALIS* L.) NA AKTIVNOST ENZIMA UKLJUČENIH U METABOLIZAM NEUROTRANSMITERA

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Matičnjak (*Melissa officinalis* L.) je poznata etnomedicinska biljna vrsta kojoj se pripisuje veliki broj pozitivnih efekata na zdravlje, posebno ukoliko se primenjuje njeno etarsko ulje, a prevashodno na funkcionisanje centralnog nervnog sistema (CNS). Neurotransmiteri su osnova funkcionisanja moždanog tkiva, a disbalans u njihovoj količini je u osnovi svih bolesti CNS-a. Njihova sinteza i metabolizam zavise od enzima, čija je aktivnost veoma precizno regulisana unutar moždanih ćelija. Cilj ovog istraživanja bio je ispitivanje inhibitornog potencijala etarskog ulja herbe matičnjaka, dobijeno iz komercijalnog izvora (Sempreviva, Niš, Srbija), na aktivnost GABA transaminaze, totalne monoamino oksidaze i glutamat dekarboksilaze (GAD) u homogenatima mozgova miševa koristeći standardne biohemijske metode. Aktivnost GABA transaminaze je bila snižena dodatkom rastućih koncentracija etarskog ulja u homogenate, a ulje je postiglo IC_{50} vrednost od 97,5 μg/mL. U isto vreme vigabatrin je postigao IC_{50} vrednost od 64 μmol/mL. Totalna aktivnost monoamino oksidaze inhibisana je za 36,6% od strane etarskog ulja u koncentraciji od 1 mg/ml, dok je standardni inhibitor iproniazid doveo do 50% inhibicije enzima u koncentraciji od 40,7 μmol/L. Na kraju, etarsko ulje, testirano u koncentraciji od 1 mg/ml, smanjilo je aktivnost GAD za oko 60%, dok je standardni kompetitivni inhibitor 3-merkaptopropionska kiselina postigla IC_{50} vrednost od 43 μmol/L. Rezultati ovog istraživanja ukazuju da etarsko ulje *M. officinalis* ispoljava najizraženije inhibitorno dejstvo na aktivnost GABA transaminaze.

Ključne reči: *matičnjak, GABA transaminaza, monoamino oksidaza, glutamat dekarboksilaza.*

Zahvalnica: *Ovo istraživanje je finansirano od strane projekta Ministarstva prosvete, nauke i tehnološkog razvoja (451-03-68/2022-14/200113). Rezultati ovog istraživanja su deo doktorske disertacije Nikole Stojanovića.*

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COMPOUNDED COSMETICS AS A NEWER CONCEPT IN SKIN CARE – OUR EXPIRIENCES

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Pharmaceutical compounding of skin care products (magistral laboratory) based on the individual approach to each user represents one of the latest world trends in the care and prevention of certain skin pathological conditions. Information obtained using instrumental methods combined with the user's analysis and the professional assistance of a pharmacist can play an important role in skin care personalization. The aim of this research was to examine the habits of users in relation to care and the effectiveness of compounded cosmetic preparations by self-assessment of the skin condition through the questionnaire respondents filled out before and three weeks after using compounded cosmetic preparations. Eighty five respondents were included in the research (the questionnaire consisted of 16 open-ended and closed-ended questions), at the Dona Pharmacy, Nis, where compounded products were prepared in the magistral laboratory based on self-assessment parameters obtained during the cosmetology consultation. Out of a total of 85 respondents who report that they have been using various commercial cosmetic products for a long time without expected results, which is the reason why they come to the cosmetology consultation,10 (11.76 %) were males, while 75 (88.24%) were females, with an average age of 38.6±5.6 years. Initial skin care habits were such that 65% of users used basic care (use of cleanser and cosmetic cream), while 35% of them used intensive care (use of cleanser with a combination of lotion or tonic, cream and serum). The initial problems that users encountered were dehydrated skin (55%), acne (35%) and increased sebum content (10%). After three weeks, the following improvements were noted: 91% reported better hydration, 30% reduction in acne and 8% reduction in sebum. Also, after three weeks, changes in the users' habits were observed, which related to the number of respondents who used basic (48%) vs. intensive care (52%). Commercial cosmetics do not usually meet the unique needs of individuals and may contain potential irritants, often overlooked by users. In the case of compounded cosmetics, this problem could be easily solved by omitting problematic ingredients by preparing it in the magistral laboratory. Individualization represents the future of the modern concept of skin care, because it enables the adaptation of user's needs, unlike commercial cosmetics, whose approach is: "one cosmetic preparation for one skin type". Our study showed an improvement in conditions (dry skin, acne, increased sebum secretion) and changes in skin care habits after applying a personalized care approach in users who were previously unsatisfied with the effects of commercial cosmetics.

Keywords: *skin care, compounded cosmetics, acne, sebum, hydration*

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PERSONALIZOVANA KOZMETIKA KAO NOVIJI KONCEPT U NEZI KOŽE – NAŠA ISKUSTVA

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Izrada personalizovanih farmaceutskih preparata u uslovima apoteke (magistralna laboratorija) zasnovana na individualnom pristupu predstavlja jedan od najnovijih trendova u nezi i prevenciji određenih patoloških stanja kože. Informacije dobijene primenom instrumentalnih metoda u kombinaciji sa samoprocenom kože, uz stručnu asistenciju farmaceuta, mogu biti važne za formulaciju personalizovanih kozmetičih proizvoda. Cilj ovog istraživanja bio je ispitivanje navika korisnika u vezi sa negom i efikasnosti personalizovanih kozmetičkih proizvoda samoprocenom stanja kože kroz upitnik koji su ispitanici popunjavali pre i tri nedelje nakon primene personalizovanih kozmetičkih preparata. U istraživanju je učestvovalo 85 ispitanika (upitnik se sastojao od 16 otvorenih i zatvorenih pitanja) u apoteci Dona u Nišu, gde su preparati izrađeni u magistralnoj laboratoriji na osnovu parametara samoprocene dobijenih tokom kozmetološkog savetovališta. Od ukupno 85 ispitanika koji prijavljuju da već duži period koriste različite preparate komercijalne kozmetike bez očekivanih rezultata, pa se zbog toga i javljaju savetovalištu apoteke, 10 (11,76 %) su bili muškarci, a 75 (88,24%) žene, prosečne starosti 38,6 ± 5,6 godina. Početne navike o nezi kože bile su takve da je 65% korisnika upotrebljavalo osnovnu negu (upotreba sredstava za čišćenje/pranje i kozmetičkog krema), dok je njih 35% koristilo intenzivnu negu (upotreba čistača uz kombinaciju losiona ili tonika, krema i seruma). Problemi sa kojima su se korisnici inicijalno susretali bili su dehidrirana koža (55%), akne (35%) i povećano lučenje sebuma (10%). Nakon tri nedelje, primećena su sledeća poboljšanja: 91% je prijavilo bolju hidrataciju, 30% smanjenje broja akni i 8% smanjenje lučenja sebuma. Takođe, nakon tri nedelje, primećene su promene u navikama korisnika koje su se odnosile na broj ispitanika koji su koristili osnovnu (48%) vs. intenzivnu negu (52%). Komercijalna kozmetika obično ne zadovoljava jedinstvene potrebe pojedinca i može sadržati potencijalne iritanse koje korisnici često zanemaruju. U slučaju personalizovane nege, magistralnom izradom u apoteci, ovaj problem bi mogao biti jednostavno rešen izostavljanjem problematičnih sastojaka. Individualizacija predstavlja savremeni koncept nege kože koji omogućava prilagođavanje potrebama korisnika, za razliku od komercijalne kozmetike, čiji je pristup: "jedan kozmetički preparat za jedan tip kože". Naše ispitivanje pokazalo je poboljšanje stanja (suva koža, akne, povećano lučenje sebuma) i promene u navikama u nezi kože nakon primene personalizovanog pristupa u nezi kod korisnika koji su prethodno bili nezadovoljni efektima komercijalnih kozmetičkih preparata.

Ključne reči: *nega kože, personalizovana kozmetika, akne, sebum, hidratacija*

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FORMULATION AND SENSORY EVALUATION OF EMULGELS CONTAINING DIFFERENT VITAMIN C DERIVATIVES

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Topical vitamin C (L-ascorbic acid) and its derivatives are widely used in cosmetic and dermatological products thanks to their versatile beneficial effects on the skin, like antioxidative, photoprotective, antiaging and antipigmentary. The present work focused on lipophilic ascorbyl-palmitate and hydrophilic magnesium ascorbyl phosphate, esterified and most commonly used active forms of vitamin C. The aim of our study was to formulate and compare the sensory characteristics of oil-in-water emulgels containing vitamin C derivatives at a concentration of 1% w/w and emulgel without active components. The emulgel preparation included formulation of the emulsionand then adding the gel phase, previously prepared by dispersing the hydroxyethylcellulose in water. The vitamin C derivatives, dissolved in the part of the oil phase, i.e. in the part of the aqueous phase of the emulsion, were added into the system when the temperature reached 40 °C. In the study, two groups of 20 healthy volunteers, of both genders, applied the examined preparations twice a day, on the inside of the forearm. The data processed from the questionnaire, about the sensory characteristics of the product before, during and after application on the skin, indicated that both emulgels are preparations with mild consistency, firmness and stickiness. They were characterized as easy-to-spread and moderately absorbed. Also, it was observed that they leave a moderate residual film on the skin after application, unlike emulgels without vitamin C derivatives. Therefore, the hydro-lipophilic properties of vitamin C derivatives did not affect the sensory characteristics of the tested emulgels.

Keywords: *emulgel, ascorbyl palmitate, magnesium ascorbyl phosphate, hydroxyethylcellulose*

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FORMULACIJA I SENZORNO ISPITIVANJE EMULGELOVA KOJI SADRŽE DERIVATE VITAMINA C

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Vitamin C (L-askorbinska kiselina) i njegovi derivati široko se koriste u kozmetičkim i dermatološkim proizvodima zahvaljujući svojim raznovrsnim blagotvornim efektima na koži, poput antioksidativnog, fotoprotektivnog, anti-age i antipigmentnog dejstva. U fokusu ovog rada bili su lipofilni askorbil-palmitat i hidrofilni magnezijum askorbil fosfat, esterifikovani i najčešće korišćeni aktivni oblici vitamina C. Cilj našeg istraživanja bio je formulisati i uporediti senzorne karakteristike ulja u vodi emulgelova koji sadrže derivate vitamina C u koncentraciji od 1% v/v i emulgela bez aktivnih komponenti. Priprema emulgelova podrazumevala je pripremu emulzije, a zatim dodavanje gel faze, koja je prethodno izrađena dispergovanjem hidroksietilceluloze u vodi. Derivati vitamina C, rastvoreni u delu masne, odnosno delu vodene faze emulzije, dodati su u sistem kada je temperatura dostigla 40 °C. U istraživanju su učestvovale dve grupe od ukupno 20 zdravih dobrovoljaca, oba pola, koji su nanosili ispitivane formulacije dva puta dnevno, na unutrašnju stranu podlaktice. Obrađeni podaci iz upitnika o senzornim karakteristikama proizvoda pre, tokom i nakon nanošenja na kožu, ukazuju da su oba emulgela preparati blage konzistencije, čvrstoće i lepljivosti. Okarakterisani su i kao formulacije koje se lako razmazuju i umereno apsorbuju nakon primene. Takođe, primećeno je da ostavljaju umeren rezidualni film na koži nakon aplikacije za razliku od emulgela koji ne sadrži derivate vitamina C. Možemo zaključiti da hidro-lipofilna svojstva derivata vitamina C nisu značajno uticala na senzorne osobine ispitivanih emulgelova.

Ključne reči: *emulgel,askorbil palmitat, magnezijum askorbil fosfat, hidroksietilceluloza*

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CASE REPORT – THE ROLE OF THE PHARMACIST IN TREATMENT OF THE POST COVID SYNDROME

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This study presents the role of a pharmacist in post covid syndrome treatment in case report form. Patient (woman, 52 years old) came to pharmacy after home treated SARS CoV 2 infection under physician's monitoring. The therapy included: ceftriaxone 2x1000mg for 10 days, prednisolone *per os* (according to the scheme) for 5 days with nadroparin injections and supplementation – vitamin D 2000 IJ and vitamin C 1000mg per day for 15 days. Bisoprolol 2.5mg per day represented chronic antihypertensive therapy. She complained of cough, and asked for a recommendation of a drug from the pharmacist. Reviewing the pharmacotherapy and biochemical results, an elevated value of D dimer was observed (643ng/mL during infection, 310ng/mL three days after exclusion of drugs). The lung findings were normal (on the day of arrival at the pharmacy), and the temperature was normal too. The patient showed symptoms of post covid syndrome – fatigue, sleep disorder and intensive, productive cough. Due to the improvement of anticoagulant effect, nattokinase 100mg per day was recommended. This is a natural the anticoagulant observed in the traditional Japanese meal nattō. For the treatment of productive cough, acetylcysteine 3x200mg per day was introduced and the patient was advised to continue supplementation with vitamin D 1000 IJ/day. The control was scheduled for 4 days, earlier if necessary. At the follow-up visit, the patient showed improvement, with decreased cough. Also, the patient was feeling and sleeping better. During the next control, in 7 days, acetylcysteine was excluded. At the last control visit, for a total of 28 days, nattokinase was discontinued, because the D dimer value was 220ng/mL (recommended value for this patient was under 260). The presented case shows that pharmaceutical care could help in the treatment of post covid syndrome.

Keywords: *post covid syndrom, pharmaceutical care, post covid cough, anticoagulant effect*

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PRIKAZ SLUČAJA – ULOGA FARMACEUTA U TRETMANU POSTKOVID SINDROMA

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Rad predstavlja prikaz slučaja postkovid sindroma i ukazuje na ulogu farmaceuta u tretmanu ovog zdravstvenog problema. Pacijentkinja, starosti 52 godine, došla je u apoteku nakon preležane infekcije SARS CoV2 virusom, lečene u kućnim uslovima pod nadzorom lekara. Terapija je uključivala: ceftriakson 2x1000 mg 10 dana, prednizolon *per os* (po shemi) 5 dana, nadroparin injekcije i vitaminsku suplementaciju (2000IJ vitamina D i 1000mg vitamina C dnevno) u trajanju od 15 dana. Od antihipertenzivne terapije koristila je 2,5 mg bisoprolola/dan. Pacijentkinja je zatražila pomoć farmaceuta i preporuku za lek zbog kašlja. Farmaceutskom anamnezom i pregledom biohemijskih rezultata, uočena je povišena vrednost D dimera (643 ng/mL tokom infekcije, 310 ng/mL tri dana nakon isključenja lekova). Nalaz pluća je bio uredan (na dan dolaska u apoteku), temperatura normalna. Pacijentkinja je pokazivala simptome postkovid sindroma u vidu intenzivnog, produktivnog kašlja, umora, poremećaja sna. Za poboljšanje efekta antikoagulantne terapije preporučena je natokinaza, peroralno 100 mg/dan. Natokinaza je prirodni antikoagulans dobijen iz tradicionalnog japanskog jela nattō. Za tretman produktivnog kašlja uveden je acetilcistein, 200 mg 3 puta dnevno i preporučena je suplementacija D vitaminom (1000 IJ/dan). Kontrola je zakazana za četiri dana, po potrebi i ranije. Na kontrolnoj poseti pacijentkinja je navela subjektivno poboljšanje, uz smanjenje kašlja i boljeg sna. Na sledećoj kontroli, za 7 dana, isključen je acetilcistein. Pri poslednjoj poseti, kroz ukupno 28 dana, ukinuta je natokinaza, jer je vrednost D dimera iznosila 220 ng/mL, (preporuka za datog pacijenta je maksimalno 260 ng/mL). Prikazani slučaj pokazuje da farmaceutska nega može doprineti uspešnom lečenju postkovid sindroma.

Ključnereči: *postkovid sindrom, farmaceutska nega, postkovid kašalj, antikoagulantni efekat*

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EFFECTS OF *PELARGONIUM SIDOIDES* EXTRACT ON CHEMOKINE LEVELS IN NASAL SECRETIONS OF PATIENTS WITH ACUTE POSTVIRAL RHINOSINUSITIS

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Acute postviral rhinosinusitis (APRS) requires the use of medications due to the prolonged duration of nasal complaints. Previous investigations suggest the use of extract from the roots of *Pelargonium sidoides* (EPs® 7630) for improving of the symptoms of APRS, due to its antimicrobial and immunomodulatory actions. The aim of this study was to evaluate the effects of EPs® 7630 on chemokine production in the nasal mucosa and clinical parameters of patients with APRS.

Twenty-six APRS patients and twenty-five control subjects were included in this prospective study. We measured the concentrations of thirteen chemokines in nasal secretions of APRS patients and controls by flow cytometry. The patients with APRS were treated by EPs® 7630 20mg oral tablets, three times daily for 10 days. We compared the chemokine levels in nasal secretions, nasal symptoms and endoscopic findings in patients, before and after therapy.

We found higher Total Symptom Score and higher concentrations of MCP-1, MIP-1α, MIP-1β, MIP-3α, ENA-78 and IL-8 in nasal secretions of APRS patients than in controls. After therapy by EPs® 7630, we found a significant decreas of all symptoms and endoscopic signs of APRS. The concentrations of MCP-1, IP-10 and MIP-1β were significantly increased and levels of MIP-1α, ENA-78, GROα and IL-8 significantly decreased in nasal fluid samples after therapy. No adverse effects were reported during the treatment.

Our results suggest the presence of modulatory effects of EPs® 7630 on the production of chemokines regulating the function of neutrophils and monocytes in the site of inflammation of the nasal mucosa in patients with APRS.

Keywords: *cytokines, rhinitis, Pelargonium sidoides, nasal mucosa, sinusitis*

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EFEKAT EKSTRAKTA *PELARGONIUM SIDOIDES* NA KONCENTRACIJE HEMOKINA U NOSNOM SEKRETU PACIJENATA SA AKUTNIM POSTVIRUSNIM RINOSINUZITISOM

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Konzervativna terapija je neophodna kod dugotrajnog održavanja nazalnih simptoma kod pacijenata sa akutnim postvirusnim rinosinuzitisom (APRS). Prethodna istraživanja su pokazala da upotreba ekstrakta dobijenog iz korena biljke *Pelargonium sidoides* (EPs® 7630) dovodi do poboljšanja simptoma APRS, zahvaljujući antimikrobnoj i imunomodulatornoj aktivnosti. Cilj rada bio je da se proceni efekat leka EPs® 7630 na produkciju hemokina u nosnoj sluznici, kao i na kliničke parametre kod pacijenata sa APRS.

U prospektivnu studiju je uključeno 26 pacijenata sa APRS, kao i 25 zdravih ispitanika koji su činili kontrolnu grupu. Merene su koncentracije 13 hemokina u nosnom sekretu pacijenata sa APRS kao i u kontrolnoj grupi, metodom protočne citometrije. Pacijenti sa APRS su lečeni tabletama EPs® 7630 u dozi od 20 mg, tri puta dnevno tokom 10 dana. Poredili smo koncentracije hemokina u nosnom sekretu, nosne simptome i endoskopski nalaz pre i nakon terapije.

U grupi pacijenata sa APRS bile su više vrednosti ukupnog skora simptoma, kao i više koncentracije MCP-1, MIP-1α, MIP-1β, MIP-3α, ENA-78 i IL-8 u nosnom sekretu u poređenju sa ispitanicima u kontrolnoj grupi. Nakon terapije EPs® 7630, došlo je do značajnog smanjenja svih simptoma i endoskopskih znaka APRS. Koncentracije MCP-1, IP-10 i MIP-1β su značajno povećane, dok su koncentracije MIP-1α, ENA-78, GROα i IL-8 značajno smanjene u uzorcima nosnog sekreta nakon lečenja. Nisu prijavljena neželjena dejstva leka tokom terapije.

Rezultati ukazuju na postojanje modulatornog efekta EPs® 7630 na produkciju hemokina koji regulišu funkciju neutrofila i monocita u inflamiranoj nosnoj sluznici pacijenata sa APRS.

Ključne reči: *citokini, rinitis, Pelargonium sidoides, nosna mukoza*

Zahvalnica: *Ovo istraživanje je sprovedeno u okviru projekta Medicinskog fakulteta VMA, Univerziteta odbrane (MF/VMA/02/19-21).*

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POSTOPERATIVE PAIN IN THORACIC PATIENTS: ADVANTAGES OF SAP BLOCK IN VATS PRCEDURES

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Pain after thoracic surgery is the most severe type of postoperative pain in surgery. It is present in 70% of the operated patients, and continuously exacerbates by breathing. The main source is an injury of the intercostal nerves. *Serratus anterior plane block* (SAP) is a regional block, blocking the thoracic intercostal nerves along with the thoracodorsal and long thoracic nerves, providing analgesia to the anterolateral and posterior part of the chest wall. Potential areas for SAP block are superficial and deep, with the difference in the duration of the block. The aim of the work is to compare the intensity of pain in patients with SAP block (10 ml bupivacaine 0.5% 10 ml with 8ml dexason) compared to patients treated with a standard protocol (acetaminophen and ketorolac). The study included 62 patients, 49 men and 13 women, with an average age of 54.9 years, divided into two identical groups by number (31 patients in each control and SAP group). Patients have undergone thoracic surgical treatment at the clinic between June and April 2022. The intensity of pain is measured by the NRS scale, three days after intervention at regular time intervals. In both of the study group in the first three hours after the surgical intervention, there is a decrease in NRS imminent period ($p<0.001$; $p<0.001$). After the first 60 minutes, there is a statistically significant difference in the NRR value between the groups examined ($p=0.021$). After 60 minutes, that is, after 1,5h; 2h; 2,5h and 3h between the examined groups, there is a statistically significant difference in NRS score values ($p<0.001$ for all measurements). The intensity of pain in patients who have been treated with an SAP block shows that NRS values after three hours are statistically significantly lower compared to all control measurements ($p<0.05$). Identical results in terms of analgesic efficiency of SAP block were obtained after the 4th, 8th and 12th postoperative hours. The intensity of pain in patients with SAP block was lower in comparison with patients who had a standard protocol for treating postoperative pain. Patients in the block group had a lower pain threshold in comparison with patients who had a standard protocol for treating postoperative pain. SAP block is a safer and cheaper alternative to epidural and paravertebral blocks.

Keywords: *SAP block, VATS, postoperative pain*

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POSTOPERATIVNI BOL KOD TORAKOHIRURŠKIH BOLESNIKA: PREDNOSTI SAP BLOKA KOD VATS PROCEDURA

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Bol nakon torakalnih operacija je najteža vrsta postoperativnog bola u hirurgiji, prisutan je kod 70% operisanih i kontinuirano se pogoršava disanjem. Glavni izvor bola je povreda interkostalnih živaca. Blok *serratus anterior plane* (SAP) je regionalni blok, koji blokira torakalne interkostalne živce zajedno sa torakodorzalnim i dugim grudnim živcem, pružajući analgeziju anterolateralnoj i delu zadnje strane grudnog zida. Potencijalni prostori za SAP blok su površinski i duboki, a razlika je u trajanju blokade. Cilj rada bio je upoređivanje intenziteta bola kod pacijenata sa SAP blokom (10 ml 0,5% bupivakaina sa 8ml deksazona) u odnosu na pacijente lečene standardnim protokolom (acetaminofen i ketorolak). Studijom su obuhvaćena 62 pacijenta, 49 muškaraca i 13 žena, prosečne starosti 54,9 godina, podeljenih u dve identične grupe (po 31 biolesnik u kontrolnoj i SAP grupi). Pacijenti su bili podvrgnuti grudno-hirurškom lečenju na Klinici u periodu od juna do aprila 2022. Intenzitet bola je meren NRS skalom, tri dana nakon intervencije u pravilnim vremenskim intervalima. U obe ispitivane grupe u prva tri sata nakon hirurške intervencije dolazi do smanjena NRS skora ($p < 0,001$; $p < 0,001$). Nakon prvih 60 minuta postoji statistički značajna razlika u vrednosti NRS između ispitivanih grupa ($p = 0,021$). Posle 60 minuta, odnosno nakon 1,5h; 2h; 2,5h i 3h između ispitivanih grupa postoji statistički značajna razlika u vrednostima NRS skora ($p < 0,001$ za sva merenja). Intenzitet bola kod pacijenata koji su bili tretirani SAP blokom pokazuje da su vrednosti NRS nakon tri sata statistički značajno manje u odnosu na sva kontrolna merenja ($p < 0,05$). Identični rezultati u smislu analgetske efikasnosti SAP bloka su dobijeni i nakon četvrtog, osmog i dvanestog postoperativnog sata. Intenzitet bola kod pacijenata sa SAP blokom bio je niži u poređenju sa pacijentima koji su imali standardan protokol za lečenje postoperativnog bola. SAP blok predstavlja bezbedniju i jeftiniju alternativu epiduralnim i paravertebralnim blokovima.

Ključne reči: *SAP blok, VATS, postoperativni bol*

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COSMETIC PRODUCTS FOR CARE AND PROTECTION OF CHILDREN'S SKIN

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Cosmetics products for children must be safe and of high quality, and special attention is paid to the formulation of these products for newborns and infants. To ensure a high level of health protection for children, the Committee of Ministers of the European Union adopted Resolution CM/ResAP(2012)1 in March 2012 on the criteria for the safety of cosmetic products intended for children (up to 3 years of age). A quality cosmetic product for the care and protection of children's skin should contain high-quality ingredients, without substances known as irritants. Special attention should be directed to the selection of preservatives, fragrances, and colors. The ingredients of products for the care and protection of children's skin are, apart from water, fatty substances, emulsifiers, humectants, active substances, preservatives, and pH adjusting agents. Children's skin care products are most often O/W creams and lotions, powders, and oils. W/O creams are most often used to protect children's skin in the diaper area and to protect them from the sun. Although the manufacturers of cosmetic product declarations provide important notes regarding use, pharmacists should draw attention to the specifics of the use of individual products, because adverse effects of cosmetic products for children, although rare, are most often caused by improper use, not by a low-quality cosmetic product.

Keywords: *cosmetic products for children, children's skin care, children's skin protection*

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KOZMETIČKI PROIZVODI ZA NEGU I ZAŠTITU DEČIJE KOŽE

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Kozmetički proizvodi za decu moraju da budu bezbedni i kvalitetni, a posebna pažnja se posvećuje formulaciji ovih proizvoda za novorođenčad i odojčad. Radi obezbeđenja visokog nivoa zdravstvene zaštite dece, Komitet ministara zemalja Evropske unije je marta 2012. godine usvojio Rezoluciju CM/ResAP(2012)[1] o kriterijumima za bezbednost kozmetičkih proizvoda namenjenih deci (do tri godine starosti). Kvalitetan kozmetički proizvod za negu i zaštitu dečije kože bi trebalo da sadrži sastojke visokog kvaliteta, bez supstanci koje su poznate kao iritansi. Posebnu pažnju je potrebno usmeriti ka odabiru konzervanasa, mirisa i boja. Sastojci proizvoda za negu i zaštitu dečije kože su najčešće, osim vode, masne materije, emulgatori, humektansi, kozmetički aktivne supstance, konzervansi i sredstva za podešavanje pH. Proizvodi za negu dečije kože su najčešće U/V kremovi i losioni, puderi i ulja. Za zaštitu dečije kože u pelenskoj regiji i za zaštitu od sunca najčešće se koriste V/U kremovi. Iako proizvođači na deklaracijama kozmetičkih proizvoda daju važne napomene u vezi sa upotrebom, farmaceuti treba da skrenu pažnju na specifičnosti upotrebe pojedinih proizvoda, jer neželjena dejstva kozmetičkih proizvoda za decu, iako retka, najčešće nastaju zbog neodgovarajuće primene, a ne zbog nekvalitetnog proizvoda.

Ključne reči: kozmetički proizvodi za decu, nega dečije kože, zaštita dečije kože

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IN SILICO STUDY OF BIOAVAILABILITY AND TOXICITY OF PYRAZOLE DERIVATIVES AND SELECTED ANTI-INFLAMMATORY DRUGS

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Pyrazoles represent noticeable classes of heterocycles due to their significant biological and pharmacological activities. Pyrazoles derivative, such as celecoxib, have been already used as drugs for the treatment of pain and inflammation. In this study, bioavailability, pharmacokinetics and toxicity of novel forty-three pyrazoles and four standard drugs were calculated by computational methods. The physicochemical, pharmacokinetic, and toxicological properties of compounds were determined using Molinspiration, SwissADME, and OSIRIS DataWarrior software. Previously, *in vivo* anti-inflammatory activities of selected pyrazoles in acute phase inflammation were analyzed. *In silico* study has shown that all compounds fulfilled Lipinski's rule of number five, indicating drug-likeness properties. Thirty-seven derivatives are predicted to have good gastrointestinal absorption, as well as for all used reference drugs. Seventeen new compounds showed promising drug-likeness scores. Eighteen pyrazoles show no toxicity and can be further evaluated as potential drug candidates. Reference anti-inflammatory drugs ibuprofen, diclofenac sodium, indomethacin and celecoxib meet Lipinski's rules and are safe for administration. Data about molecular properties, bioactivity score and toxicity of pyrazoles and comparison with standards could improve the creation of new potent and safe anti-inflammatory agents.

Keywords: *Pyrazoles, Anti-inflammatory agents, Bioavailability, Toxicological characteristics.*

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IN SILICO STUDIJA BIOASPOLOŽIVOSTI I TOKSIČNOSTI DERIVATA PIRAZOLA I ODABRANIH ANTIINFLAMATORNIH LEKOVA

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Pirazoli predstavljaju važnu klasu heterociklusa zbog njihove značajne biološke i farmakološke aktivnosti. Derivati pirazola, kao što je celekoksib, već su korišćeni kao lekovi za lečenje bola i upale. U ovoj studiji računarskim metodama su izračunate bioraspoloživost, farmakokinetika i toksičnost novih četrdeset tri pirazola i četiri standardna leka. Fizičko-hemijska, farmakokinetička i toksikološka svojstva jedinjenja određena su korišćenjem softvera Molinspiration, SvissADME i OSIRIS DataVarrior. Prethodno su analizirane *in vivo* anti-inflamatorne aktivnosti odabranih pirazola u akutnoj fazi inflamacije. Studija *in silico* je pokazala da su sva jedinjenja ispunila pravilo broja pet Lipinskog, što ukazuje na svojstva slična lekovima. Na osnovu dobijenih rezultata predviđa se da će trideset sedam derivata imati dobru gastrointestinalnu apsorpciju, kao i svi korišćeni referentni lekovi. Sedamnaest novih jedinjenja pokazalo je obećavajuće rezultate sličnosti sa lekovima. Osamnaest pirazola nije pokazalo toksična svojstva i mogu se dalje ispitativati kao potencijalni kandidati za lek. Referentni protivupalni lekovi ibuprofen, diklofenak-natrijum, indometacin i celekoksib ispunjavaju pravila Lipinskog i bezbedni su za primenu. Podaci o molekularnim svojstvima, rezultatima bioaktivnosti i toksičnosti pirazola i poređenje sa standardima mogli bi da doprinesu stvaranju novih moćnih i bezbednih antiinflamatornih agenasa.

Ključne reči: *pirazoli, antiinflamatorni agensi, bioraspoloživost, toksikološke karakteristike*

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