

ANALYSIS OF PHENOLIC COMPOUNDS IN LEAVES OF WILDLY GROWN *COTINUS COGGYGRIA*

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INTRODUCTION: *Cotinus coggygia* Scop. (Anacardiaceae) or the European smoketree is a very common deciduous shrub or a small tree. It is a well-known medicinal plant that contains tannins and other groups of phenolic substances due to which it has applications in the treatment of conditions such as hemorrhoids, paradontosis, hyperhidrosis of the feet, it is used externally for small wounds and others. Numerous therapeutic effects of smoketree have been studied, e.g., antibacterial, antifungal, anti-viral, antiseptic, antioxidative, anticancer, antigenotoxic, hepatoprotective, and anti-inflammatory.

AIM: The aim of the present study was to quantify and compare the total polyphenol, tannin, flavonoid, and phenolic acid content of leaves of wildy grown smoketree. Phenolic substances can be used as a tool to assess the quality of medicinal plants.

MATERIALS AND METHODS: Plant substance was gathered from two localities in the North-East floristic region of Bulgaria in different months in late spring and summer. It was air-dried in darkness at room temperature and, before analysis, grounded and sieved through a 500 µm sieve. The determination of phenolic compounds in the herbal drug was performed according to the European and Russian Pharmacopoeia.

RESULTS AND CONCLUSION: The results for May and June showed differences between localities. There was an increase in most phenolics at one site and a decrease at the other. Thus, choosing the right time for harvesting of medicinal plants refers also to a specific location. In conclusion, in order to produce more effective herbal products, spectrophotometry could be integrated in assessing the quality of herbal substances as being simple and inexpensive method.

Keywords: *total polyphenols, tannins, flavonoids, phenolic acids, spectrophotometry, Cotynus coggygia*

METHODS FOR EXTRACTION OF BIOACTIVE COMPONENTS FROM GREEN SOURCE ENERGY

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INTRODUCTION: The extraction of bioactive components from plant origin is essential for pharmaceutical technologies in the development of new medicinal products and nutritional supplements. However, the preparation of these compounds by the classical extraction techniques of the Soxhlet method, maceration, percolation, infusion, and hydrodistillation is associated with the use of expensive solvents, long extraction period, and heat treatment of thermally unstable compounds.

AIM: The purpose of the study is to present the characteristics of unconventional extraction techniques such as ultrasonic and microwave extraction to reduce the duration of the process, increasing the purity and yield of the desired bioactive component.

MATERIALS AND METHODS: Two green techniques were applied for extracting phycocyanin and total chlorophyll content of spirulina from a bioreactor in Bulgaria. For this purpose, ultrasonic extraction was used to optimize temperature, frequency, time, and type of solvent.

RESULTS AND CONCLUSION: Phycocyanin yield and purity in both green extraction methods were higher than those obtained by classic extraction. Using the classic method with extraction time of 2 hours and a temperature of 20°C, the yield of phycocyanin is 2.5 mg/g with a purity of 0.6. Under the same conditions, using ultrasound with a frequency of 35 kHz., a result of 10.68 mg/g with a virtue of 1.22 was obtained. The highest chlorophyll content was obtained when extracted with 96% ethanol at a temperature of 40°C, an extraction time of 2 hours, and frequency of 45 kHz. Green extraction methods enable the extraction of biological components with a relatively high yield and purity, suitable for their inclusion in medicines, food supplements, and cosmetic products.

Keywords: *spirulina, extraction, phycocyanin, chlorophyll*

CHEMOSELECTIVE RADIOFLUORINATION WITH [¹⁸F]-FDG

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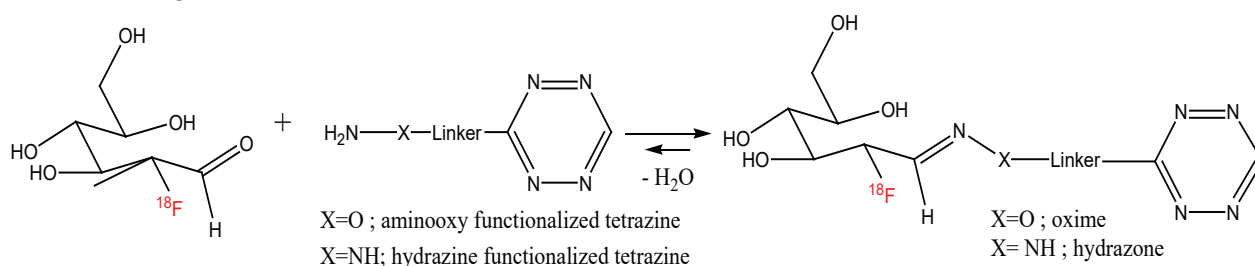
INTRODUCTION: 2- [¹⁸F]-fluoro-2-deoxy-D-glucose ([¹⁸F]-FDG) is the most important radiotracer for positron emission tomography (PET-CT) imaging in the nuclear medicine. The highly efficient radiosynthesis makes this radiotracer available in almost every PET center worldwide. It is used in the assessment of oncological, cardiac and neurological diseases. In addition to being a versatile PET radiopharmaceutical, [¹⁸F]-FDG finds application as an F-containing prosthetic group.

AIM: The aim is to research the possibility of using [¹⁸F]-FDG as a prosthetic group for indirect radiolabeling.

MATERIALS AND METHODS: The [¹⁸F]-FDG is produced in the Clinic of Nuclear Medicine at the St. Marina University Hospital, Varna by nucleophilic radiofluorination, using mannose triflate as a precursor. In the present work, we describe a methodology for indirect radiofluorination with [¹⁸F]-FDG by chemoselective oxime or hydrazone formation. Bifunctional tetrazine derivatives were used as precursors for the radiolabeling. As optimal conditions for these processes, we found a temperature of 70–75°C and a pH of the medium around 4–4.2 as well as the presence of a p-diaminobenzene catalyst.

RESULTS: [¹⁸F]-FDG modified products were obtained with radiochemical yields between 20 and 80%. The progress of the reactions was monitored by radio-TLC and HPLC. The radiolabeled tetrazine product will be used for future bioorthogonal click reactions with trans-cyclooctene under physiological conditions.

Keywords: radionuclide ¹⁸F, PET-CT, ¹⁸F-FDG, prosthetic group, hydrazone, oxime, click chemistry, tetrazine, bioorthogonal reaction.



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THE FUTURE OF THE TREATMENT OF SOCIALLY SIGNIFICANT DISEASES (GENE AND CELL THERAPIES)

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INTRODUCTION: As technologies such as cheap genome sequencing, big data analytics, deep learning appear on the stage of healthcare, it becomes possible to get down even more deeply to the roots of diseases and treatments. The “one-size-fits-all” strategy will start to change. In oncology there are various trends in fighting against cancer with more precise methods as before.

AIM: The aim of this article is to predict what the future developments in the treatment of socially significant diseases with focus on the gene and cell therapies will be.

RESULTS AND DISCUSSION: The Human Genome Project began in 1990 with the aim of mapping the whole structure of the human genome and sequencing it. Nowadays, with the development of more affordable gene tests, HCPs and patients can use their unique gene sequence to understand better sensitivity to drugs, genealogy, information about monogenic medical conditions, and information about multifactorial medical conditions. The advances in genome understanding could lead to a new era of treatment of diseases, helping to address unmet medical needs and design new innovative drugs. Gene therapy is a medical approach that treats or prevents disease by correcting the underlying genetic problem. Gene therapy techniques allow doctors to treat a disorder by altering a person’s genetic makeup instead of using drugs or surgery.

CONCLUSION: A newer technique, called genome editing (an example of which is CRISPR-Cas9), uses a different approach to correct genetic differences. Instead of introducing new genetic material into cells, genome editing introduces molecular tools to change the existing DNA in the cell.

Keywords: *CRISPR-Cas9, human genome, gene therapy*

THE INFLUENCE OF EMOTIONS AND RATIONAL THINKING ON PERSONAL AND PROFESSIONAL PROFILING IN THE VIRTUAL ENVIRONMENT

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INTRODUCTION: The development of the modern world has moved steadily into the field of technology, social networks and has built an entirely new, parallel digital world. This also has put personal and professional profiling in the virtual environment on a new footing. And although the digital world differs significantly from the real world, it is again influenced by certain psychological constructs that are well studied based on interactions in the real world.

AIM: The purpose of this article is to outline the possibilities and benefits of digital profiling, as well as to show the mechanisms of influence associated with it.

MATERIALS AND METHODS: Several concepts related to the construction of systemic connections between the individual elements of the digital image, as well as how emotions influence decision-making and related hormonal cocktails in the digital environment, are reviewed.

RESULTS AND DISCUSSION: From the analysis of the literature, scientific articles and research, as well as some research of our own, it is clear that the choices we make and the things we like in the digital space are again entirely emotional and non-rational, even though our brains try to give them a rational meaning.

CONCLUSIONS: Digital profiling should take into account all the emotional and primal actions of our brain if we want to achieve a certain rational goal. The digital space has its technological specifics, but from an emotional point of view, it is close to the interaction in the real world and obeys the same behavioral patterns.

Keywords: *emotions, rational thinking, digital profile, social network*

APPLICATION OF ROPIVACAINE IN TRANSVERSAL ABDOMINAL PLANE

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INTRODUCTION: Ropivacaine is a well-established, long-acting, amino-amide local anesthetic. It is the first local anesthetic, produced as a pure S(-)-enantiomer. Its lipophilicity is reduced, compared with the other local anesthetic agents. That leads to a decreased potential for central nervous system toxicity and cardiotoxicity. Ropivacaine can be applied as infiltration, for peripheral nerve blocks, and in an intrathecal and epidural way. Intravenous administration is not recommended. The drug displays linear and dose-proportional pharmacokinetics (up to 80 mg administered intravenously). It is metabolized extensively in the liver and excreted in urine.

AIM: The aim of this article is to analyze the analgetic benefits of ropivacaine application in the transversal abdominal plane (TAP) for hysterectomy via the Pfannenstiel approach.

MATERIALS AND METHODS: Forty-six women, admitted for intervention, were randomized. A group with an application of bilateral, preincisional TAP block with ropivacaine (n=23) and a control group (n=23) were created. The postoperative pain relief for all the participants consisted of a monocomponent, patient-controlled morphine analgesia. The amount of total 24-hour morphine consumption and intraoperative fentanyl use was calculated. Pain at rest and in motion was assessed on a verbal numerical rating scale (vNRS). The incidence of postoperative nausea and vomiting was registered.

RESULTS: Transversal abdominal plane block with ropivacaine reduced the 24-hour postoperative cumulative morphine requirements. Mean \pm SD morphine consumption of the TAP block group (14.5 mg \pm 4 mg) was statistically significantly lower than the control one (21.7 mg \pm 6.8 mg). Ropivacaine decreased the intraoperative use of fentanyl and the postoperative vNRS scores at rest and in motion. The groups did not demonstrate any difference in the incidence of nausea and vomiting after surgery. There were no complications attributable to ropivacaine in TAP.

CONCLUSION: Our study showed that adding ropivacaine in TAP leads to superior analgesia in patients undergoing total hysterectomy.

Keywords: Pfannenstiel incision, ropivacaine, peripheral nerve block, morphine consumption

INNOVATIVE METHODS OF OVERWEIGHT MANAGEMENT

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INTRODUCTION: Overweight has become a global problem, and is not by chance called the pandemic of the 21st century, or simply „globesity”. Obesity is a major health and economic problem reducing productivity and life expectancy and increasing disability, closely related to increased mortality and morbidity, and directly linked to many co-morbidities.

AIM: The aim of this article is to describe innovative methods used for overweight management.

MATERIALS AND METHODS: Data collection was based on a scientific literature search of review articles in well-established sources. A search with pre-defined keywords in electronic databases PubMed, ScienceDirect, Medline, and Google Scholar was conducted.

RESULTS: WHO data shows that the prevalence of obesity has almost tripled in 40 years. The rapid spread of obesity provides grounds for a continuous search for new methods of body weight control. Innovations in pharmacotherapy aim at discovering new mechanisms for safe and effective weight reduction. Bariatric surgery is gaining popularity with its effectiveness, especially in morbid obesity. There are also more unconventional methods related to the use of mobile applications, psychoeducational groups, especially for patients with eating disorders, and even some insurance companies are involved with programs rewarding a healthy lifestyle.

Conclusion: Obesity is a complex disease and it is necessary to apply an individual and multidisciplinary approach to its treatment. Along with pharmacotherapeutic and/or surgical treatment, it is necessary to apply methods that help the patients to completely change their lifestyle. Innovative methods, such as mobile applications or psychoeducational support groups, are a useful tool, for reducing body weight and long-term maintenance of a healthy lifestyle.

Keywords: *overweight, obesity, innovative, treatment*

INVESTIGATING THE OPPORTUNITIES FOR OPTIMIZING THE STRATEGY OF PREEMPTIVE ANALGESIA

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INTRODUCTION: Laparoscopic surgery as fast-track surgery recovery programme has become the gold standard in the elective management of colorectal disease. There is no accepted consensus with regard to the optimal perioperative analgesic regime with a number of options available with a focus on cost-effectiveness and outcome in terms of quality of life, a short period after the surgery. This study aims to explore any differences in analgesic strategies related to cost-effectiveness and the pain-reducing effects of strategies with lower usage of opioid medication.

BACKGROUND: Improving perioperative efficiency and cost-effectiveness prognosis has become increasingly important in the modern practice of anesthesiology. Fast-track surgery represents a multidisciplinary approach to improving perioperative efficiency by facilitating recovery after both minor (i.e., outpatient) and major (inpatient) surgery procedures. In this article we focus on the expanding role of the anesthesiologist in fast-track surgery. The aim of the study is to present the effectiveness of preemptive analgesic strategy in selected patients as a cost-effectiveness model.

METHODS: A multidisciplinary group of clinical investigators – both the Department of General Surgery and Anesthesiology and the Department of Intensive Care, discuss current anesthetic and surgical practices directed at improving the post-operative recovery process in laparoscopic abdominal surgery procedures. The topic is related to the role of the anesthesiologist in perioperative and post-operative pain management and in improving the cost-effectiveness of the procedures. Data are collected over a consecutive 2-year period within pre-operative patient evaluation. Outcome measures include post-operative pain score, post-operative opioid analgesic use and side effects, alternative magnesium sulphate usage, selected venous paracetamol and lidocaine infusion, compared with non-steroid pain relief medication.

RESULTS: Anesthesiologists play a key role in fast-track surgery through their preoperative patient evaluation, strategy for medication, anesthetics and techniques, use of prophylactic drugs to minimize side effects (e.g., pain, nausea and vomiting, dizziness), as well as the administration of adjunctive drugs to maintain major organ system functions during and after surgery. Outcome measures include assessment of post-operative pain, quantifying post-operative use of opioid analgesics and NSAIDs, and accounting for their side effects, versus alternative use of magnesium sulfate, dose-dependent intravenous infusion of paracetamol, and lidocaine.

CONCLUSION: The decisions of the anesthesiologist as a key perioperative physician are of critical importance to the surgical care team in developing a successful fast-track surgery program. The efficiency and cost-reduction strategy of analgesia is not just an important part of improving the gold standards for laparoscopic fast-track procedures in terms of their cost-effectiveness, but with it also plays a key role in the management of the outcomes related to the quality of life of the patients. Magnesium sulfate, lidocaine, and paracetamol, combined with dose reduction of opioid therapy are essential in improving analgesia and minimizing side effects in the early post-operative period.

Keywords: *laparoscopic surgery, preemptive analgesia, cost-effectiveness model*

MYOFUNCTIONAL THERAPY OF HABITUAL MOUTH-BREATHING CHILDREN

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INTRODUCTION: Breathing through the nose allows proper growth and development of the craniofacial complex. Human beings evolved to breathe through the nose. Mouth breathing is a dysfunctional breathing pattern.

AIM: The aim of this study is to evaluate the effect of orofacial myofunctional therapy on the reestablishment of a nasal breathing by stabilizing a proper position of the tongue and lips at rest

MATERIALS AND METHODS: A total of 79 children, diagnosed with habitual mouth breathing, took part in the study. We performed myofunctional treatment for 6 months to improve the functions of swallowing, tongue, oral breathing, and rest posture of lips, tongue, and cheeks.

Results: Myofunctional therapy reduced mouth breathing (86% vs. 14%, $p < 0.0002$) and lip hypotonia (80% vs 20%, $p < 0.003$), and restored normal tongue position (70% vs. 30%, $p < 0.04$).

CONCLUSION: Orofacial myofunctional therapy appears to effectively modify tongue position, reduce oral breathing and may thus play a role in the treatment of habitual mouth-breathing children

Keywords: *myofunctional therapy, habitual mouth breathing*

CURRENT CHANGES IN THE ALLOCATION AND PAYMENT OF MEDICAL DEVICES IN BULGARIA

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INTRODUCTION: People with disabilities in Bulgaria have the right to prostheses, hearing aids, equipment, and medical devices outside the scope of compulsory health insurance, determined individually with a medical document issued by the medical advisory commissions, the Territorial Expert Medical Commission, or the National Expert Medical Commission, based on their specific needs and according to a specification, approved by the National Health Insurance Fund.

AIM: The aim of this article is to analyze the new procedure for the financing of prostheses, hearing aids, equipment, and medical devices in Bulgaria, and to make a comparative analysis between the new and the old procedure, determining the main benefits of the new one.

MATERIALS AND METHODS: The study contains a comparative analysis of the extracted and summarized information from official normative documents of the Directorate of Social Assistance and the National Health Insurance Fund governing the order of granting and payment of aids, devices, equipment, and medical devices.

RESULTS: The main advantages of the new procedure are the submission of an application by electronic means directly after receiving a protocol from the LMC/TEMC/NEMC without the need for subsequent visits to other institutions and filling out documents. Paper documents are not provided to the retailer either, only identification with the PIN, names, number, and date of approval for granting the ADEMD, which is received by e-mail or SMS, is required.

CONCLUSION: Generally, all procedures for prescribing and dispensing both medicinal products and aids, and medical devices are carried out through the electronic system of the NHIF. All these results lead to the conclusion that the Bulgarian healthcare system is increasingly moving to an electronic environment and this, in turn, improves access to healthcare services for patients.

Keywords: *payment, NHIF, medical devices*

NOVEL MEDICINES FOR NON-SMALL CELL LUNG CANCER (NSCLC) APPROVED BY FDA AND TARGETING EGFR EXON 20 INSERTION MUTATIONS— A PHARMACOLOGY PERSPECTIVE

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INTRODUCTION: In 2021 FDA approved mobocertinib and amivantamab for locally advanced/metastatic non-small cell lung cancer (NSCLC) with (EGFR) gene exon 20 insertion (ex20-ins) mutations. The EGFR ex20-ins mutations are an uncommon and heterogeneous group, resistant to conventional EGFR tyrosine kinase inhibitors (TKIs) and have been considered as an “undruggable target” for a long time. A study reports that EGFR ex20-ins mutations are available in advanced NSCLC with a prevalence of 0.5% in all NSCLC cases and 4.0% in EGFR-positive NSCLC.

AIM: Both medications have different pharmacokinetic and pharmacodynamic characteristics. Our aim is to present both drugs from a pharmacological perspective, focusing on drug-drug interactions, adverse drug reactions (ADRs), and proven efficacy in clinical trials.

MATERIALS AND METHODS: Review of the regulatory information by the marketing authorization holder and the published data from the clinical trials was conducted.

RESULTS: Amivantamab is a fully-human immunoglobulin G1 bispecific antibody with immune cell-directing activity that targets epidermal growth factor receptor (EGFR) mutations and mesenchymal-epidermal transition (MET) mutations and amplifications, while mobocertinib is an EGFR TKI. Amivantamab has no contraindications and it is not tested for drug-drug interactions, but mobocertinib has drug interactions with CYP3A inhibitors, inducers, and substrates. The most common ADRs of amivantamab are infusion-related reactions, while mobocertinib can cause QTc prolongation and has black box warning. The overall survival with mobocertinib is 24.8 months, compared with 22.8 with amivantamab (HR=0.95, 95% CI=0.55–1.67).

CONCLUSION: Amivantamab has a more favorable safety profile and less ADRs. Both medications appear to have similar efficacy.

Keywords: non-small cell lung cancer (NSCLC), exon-20 insertion (ex20-ins) mutations, mobocertinib, amivantamab

CURRENT BULGARIAN LEGISLATION IN THE FIELD OF SAFETY AND HEALTH AT WORK ADDRESSING SPECIALIZED EDUCATION IN THIS DOMAIN

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INTRODUCTION: First aid is provided in the event of an accident, when there is damage to health, by persons who happened to be present at the place, using means at hand or previously prepared kits (first aid kits from a car, office or others). The aid aims to stabilize the victim's condition, limiting the possibility of disability or death, limiting pain and suffering. First aid is legally regulated, as part of the activities to ensure healthy and safe working conditions, requires the same knowledge and skills from all workers (doctor, pharmacist, miner, teacher, etc.) and does not take into account all the specifics of work environment and potential risks.

AIM: The aim of this article is to analyze the existing regulations in Republic of Bulgaria regarding the organization and conduct of first aid training at the workplace.

MATERIALS AND METHODS: Analysis of the current regulatory framework regulating the organizing and conducting of specialized first aid training in Bulgaria was conducted. A documentary method was used and the results are presented tabularly and graphically.

RESULTS: The regulatory framework allows the formalization of first aid training, being non-specific regarding the duration, scope, degree of knowledge and skills a worker must acquire to be considered able to provide first aid, documentation and other aspects of organizing and conducting trainings. Analyzed: Law on health and safety at work (OHS); Ordinance No. 3 of 25.01.2008 on the terms and conditions for carrying out the activities of occupational medicine services; Order No. RD 09-410 of 13.10.1994 of the Minister of Health and the Minister of Labor and Social Welfare, the rules for rendering first aid at work, in force from 1.01.1995, and other documents.

CONCLUSION: Legislation allows each employer and company to determine its own policy regarding first aid training, thereby ensuring overall health and safety at work. We believe that it is necessary to amend the regulatory framework by regulating minimum requirements for first aid training in order to guarantee effective knowledge and skills.

Keywords: *legislation, safety at work, first aid, training*

COVID-19 AND ATRIAL FIBRILLATION: DRUG INTERACTIONS BETWEEN ANTIARRHYTHMICS AND ANTI-COVID-19 MEDICATIONS

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INTRODUCTION: Atrial fibrillation (AF) is a common clinical manifestation in patients with COVID-19. Some antiarrhythmics used in AF and anti-COVID-19 medications can interact on pharmacokinetic and pharmacodynamic levels, causing drug-related toxicity.

AIM: The aim of the review is to increase the awareness of potential drug-drug interactions between antiarrhythmics and anti-COVID-19 medications in COVID-positive patients with AF.

MATERIALS AND METHODS: Our survey was performed by researching scientific databases—Google Scholar and PubMed.

RESULTS: Medications can interact on a pharmacokinetic level by decreasing the CYP450 enzyme superfamily and P-glycoprotein activity. Ritonavir, a strong inhibitor of CYP3A4, is combined with nirmatrelvir to increase its efficacy against SARS-CoV-2. Due to CYP3A4 inhibition, ritonavir may also increase blood concentrations and potentiate the toxicity of antiarrhythmic drugs used in AF, such as amiodarone and propafenone. Azithromycin and ritonavir are P-glycoprotein inhibitors that prevent renal and intestinal efflux of digoxin, which can lead to a prolonged PQ-interval and second or third degree AV block. Furthermore, on pharmacodynamic level, coadministration of drugs that block the I_{KR}-potassium channels and prolong the QT interval, like class IA and III antiarrhythmics, hydroxychloroquine, increases the risk of cardiac arrhythmias. Therefore, to manage AF in patients with COVID-19, it is imperative to provide special considerations for each patient.

CONCLUSION: It is crucial for clinicians to be aware of the indications, contraindications, and key drug-drug interactions. The choice of antiarrhythmics for COVID-19 patients with AF should be individualized. A baseline ECG before the initiation of antiarrhythmics is recommended.

Keywords: COVID-19, atrial fibrillation, antiarrhythmics, drug interactions

EFFECTS OF PRETREATMENT WITH AQUEOUS INFUSION OF *KOCHIA SCOPARIA* SEEDS IN A MODEL OF PARACETAMOL-INDUCED HEPATOTOXICITY IN RATS

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INTRODUCTION: *Kochia scoparia* (KS) is widely used in traditional Chinese medicine.

AIM: The aim of the present study was to investigate the effects of pretreatment with aqueous infusion of KS seeds in a model of paracetamol-induced hepatotoxicity in rats.

MATERIALS AND METHODS: The study included 50 male Wistar rats divided into 5 groups: control (I), paracetamol (II), and 3 groups with paracetamol-induced hepatotoxicity pretreated with aqueous infusion of KS seeds, prepared by soaking of 15 g (III), 30 g (IV), and 60 g (V) seeds in 1 L of boiling water. For 10 days, groups III, IV, and V received the corresponding infusion instead of drinking water. Hepatotoxicity was induced in groups II–V by intraperitoneal injection of paracetamol (0.1 g/100 g). After 48 hours, body and liver weights were measured, serum concentrations of liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), and gamma-glutamyl transferase (GGT) were estimated, and oxidative stress was evaluated by the serum thiobarbituric acid reactive substances (TBARS).

RESULTS: Group II had lower body and liver weights and higher serum levels of AST, AP, GGT, and TBARS compared to group I. The serum concentrations of AST and ALT were significantly lower in group V compared to group II. The other indicators of liver damage were not alleviated by the pretreatment.

CONCLUSION: The present study demonstrates that the pretreatment with aqueous infusion of KS seeds might exert hepatoprotective effects in the highest dose used in a model of paracetamol-induced hepatotoxicity in rats.

Keywords: *Kochia scoparia*, hepatotoxicity, rats, liver enzymes

ASSESSMENT THE LEVELS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAHS) IN HERBAL TEAS

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INTRODUCTION: Herbal teas are used by people for both prophylactic and medicinal purposes. Medicinal plants may be contaminated with polycyclic aromatic hydrocarbons (PAHs) from the environment during their growth, collection, and storage. These contaminants can be transferred from the herbs into the infusions, when herbal teas are prepared. The European Food Safety Authority (EFSA) lists four priority PAHs in dried herbs (including plant extracts)—benzo[a]anthracene, chrysene, benzo[b]fluoranthene, and benzo[a]pyrene.

AIM: The aim of the study was to determine the PAH levels in thyme and yarrow tea infusions and to assess exposure to PAHs by their consumption.

MATERIALS AND METHODS: The PAH concentrations were determined in dry thyme (*Thymus serpyllum* L.) and yarrow (*Achillea millefolium* L.) teas and their water extracts. The levels of 13 PAHs in the samples were analyzed by gas chromatography with massspectrometry (GC-MS). The exposure to PAHs was estimated by daily intake (DI) and hazard quotient (HQ).

RESULTS AND DISCUSSION: The concentrations of phenanthrene were predominant in the dry tea (*Achillea millefolium* L., 71.52 ng/g) and in tea infusion (infusion of *Thymus serpyllum* L., 12.72 ng/g). The daily intake of phenanthrene was calculated as the highest. It was determined for thyme tea infusion (0.364 ng/kg body weight per day). The sum of 13 PAHs in dry thyme tea (138.46 ng/g) is greater than in yarrow tea (108.30 ng/g). The four priority PABHs were not found in the dried teas and their infusions. The maximum HQ value (0.0000061) was estimated for fluorene in thyme tea infusions and was much lower than 1, suggesting that tea consumption would not pose any health risk.

CONCLUSION: The safety assessment of thyme and yarrow teas indicates that their consumption would not pose a risk to the user's health.

Keywords: *polycyclic aromatic hydrocarbons (PAHs), risk assessment, hazard quotient (HQ)*

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OBESITY AND ORGAN DAMAGE—A REVIEW

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INTRODUCTION: Obesity is a global problem nowadays, affecting even children. Of particular importance is its role in metabolic syndrome and health problems originating from this syndrome. As a matter of fact, one-third of obese people are metabolically healthy, however, the risk of developing non-communicable diseases is still high to these individuals.

AIM: The purpose of the present review was to summarize the available documents about organ damage caused by obesity and the mechanisms involved.

MATERIALS AND METHODS: Various web-based database such as Pubmed, Google Scholar, and Science-Direct were used for the review.

RESULTS: Adipocytes secrete numerous factors that influence homeostasis. Consuming high-calorie diet activates the renin-angiotensin system resulting in increased blood pressure. In the kidneys, it causes hemodynamic alterations by an unknown mechanism, such as increased renal flow, glomerular capillary pressure, and glomerular filtration rate, which are risk factors for the development of microalbuminuria and renal damage. The increased sympathetic tone contributes to hypertension. A small number of mechanisms that have been postulated as causative in the genesis of endothelial dysfunction in obesity are vascular pro-inflammatory factors, oxidative stress, reduced antioxidant defense, and oxidized low-density lipoproteins. As a consequence, vascular accidents occur. The low-grade inflammation also contributes to liver damage, from simple steatosis to steatofibrosis. Obesity has an impact on the heart by increasing blood volume and heart rate in addition to elevated systolic and diastolic blood pressure. This adjustment influences cardiac geometry.

CONCLUSION: Obesity impairs the health status even in metabolically healthy overweight patients. Reducing the adiposity improves obesity-induced organ changes.

Keywords: *obesity, organ damage, heart, kidney, liver*

IBX – AN EFFICIENT REAGENT FOR THE CHEMOSELECTIVE OXIDATION OF THE ALKALOIDS QUININE, QUINIDINE, AND ATROPINE

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INTRODUCTION: Chemoselectivity is a property inherent to those reagents that interact preferentially with one of two or more different functional groups. Hypervalent organoiodine reagents (IBX, DMP, etc.) also exhibit chemoselectivity. Their specific reactivity towards primary and secondary alcohol groups is well known. The application of these reagents in the synthetic practice is indisputable. That is why our attention was focused onto the hypervalent IBX reagents, and more specifically onto utilizing them in the pharmaceutical practice.

AIM: The aim of this article is to evaluate the chemoselectivity of the hypervalent IBX reagent in the oxidation of primary (*atropine*) and secondary (*quinine* and *quinidine*) alcohol groups.

MATERIALS AND METHODS: All necessary reagents were purchased from Acros Organics. Each synthesis was performed under mild conditions with standard laboratory equipment using 2-iodoxybenzoic acid (IBX) as a chemoselective oxidizing reagent. The compositions of the obtained crude reaction products were spectrally (FTIR) and chromatographically (HPLC) analysed.

RESULTS: All alkaloids studied were successfully oxidized using the title reagent, but in lower than expected yields. The applied experimental conditions were also assessed as fully appropriate. Furthermore, the appearance of any side, non-selective oxidation products was not detected.

CONCLUSION: The selective synthesis of oxo-derivatives of the three pharmacopoeial alkaloids has been realized. The possibility of the appearance of N-O forms of the three alkaloids has also been eliminated. Further studies aimed at increasing the yield of the final oxo compounds are in progress.

Keywords: *IBX, chemoselective oxidation, alkaloids*

ASSOCIATION ENERGY AND CONTAGIOUSNESS OF CORONAVIRUS MUTANTS

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INTRODUCTION: The coronavirus binds to epithelial cells by electrostatic attractive forces between the positively charged spike (S) protein and the negatively charged ACE2 receptors. Every point mutation which changes the number of the positively charged amino groups ($-\text{NH}_3^+$) and negatively charged carboxyl groups ($-\text{COO}^-$) in the receptor-binding domain (RBD) of the S1-subunit alters the electrostatic potential and thereby the association energy and contagiousness of the mutant.

AIM: The aim of this article is to calculate the electrostatic potential on RBD and S1-ACE2 association energy.

MATERIALS AND METHODS: Our research consisted of 5 stages: (1) selection of mutants with changed electrical charges in the RBD; (2) determination of the 3D coordinates and reconstruction of the S1-subunit structure; (3) computation of the electrostatic potential of the S1-subunit; (4) visualisation of the electrostatic potential on the surface of RBD; (5) computation of the S1-ACE2 association energy.

RESULTS: Our results show an increase of the positive net charge in RBD in the 4 most widespread coronavirus variants: +3 (wild type), +4 (β -variant), +5 (δ -variant), and +6 (o-variant), which determines the increasing association energy and contagiousness of these mutants.

The results also explain the higher contagiousness but lower pathogenicity of the omicron variant by pH dependence of its association energy which is higher in the respiratory tract (pH 5) and lower in the blood vessels (pH 7.4).

CONCLUSION: By computing the energy of S1-ACE2 association we can predict the contagiousness of newly emerged coronavirus variants.

Keywords: *coronavirus, ACE2 receptor, receptor-binding domain, point mutation, association energy, contagiousness*

Acknowledgements: The study was supported by the National Research Fund (project KP-06-M49/1-2020).

CHALLENGES FACING PHARMACIES RELATED TO THE DRUG SUPPLY PROCESS DURING THE COVID-19 PANDEMIC

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According to the Good Pharmaceutical Practice guidelines, Masters of Pharmacy are obliged to be active in the implementation of the manufacturer-wholesaler-pharmacy relationship. As the last link in the drug supply process responsible for the dispensing of medicinal products to patients, they provide expert feedback to manufacturers and wholesalers regarding the quality, efficacy, and safety of the medicine offered. Masters of Pharmacy are medical professionals who can assist the patient in the absence of a medicinal product by discussing with the attending physician a generic substitution of the product to prevent interruption in the patient's treatment. This is of particular importance during a pandemic, when there is a sharp increase in the consumption of certain drugs, which leads to their shortage in the pharmacy network. In the context of a global pandemic, this shortage is directly related to the delayed import of drugs, because manufacturers must quickly produce additional quantities above the planned ones. One of the main challenges of the drug supply process is to provide the necessary quantities of drugs according to the increased needs of patients during a pandemic. The COVID-19 pandemic has highlighted the significant challenges to the supply of important and necessary medicines, as well as the impact such a spread can have on the EU medicine supply chain. In its guidelines, the European Commission emphasizes the rational supply, distribution, and use of vital medicines for the treatment of coronavirus patients, as well as medicines for which there may be a risk of shortages due to the pandemic.

Keywords: *challenges, Master of Pharmacy, COVID-19 pandemic, drug supply process, guidelines*

FACTORS INFLUENCING PHARMACY ACCESS IN BULGARIA

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INTRODUCTION: In Bulgaria, the financial, geographical, temporal, and administrative restrictions on citizens' free access to a pharmacy network have been steadily deepening over the years. As of August 2022, there are over 3,000 active pharmacies in the country, but they are concentrated in large urban regions. Only 1% of all pharmacies in the country are open 24/7 and this prevents timely access to medicines. Another barrier to access is a contract between pharmacies and the National Health Insurance Fund, which mostly impacts individuals with chronic diseases.

AIM: The goal of the current study is to investigate the reasons preventing access to a pharmacy network in the country. Geographical, temporal, and administrative barriers are investigated. The study did not take into account patients' financial limitations in getting access to a pharmacy network.

MATERIALS: The data from the National Health Insurance Fund, National Statistical Institute and Bulgarian Drug Agency electronic databases were used to assess variations in the access to a pharmacy.

RESULTS: The South-Central and South-West regions have the highest proportion of pharmacies. Residents of the North-West region suffer the most difficulties, including 11,551 citizens from seven municipalities without access to a pharmacy. Only 30 of the total 3068 pharmacies are open 24 hours a day, seven days a week. People with chronic diseases from Silistra, Shumen, Vidin, Montana, and Razgrad have the most difficulty obtaining the medications they require.

CONCLUSION: Inequalities in access to pharmacies in the country can have a substantial detrimental impact on the population's health. This necessitates major actions to reduce potential negative consequences.

Keywords: *barriers to access, pharmacy retail, regions*

IMPACT OF THE COVID-19 PANDEMIC ON ANTIBIOTIC RESISTANCE IN BULGARIA

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INTRODUCTION: Antibiotic resistance and its rising levels in recent years are among the most serious issues confronting modern healthcare systems. A significant portion of the negative effects are related to a decrease in the body's defenses, prolonged periods of illness, increased mortality, increased healthcare costs, and economic losses due to reduced levels of work capacity. Due to the widespread use of antibiotic treatments, the COVID-19 pandemic has increased the risk of rising levels of antibiotic resistance. Antibiotic resistance has been steadily increasing in Bulgaria over the years, and the pandemic is expected to accelerate this negative trend in the future.

AIM: The study's aim is to look into the rate of antibiotic use among individuals who have COVID-19.

MATERIALS AND METHODS: A national online survey was conducted in September 2022 among citizens who had been diagnosed with COVID-19. A total of 213 respondents participated in the survey.

RESULTS: In the study, 50% of the participants were prescribed antibiotic treatment with broad-spectrum antibiotics. In a majority of respondents (66%), treatment was prescribed by the GP without prior laboratory testing. About 36% of the respondents had taken antibiotic, more than once, in the last one year for some other medical reason.

CONCLUSION: Antibiotics were prescribed to the majority of respondents who recovered from COVID-19. This will exacerbate the country's antibiotic resistance problem, negatively affecting the healthcare system.

Keywords: *antibiotic resistance, COVID-19, antibiotic use*

THE IMPACT OF THE COVID-19 PANDEMIC ON DIETARY SUPPLEMENT USE IN BULGARIA

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INTRODUCTION: The COVID-19 pandemic has significantly increased global demand for dietary supplements. The primary reasons are related to people's desire to protect themselves against the SARS-CoV-2 infectious agent on the one hand, and their use as the primary treatment of the disease at the place of residence on the other. Dietary supplement sales in Bulgaria achieved an all-time high during the pandemic, particularly at the beginning of the country's declared state of emergency in March 2020. During this time, pharmacists consistently reported nutrient, microelement, and immunostimulant deficiencies.

AIM: The study's aim is to look at the factors that influenced the consumption of nutritional supplements during the COVID-19 pandemic in Bulgaria.

MATERIALS AND METHODS: An online questionnaire was used in September 2022 to conduct the research. The survey included 186 participants in total.

RESULTS: Approximately 30% of the respondents reported they used nutritional supplements to prevent infection with the SARS-CoV-2 virus. They were discharged as treatment for COVID-19 illness in 22.6% of the cases, and as follow-up therapy for post-COVID syndrome in 19.9% of the instances. Vitamin C (73.8%), vitamin D (49.7%), zinc (66.9%), selenium (66.9%), omega-3 fatty acids (63.6%), ginger (63.6%), and bee products (62.1%) were the most frequently used supplements among respondents.

CONCLUSION: The variables that have had the greatest influence on the consumption of nutritional supplements in the country are connected to their use as prevention against the coronavirus infection, as well as their use in the treatment of COVID-19 and its sequelae.

Keywords: *dietary supplements, COVID-19, treatment of COVID-19*

ACCESS TO MEDICINES IN BULGARIA DURING THE COVID-19 PANDEMIC

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INTRODUCTION: The high prevalence of COVID-19 necessitated an urgent redirection of all healthcare resources, including medications, to medical facilities for inpatient care. This impeded patients' free access to essential medications. Individuals suffering from chronic diseases, pregnant women, and children were among the most vulnerable groups affected in Bulgaria. Numerous reports were received by the Ministry of Health about a lack of antibiotics, drugs for the treatment of lung diseases, and blood-clotting medications.

AIM: The aim of the study is to investigate the difficulties individuals encountered in obtaining the medicines they needed during the COVID-19 pandemic in Bulgaria.

MATERIALS: A pilot study was conducted in September 2022 using an online survey. A total of 80 citizens participated in the study.

RESULTS: The majority of respondents (66.3%) were parents of children under the age of 18. Half of those polled (50%) said they had difficulty obtaining medicines, with chronic disease patients and parents of children suffering the most. Access was most limited in the country during the first and second waves of the pandemic. The medications with the most impaired access were antibiotics (55.3%), corticosteroids (46.8%), and coagulants (23.4%). All respondents who stated difficulties in obtaining necessary medications said that this had a negative impact on their health.

CONCLUSION: Regardless of the reason for its presence, limited access to medication can have serious consequences for the population's health. This necessitates the implementation of preventive measures in order to reduce the likelihood of such situations occurring.

Keywords: *access to medications, chronic diseases, COVID-19*

ETHNOBOTANICAL STUDY OF TRADITIONAL KNOWLEDGE AND USE OF MEDICINAL PLANTS USED FOR PREVENTION AND TREATMENT OF COVID-19 AMONG THE PEOPLE IN BULGARIA

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INTRODUCTION: The COVID-19 pandemic has turned into the most important public health problem and has had severe health and socioeconomic impact. Many people turn to herbal therapy to prevent infection with the virus or alleviate the symptoms caused by it.

AIM: The aim of our study was to conduct an ethnobotanical survey of indigenous knowledge of the use of medicinal plants for prevention and treatment of COVID-19.

MATERIALS AND METHODS: Data about the use of medicinal plants during the pandemic by a random sample of Bulgarian people was gathered via Google Forms questionnaire.

The collected information about herbal use was divided based on the symptoms of the disease. Results were analyzed with fidelity level (FL) and important value index (IVI).

RESULTS: One third of the respondents (32.65%) reported using medicinal plants for prevention and treatment of COVID-19. Most of the respondents used herbal therapy in combination with conventional treatment to avoid further complications. A total of 32 different medicinal plants were mentioned, 22 of which are local species and 10 imported species. According to the calculated IVI, the most important medicinal plants used for treatment and prevention of COVID-19 were *Thymus spp.* (IVI=0.46), *Matricaria chamomilla* L. (IVI = 0.38), *Zingiber officinale* Roscoe (IVI=0.35), and *Tilia spp.* (IVI=0.35). The highest FL coefficient in the category plants for cough treatment was for *Thymus sp.*, *Matricaria chamomilla* L., *Zingiber officinale* L. and *Brassica nigra* L. The highest FL coefficient in the category: medicinal plants with antiviral properties used during the pandemic was for *Thymus spp.*, *Mentha spp.*, and *Sideritis scardica* Griseb.

CONCLUSION: Positive attitude toward herbal treatment as complementary therapy of COVID-19 is observed. According to the results, the medicinal plants with most cultural significance for prevention and treatment of COVID-19 were *Thymus spp.*, *Matricaria chamomilla* L., and *Zingiber officinale* Roscoe.

Keywords: *ethnobotany, medicinal plants, COVID-19*

ALVEOLAR SURFACTANT: CHARACTERISTICS, FUNCTIONS, AND ROLE IN RESPIRATORY DISORDERS

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INTRODUCTION: Alveolar surfactant is a complex heterogeneous lipoprotein complex forming a thin layer covering the air-water interface in the lungs. Its presence is vital for efficient gas exchange because it maintains the structural integrity and optimal size of the alveoli. Surfactant provides lung tissue elasticity, increases lung compliance, thereby reducing the work that inspiratory muscles do during inhalation, and prevents pulmonary atelectasis. Its main biophysical characteristic is the ability to lower surface tension, eliminating the danger of alveolar collapse.

AIM: The aim of this article is to show the main characteristics and functions of alveolar surfactant and its importance in regulating the biomechanics of breathing. Furthermore, the study presents modern treatment strategies with exogenous surfactant therapy for various respiratory diseases.

MATERIALS AND METHODS: Numerous biochemical and biophysical studies using modern imaging techniques and diagnostic tests prove that changes in surfactant's amount, contents, or its function lead to disorders such as neonatal respiratory distress syndrome, obstructive lung disease, pulmonary alveolar proteinosis, asthma, and coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), etc.

RESULTS AND CONCLUSION: The pandemic of SARS-CoV-2 led to the discovery that coronaviruses penetrate mainly through the respiratory tract and attack and damage type II alveolar pneumocytes, resulting in the suppression of surfactant synthesis and secretion as well as the immune protection it provides. This causes severe respiratory failure, which can be prevented by exogenous surfactant therapy. Due to this now routine therapy, improved oxygenation, and gas exchange, as well as symptom relief are ensured.

The article was prepared in connection with the student session *Biophysics—Clinical Applications: Principles, Concepts, Methods* at the Department of Physics and Biophysics.

Keywords: *alveolar surfactant, alveoli, lungs, gas exchange, surface tension, SARS-CoV-2*

OBESITY AND CONTEMPORARY APPROACHES TO ITS PHARMACOLOGICAL MANAGEMENT

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INTRODUCTION: Although obesity is largely preventable, according to the WHO today, almost 40% of adults are overweight and 13% are obese. As a result, this increases the risk of cardiovascular, kidney and respiratory diseases, as well as diabetes, dementia, cancer, and osteoarthritis.

AIM: The alarming epidemiological data concerning obesity, as well as the growing interest in drugs reducing body weight, require the summarization of the available pharmacological possibilities for influence as well as the risks associated with them.

MATERIALS AND METHODS: A systematic review of the scientific databases in PubMed, Science Direct and Google Scholar was conducted.

RESULTS: The treatment of overweight and obesity requires a complex approach, such as lifestyle and nutrition changes with increased physical activity. If satisfactory results are not achieved within 3 months, drug therapy may be included. Pharmacological treatment could include orlistat—a reversible lipase inhibitor, which disables the hydrolysis of dietary fats in the intestine and reduces their absorption by up to 30%. The selective 5-HT_{2C} receptor agonist lorcaserin is another option that reduces food intake by increasing satiety through its serotonin anorectic effect and by stimulating the hypothalamus. Phentermine and the combination of naltrexone and bupropion also reduce appetite. However, recently there has been a growing interest in liraglutide—an injectable glucagon-like peptide 1 agonist, originally approved for the treatment of type 2 diabetes. It is used because it is not only showing a good safety profile, but clinical data demonstrates a significant reduction in cardiovascular events.

CONCLUSION: As non-pharmacological approaches do not always provide satisfactory results, knowledge of antiobesity pharmacotherapy is crucial given its role in achieving clinically significant weight loss and preventing the development or exacerbation of comorbid conditions.

Keywords: *obesity, overweight, liraglutide, glucagon-like peptide 1*

MEDICATION-INDUCED OCULAR SIDE EFFECTS

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INTRODUCTION: About eighty-five percent of our perception, cognition, and activities are mediated through the visual apparatus. There are many external factors that can damage our vision, including the intake of certain drugs.

AIM: The aim of the present study was to evaluate the relationship between the use of certain drugs and their ocular side effects.

RESULTS: Different classes of drugs can lead to varying degrees of visual impairment. It is reported that it can be caused by several groups of currently available drugs, including antiepileptics, retinoids, antineoplastic and immunotherapeutic drugs, glucocorticoids, cephalosporins, antiretroviral drugs, and topical beta blockers. Intriguingly, some preservatives, like benzalkonium chloride, which is the most commonly used one, can also cause different optical complications. Individual side effects can be observed, including ocular motility dysfunction, retinopathy, maculopathy, glaucoma, myopia, optic neuropathy, dry eye syndrome, uveitis, keratitis, and many other acute conditions.

CONCLUSION: Being aware of the possible and probable medication-induced side effects is always beneficial for patients. As the eye is one of our most important sensory organs, minimalizing the risks of drug complications is crucial. Regular consultation with specialists is recommended, as well as adequate treatment and usage of pharmaceuticals.

Keywords: *vision, visual complications, glaucoma, uveitis, side effects*

SUICIDE RISK-INCREASING DRUGS

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INTRODUCTION: According to WHO over 700 000 people around the world lose their life because of suicide, with the unsuccessful attempts being much more. The use of drugs could be one of the reasons for the increasing number of patients with self-harm behavior.

AIM: The aim of the present work was to shed light on the drugs that increase the risk of suicide in order to increase patients' vigilance.

MATERIALS AND METHODS: For the purposes of the study, the data resources of Google Scholar, PubMed, and MDPI were used.

RESULTS: The main groups of drugs we considered are CNS-active and cardiovascular. Regarding antidepressants, it has become clear that the risk of suicide during treatment with the older one representatives is approximately 1:3000. Younger patients in particular appear to be at higher risk. Antiepileptics also stand out as a risk group, as patients taking some of them had twice the risk of suicidal behavior compared to those receiving placebo. The sedative-hypnotic drugs also showed alarming data. Anesthetics have proven to be dangerous for the medical doctors who work with them, according to a study among anesthesiologists. According to some studies, the high and medium lipid-soluble beta blockers and calcium channel blockers may be associated with an increasing risk of suicide behavior because of their ability to cross the blood-brain barrier. No significant evidence was found for ACE inhibitors.

CONCLUSION: The risk of suicidal behavior for cardiovascular drugs is insufficient and more studies are needed. On the other hand, for the CNS drugs in question, the data are significant and should be taken into account when carrying out health consultations.

Keywords: *suicide, antidepressants, antiepileptics, sedatives, cardiovascular drugs*

THE MECHANISM OF VALPROATE- AND METHOTREXATE-INDUCED HEPATOTOXICITY

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INTRODUCTION: The liver is the most important organ involved in the metabolism of drugs. Its proper functioning is essential for maintaining homeostasis. Drugs are among the most common causes of hepatotoxicity. Two of them are the widely used methotrexate and valproate.

AIM: The aim of this report is to discuss methotrexate- and valproate-induced hepatotoxicity and the mechanism of its occurrence.

MATERIALS AND METHODS: The databases PubMed and Google Scholar were searched for relevant studies with the keywords: “drug-induced hepatotoxicity”, “methotrexate”, and “valproate”. Data published in the last 5 years was analyzed. Articles not written in English were excluded.

RESULTS: Valproates are commonly used antiepileptic drugs. Hepatotoxicity can occur when the dose is increased to achieve therapeutic effect or unbound drug fractions are increased due to hypoalbuminemia or renal failure. The mechanism of hepatotoxicity is the mitochondrial damage in hepatocytes caused by inhibition of beta-oxidation, reduced levels of carnitine, and accumulation of reactive oxygen species. Methotrexate is effective in the treatment of different diseases, however, its application is limited due to induction of hepatotoxicity. Suppressed activity of peroxisome proliferator-activated receptor- γ (PPAR γ) and antioxidant markers (superoxide dismutase and catalase) are reported. Methotrexate induces also elevated levels of pro-inflammatory cytokines (tumor necrosis factor- α (TNF- α), nuclear factor- κ B (NF- κ B), and interleukin 6 (IL-6).

CONCLUSION: Higher doses of methotrexate and valproate are associated with an elevated risk of hepatotoxicity. This should be taken into account when the therapeutic dosage is considered. Hepatoprotectors and regular check-ups of the liver function biomarkers could decrease the risk.

Keywords: *hepatotoxicity, valproate, methotrexate, drug-induced*

ECOLOGICAL IMPACT OF THE CHEMICAL FILTER OCTOCRYLENE ON MARINE FLORA, FAUNA, AND HUMANS

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INTRODUCTION: Octocrylene is one of the most commonly used chemical filters in sunscreens. It was established that over time it can degrade into benzophenone, which is reported to exhibit toxic, carcinogenic properties. This compound may cause hormonal imbalance and it is not allowed to be used in food and food packaging by the FDA. However, octocrylene is still considered safe according to the Scientific Committee on Consumer Safety (SCCS), when used in concentration of up to 10% in cosmetic products. The use of this chemical filter is often associated with negative influence on the aquatic flora, fauna, increased risk of coral bleaching, as well accumulation in the fish.

AIM: The aim of the study is to evaluate the ecological impact of octocrylene on marine flora, fauna, and humans.

MATERIALS AND METHODS: A search in the PubMed, ScienceDirect, and Web of Science databases was performed, summarizing the latest information relevant to the topic.

RESULTS AND CONCLUSION: The use of sunscreens is prohibited in some regions of the world due to the lipophilicity of UV filters, which bioaccumulate in aquatic flora and fauna. It was reported that octocrylene may disrupt the endocrine system in fish, affecting their reproductive system. The risk of using sunscreen products containing octocrylene in humans is associated with an increased in time concentration of benzophenone in the packaging, due to the aging of the product. Hereof it is worth to (re)evaluate the safety profile and environmental influence of octocrylene.

Keywords: *benzophenone, coral bleaching, octocrylene, UV protection*

SAFETY ASSESSMENT OF THE MOST COMMONLY USED FILTERS IN SUNSCREEN PRODUCTS

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INTRODUCTION: The direct exposure to ultraviolet (UV) light is often associated with the occurrence of various skin disorders (sunburn, wrinkles, freckles, age spots, hyperpigmentation) and is also part of the pathogenesis of different types of skin cancer. In this regard, sunscreen products, containing chemical or physical filters, are widely used for skin protection from UVA1, UVA2, and UVB radiation. The chemical filters (i.e., oxybenzone, octinoxate, homosalate, 3-benzylidene camphor) are reported to absorb the ultraviolet radiation, whereas the physical filters (titanium dioxide, zinc oxide) are known to reflect or refract the UV radiation. Although they are generally recognized as safe, some studies report that the UV filters used in sunscreen products, in certain doses, can cause hormonal disbalance or have mutagenic effect or carcinogenic effect.

AIM: The study aims to summarize the latest information about the most commonly used chemical and physical UV filters in sunscreen products and their effects on human health.

MATERIALS AND METHODS: A thorough research through the PubMed, ScienceDirect, and Web of Science databases has been conducted, summarizing the information from latest relevant articles and outcomes from clinical studies.

RESULTS AND CONCLUSION: According to the obtained results, some of the UV filters used in sunscreen products have or may have harmful effects on the human body. Thereof, knowing their safety profile gives the consumers the possibility to make an informed decision. The use of sunscreen products may carry some risks, but undoubtedly has its benefits—protecting our skin from the harmful effects of the sunlight.

Keywords: *chemical filters, physical filters, skin damage, sunscreen, UV protection*

NANOEMULSIONS—SOME INNOVATIVE APPLICATIONS IN PHARMACEUTICAL TECHNOLOGIES

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INTRODUCTION: The speed of research, design, and production of nanoemulsions is increasing due to their frequent use in pharmaceutical technologies. These systems have great potential to deliver hydrophobic bioactive substances, stabilize bioactive agents, and increase their water dispersibility and bioavailability.

AIM: This review examines the advantages of nanoemulsions over emulsions and microemulsions, which have been used to prepare dosage forms of significant interest in recent years.

MATERIALS AND METHODS: Scientific data on cannabidiol (CBD), flavonoid quercetin, and its incorporation in various nanoemulsions were collected from ScienceDirect, ResearchGate, PubMed, and others over the last five years.

RESULTS AND CONCLUSIONS: Cannabidiol and flavonoid quercetin have found interesting applications in nanoemulsions. The latter is included in the forms mentioned above to increase its absorption and bioavailability in the body in the fight against excess weight. Ultrasonication and two-stage high-pressure homogenization were used to obtain reliable formulations with CBD in nanoemulsions. Cannabidiol oil, included in a nanoemulsion, has been proven to be effectively used for skin hydration and discoloration. Nanoemulsions also have a high potential to modify the bioavailability of poorly soluble drug substances.

Keywords: *nanoemulsions, quercetin, cannabidiol*

NANOTECHNOLOGY-BASED FUSIDIC ACID FORMULATIONS—NEW APPROACHES FOR ENHANCED ANTIBACTERIAL ACTIVITY

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INTRODUCTION: Fusidic acid (FA) is a fungal metabolite with a fusidane triterpene structure, derived from *Fusidium coccineum* and possessing bacteriostatic activity. Fusidic acid can be characterized as a relatively narrow-spectrum antibiotic—it is effective mostly against Gram-positive cocci, including methicillin-resistant *Staphylococcus aureus* (MRSA), but it does not possess any activity against Gram-negative microorganisms. The inadequate bioavailability due to poor absorption from the available formulations is the main limitation of the clinical potential of FA in treating infectious skin diseases.

AIM: The main objective of the review is to investigate nanotechnological strategies for improved FA topical delivery presented in terms of enhanced antibacterial activity.

MATERIALS AND METHODS: Scientific data on FA and its incorporation in various nanoscaled drug-delivery systems was collected from ScienceDirect, ResearchGate, PubMed, and others for the last ten years.

RESULTS AND CONCLUSION: Various nanoreservoirs were found to be effective for the purpose described above. Compared to a commercial FA topical product, shea butter-based solid lipid nanoparticles demonstrated enhanced inhibition of *S. aureus*. In addition to the augmented antimicrobial effect, essential oil-loaded nanoemulsions and fusogenic liposomes containing FA showed an expanded spectrum, affecting Gram-negative bacteria. An enhanced activity against different *S. aureus* strains, including MRSA, was observed for a bilayered nanoemulsion and chitosan-coated lipid nanoparticles.

Topical delivery of FA via different colloidal carriers can successfully provide an improved bacterial inhibition and broadened antibacterial spectrum, resulting in potentially expanded therapeutic relevance.

Keywords: *fusidic acid, nanotechnology, dermal drug delivery, antibacterial activity*

CURRENT TRENDS IN LIPOSOME DEVELOPMENT AND CLINICAL APPLICATIONS

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INTRODUCTION: Liposomes are vesicular drug delivery systems, resulting from the self-assembly of phospholipids and cholesterol in aqueous media. They can accommodate hydrophobic and hydrophilic compounds, improving their solubility, and bioavailability and providing controlled and sustained drug release. Liposomes are biocompatible, biodegradable, and non-toxic, which further contributes to their implementation in clinical practice. Liposome-based products have been successfully used in various therapeutic areas, such as oncology (ONIVYDE[®], DepoCyt[®]), antifungal diseases (AmBisome[®]), and photodynamic therapy (VISUDYNE[®]). Their continuous development is closely related to the application of novel techniques to improve liposomal physicochemical characteristics or stability issues and further expand of their application areas (i.e., elaboration of liposomes-based vaccines/imaging agents).

AIM: The study aims to summarize the advances in the liposomal development process, including recent technological approaches to overcome associated liposomal drawbacks (aggregation, precipitation, etc.), as well as to outline current directions in their biomedical application.

MATERIALS AND METHODS: The study is based on comprehensive research in the PubMed, ScienceDirect, and Web of Science databases, summarizing articles within the last 5 years.

RESULTS AND CONCLUSION: Based on the reported results, different drying techniques (freezing/spray drying) can improve liposome stability. Therefore, liposomes are successfully used as antigen and imaging agent carriers in addition to their role as drug delivery platforms.

Keywords: cancer, diagnostic imaging, liposomes, nanomedicine, vaccine development

PROSPECTS, PRODUCTION, AND APPLICATION OF LU-177-LABELED RADIOPHARMACEUTICALS IN BULGARIA

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INTRODUCTION: Lutetium-177 (Lu-177) is currently the most used radiometal for targeted radionuclide therapy due to its availability and its clinical success for the treatment of neuroendocrine tumors and prostate cancer.

AIM: The aim of the present study is to review the application of Lu-177-labelled radiopharmaceuticals abroad and to discuss the prospects of introduction of Lu-177 therapy in Bulgaria.

MATERIALS AND METHODS: We used PubMed and Google Scholar to search for scientific articles related to Lu-177. The keywords used were “Lu-177”, “radiopharmaceuticals”, and “cancer therapy”. The data on the registered patients with prostate cancer in Bulgaria are from the National Health Insurance Fund.

RESULTS: Lu-177 is a medium-energy β -emitter ($E_{\beta\max} = 0.497$ MeV) that deposits its energy in tissues within a short range (maximum of 2 mm). This reduces the toxic effects on normal tissues and makes it very suitable for the treatment of disseminated metastatic carcinoma. The convenient half-life and the co-emission of low-energy gamma rays make Lu-177 a leading candidate for theranostic applications.

CONCLUSION: Despite the excellent nuclear characteristics of that radionuclide, it is still not easily accessible to patients in Bulgaria. The introduction of the most suitable methods for the synthesis of Lu-177 and the preparation of Lu-177-labeled radiopharmaceuticals in Bulgarian radiopharmacies would lead to a significant facilitation of access to this type of therapy. A total of 824 patients with malignant neoplasms of the prostate registered in Bulgaria will potentially benefit from Lu-177-based treatment and necessary administrative steps should be taken to allow access to that specific treatment.

Keywords: cancer, patients, radiometal, radionuclide, radiopharmacy, therapy

DETERMINATION AND COMPARISON OF TOTAL PHENOLIC CONTENT AND TOTAL HYPERICINS IN A MEDICINAL PRODUCT AND FOOD SUPPLEMENT CONTAINING ST. JOHN'S WORT

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INTRODUCTION: Medicines and food supplements containing St. John's wort are used mainly for their antidepressant effect, which is comparable to that of SSRI antidepressants. The lack of strict legal control over the production and distribution of food supplements makes this market more vulnerable to dishonest manufacturers.

AIM: The aim of the study was to conduct a comparative analysis of the total phenolic content and total hypericins in a standardized medicinal product and in a food supplement containing St. John's wort extract in order to establish compliance with the values declared by the manufacturers.

MATERIALS AND METHODS: A literature review was conducted and suitable spectrophotometric methods were identified for the analysis of total phenolic content and total hypericins in phytoproducts, with consideration that these are the main constituents responsible for the pharmacological activity of St. John's wort and can cause toxicity.

After appropriate sample preparation, absorbance was measured at 765 nm for total phenols and at 587 nm for total hypericins on a UV-VIS spectrophotometer T60 UV with UVWin Software 6.0.

RESULTS: After the analysis, it was found that the values declared by the manufacturer for phenolic content and total hypericins for the medicinal product, correspond to the results of our studies.

For the dietary supplement containing St. John's wort, however, the value for total hypericin was found to be higher than that declared on the label by the manufacturer.

CONCLUSION: In order to ensure patient safety, stricter analytical control of food supplements is needed, especially when it comes to products with many drug interactions and potential toxic effects in case of improper use or dosage, as is the case with St John's wort supplements.

Keywords: *St. John's wort, total phenols, hypericin, food supplement, UV-VIS spectroscopic analysis*

POLYMERIC NANOPARTICLE-ENCAPSULATED CURCUMIN AND ITS POTENTIAL FOR BIOMEDICAL APPLICATIONS

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INTRODUCTION: Curcumin, a yellow polyphenol extracted from the rhizome of turmeric (*Curcuma longa*), is commonly used as a spice and nutritional supplement. It exhibits many pharmacological activities such as anti-inflammatory, anti-bacterial, anti-fungal, and has potent anti-cancer properties. However, the therapeutic application of this relatively efficacious agent has been limited due to rapid metabolism, low bioavailability, poor water solubility, and systemic elimination.

AIM: The purpose of the present study was to review the available data about polymeric nanoparticle encapsulated formulation of curcumin—nanocurcumin, and to compare its properties with those of free curcumin.

MATERIALS AND METHODS: A search was conducted in the scientific databases PubMed, Google Scholar and ResearchGate.

RESULTS: In a study numerous curcumin-loaded polymeric micelles (Cur-M) have been developed through different methods. Compared to free curcumin, Cur-M showed a sustained release behavior at pH 7.4 in vitro and ~ 60% of drugs were released in one week. Moreover, enhanced accumulation of curcumin in the brain was detected and it may be related to the breakthrough of the blood-brain barrier (BBB) because of the smaller diameter and the nearly neutrally charged property of curcumin-loaded polymeric micelles. The results showed that curcumin-loaded nanoparticles significantly inhibited cell proliferation, induced apoptosis, and enhanced anti-tumor immunity stimulation. In order to increase the intracellular uptake and improve therapeutic efficacy, the surface of micelles was modified with various targeted ligands to recognize tumor cell surface-overexpressed receptors.

CONCLUSION: Integrating curcumin into nanocarriers through various methods is an appropriate choice to upsurge the biological activity of curcumin, which increases its bioavailability and solubility, prolonged circulation, and retention in the body, and overcomes the physiological barriers of curcumin.

Keywords: *curcumin, nanotechnologies, polymeric micelles*

SYNTHESIS, IR AND UV-VIS SPECTROSCOPIC ANALYSIS OF METHYL ESTER OF 4-[1-(3,5,5,8,8-PENTAMETHYL-6,7-DIHYDRONAPHTHALEN-2-YL)ETHENYL]BENZOIC ACID (BEXAROTENE)

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INTRODUCTION: An ester is a chemical compound derived from an acid (organic or inorganic) in which at least one –OH hydroxyl group is replaced by an –O– alkyl (alkoxy) group, as in the substitution reaction of a carboxylic acid and an alcohol. When talking about medicinal substances, the esterification of the carboxylic group results in the formation of the so-called prodrugs.

A prodrug is a medication or compound that, after administration, is metabolized (i.e., converted within the body) into a pharmacologically active drug.

In this work we discuss the possible ways of bexarotene esterification and the possibilities for analysis of the newly synthesized methyl ester using IR and UV-VIS spectroscopy.

AIM: The purpose of this study is to synthesize a prodrug of bexarotene and to conduct FTIR and UV-VIS spectroscopic analysis of a newly synthesized ester of bexarotene.

MATERIALS AND METHODS: A newly synthesized ester derivative was obtained according to the basic scheme of esterification using an alcohol as a solvent and an inorganic acid chloride mainly used as a reagent to prepare carboxylic acid chlorides from carboxylic acids, after which an ester is formed.

Infrared spectra 500-4000 cm^{-1} were taken on a Bruker FTIR spectrometer using ATR—a plug with Smart iTR adapter. Spectra in the range of 190–400 nm were recorded using UV-VIS spectrophotometer T60 UV with UVWin Software 6.0.

RESULTS: After a detailed comparison of the data obtained from the IR analysis of bexarotene and the newly obtained ester, a similar position and intensity of the spectral bands are reported. However, there are displacements in spectral bands and significant differences corresponding to the structural changes that have occurred. Different values for the wavelength of maximum absorption was measured with UV-VIS spectrophotometer for bexarotene and the newly synthesized ester.

CONCLUSION: In order to confirm the data obtained by FTIR and the UV-VIS spectroscopy, a further reversed-phase HPLC-UV analysis of the new hydrazone derivative should be performed.

Keywords: *retinoids, bexarotene, esters, pro-drugs, FTIR spectral, UV-VIS spectroscopic analysis*

THE EMERGING PHARMACIST ROLE IN PHARMACOVIGILANCE FOR GENE AND CELL THERAPIES

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INTRODUCTION: Medical science agrees that pharmacovigilance plays an important role in ensuring patients' drug safety and providing high quality medical care. It is known to be an essential tool for the effective use of drug therapy. Gene therapy involves the transfer of genetic material in a carrier or vector and the uptake of the gene into targeted cells. Cell therapy refers to the transfer of cells with relevant/desired function into the patient. There are some protocols that use both gene and cell therapy: stem cells are isolated from the patient, genetically modified in culture to express a new gene, typically using a viral vector, expanded to sufficient numbers and then returned to the patient. Drug safety of these type of product is essential for their marketing authorization.

AIM: The purpose of this work is to examine and analyze the role of the pharmacist in pharmacovigilance for gene and cell therapies. Pharmacists, along with other healthcare professionals, play a key role in collecting and interpreting adverse drug reactions and medication errors, and therefore very much welcome the recognition of this role, and the possibility of specific obligations being given a legal basis in the Pharmacovigilance Directive.

MATERIALS AND METHODS: Documentary method was applied and a search in various electronic scientific databases was performed.

RESULTS AND CONCLUSION: Pharmacovigilance basically targets the safety of a medicine. Pharmacists play a crucial role in health systems in maintaining the rational and safe use of medicines since they are drug experts who are specifically trained in this field. Effective use of pharmacists' workforce will improve the outcome of the pharmacotherapy as well as decrease global health costs. In Europe, the implementation of renewed pharmacovigilance legislation (Directive 2010/84/EU) has also implemented the pharmacovigilance activity and risk management system in clinical settings, defining the system as "a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions". Nevertheless, the so-called underreporting in pharmacovigilance remains a relevant phenomenon, mainly due to the refusal or failure to report adverse events by health personnel.

Keywords: *pharmacovigilance, pharmacist, adverse drug reactions (ADR), gene, cell therapies*

INTRODUCING THE STUDENT-CENTRED LEARNING CONCEPT IN UNIVERSITY EDUCATION

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INTRODUCTION: Student-centred learning (SDL) alters the role of students in such a way that they become the owners of their learning process. The Flipped Classroom, Project-Based Learning, Jigsaw and Inquiry-Based Learning are popular examples of SCL. Taking a more active role in their own education is empowering students not only with academic knowledge, but with the skills to pursue their goals and make a difference in their communities.

AIM: The principal objective of this work is to learn about the four types of SDL and which ones would be the most beneficial in different disciplines in students' education.

MATERIALS AND METHODS: We have collecting information about the idea of student centrality. We used an analytical method to address the key factors that emphasize students' responsibility and the necessary of guidance and support in the process.

RESULTS AND CONCLUSION: The impact of the pandemic made it clear that the education in the future must be personal, adaptable, and driven by students. By modifying well-known teaching methods, students would develop more skills during their studies. They will develop their presentation and critical thinking skills and understand evidence-based reasoning and creative problem solving.

Keywords: *student-centred learning (SCL), teaching, skills, classroom*

THE ROLE OF COMMUNITY PHARMACISTS IN THE MENTAL HEALTH CARE OF PATIENTS WITH DEPRESSIVE DISORDERS AND COMORBID CHRONIC CONDITIONS

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INTRODUCTION: Recognition of depressive disorders is often challenging in comorbid patients, as well as monitoring the effectiveness of the pharmacotherapy for multiple medical conditions. Thus, the role of community pharmacists is very important for improving patients' quality of life and therapy.

AIM: The aim of this article is monitoring the ongoing therapy and current psychological state in comorbid patients.

MATERIALS AND METHODS: The survey was conducted among patients with anxiety-depressive disorders and other chronic diseases in a community pharmacy between April 2022 and June 2022. The research included sociodemographic characteristics of the patients, medical therapy, comorbidity, and the Patient Health Questionnaire (PHQ-9).

RESULTS: The number of participants corresponding to the criteria was 37. More than 67% have had comorbid chronic conditions for less than 10 years, 32%—for more than 10 years. 77% have not had a psychiatric consultation. The PHQ-9 score showed mild or no depression.

CONCLUSION: The psychological state of the patients was relatively stable which indicated that they could be an active part of the community despite their illnesses. The absence of psychiatric consultation was concerning. The role of the community pharmacist in monitoring and cooperating with the therapy is important for the patients' psychological and physical well-being.

Keywords: *depression, chronic diseases, therapy, monitoring, community pharmacists*

OPTIMIZATION OF THE WORK PROCESS IN A HOSPITAL PHARMACY WITH STANDARD OPERATIVE PROCEDURES

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INTRODUCTION: The hospital pharmacy is an essential department in the hospital structure and as such, the qualification of hospital pharmacists, their motivation for work, and their collaboration with the rest of the medical specialists are very important.

AIM: The aim of this research is to prove that the implementation of standard operating procedures in the work process in a hospital pharmacy and the improvement of interpersonal communication will have a positive influence on the hospital.

MATERIALS AND METHODS: The study used a method of observation of the work process in a hospital pharmacy, did an interview with hospital pharmacists, and a documentary method.

RESULTS: The results show that hospital pharmacists approve the implementation of standard operating procedures. They think that coordinating the responsibilities of healthcare providers will achieve high quality of provided medical care and hospitalized patients will be satisfied as well.

CONCLUSION: The quality and safety of medical care play a major role in maintaining the health of the population. Hospitals should focus on the needs and expectations of patients, if they want to provide effective medical care.

Keywords: *hospital pharmacy, standard operative procedures, medical errors*

INNOVATIVE HEALTH TECHNOLOGIES RELATED TO IMPROVING PATIENT COMPLIANCE

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INTRODUCTION: The patient's agreement with the specialist's decision—medication intake, diet regimen, lifestyle change, is called compliance. It is quite common to observe non-adherence to the therapy on the part of the patient by which the patient's condition worsens or the outcome of the therapy does not show positive results. Various tools and technologies have been developed to improve compliance; some are specially developed by pharmaceutical companies for easier use of their medicinal product. The development of technologies also leads to the introduction of new medical devices to facilitate therapy and improve treatment.

AIM: The aim of this article is to explore the various health technologies used to improve compliance to prescribed therapy.

MATERIALS AND METHODS: To achieve the purpose of the study, a documentary method was used for the analysis of a scientific database (PubMed, Scopus, Google scholar). A historical review of health technologies used to improve adherence to therapy has been made.

RESULTS: Based on the conducted research, four main groups of health technologies used to improve compliance were formed:

1. Dosing boxes
2. Mobile health applications
3. Medicinal products combined with medical devices
4. Medical devices that serve to monitor the condition of a given disease and the intake of medicinal products if necessary

CONCLUSION: Innovative health technologies increase compliance, however, in cases where a positive benefit/risk ratio is not proven, they fall out of use.

Keywords: *medical devices, adherence, compliance*

EXPLORING THE DIGCOMP FRAMEWORK FOR ADAPTING DIGITAL TECHNOLOGIES FOR TEACHING AND LEARNING

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INTRODUCTION: The educational system has seen a big change in recent years. As a result of the pandemic, it has become necessary to use digital technologies for educational and public purposes. In January 2018, the European Commission adopted an action plan in the field of digital education, which included 11 initiatives to support the use of technology and the development of digital skills in education, and published the European Digital Competence Framework for Citizens, also known as DigComp, which offers a tool to assess and improve citizens' digital competences.

AIM: The purpose of this work is to examine and analyze one of the first projects in Europe for digital literacy and inclusion, implemented successfully in Italy, which is called Bread and Internet (Pane e Internet) (an introduction to a zero level for users and the relevant training). It also aims to do an assessment of how much its replication in Bulgaria may contribute to improving the population's digital literacy.

MATERIALS AND METHODS: A search in various electronic databases was performed. Only studies using validated instruments to assess digital literacy among older adults were selected.

RESULTS AND CONCLUSION: After the analysis of the phases of the project and final results, it was concluded that the introduction of a "zero" level for users could significantly improve the adaptation to digital education. It also may improve the learning outcomes, which is very relevant for Bulgaria, where a majority of students and teachers have met the challenge of distance learning for the first time.

Keywords: *DigComp, digital technologies, digital education, distance learning, Bread and Internet*

PARACETAMOL—NEW EFFECTS ON RISK-TAKING AND POSITIVE EMPATHY

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INTRODUCTION: Paracetamol is one of the most used painkiller and fever-reducing medication worldwide. It can be found in numerous products either alone or in combination with other drugs.

AIM: The purpose of this review is to summarize the latest information published in different scientific articles regarding the use of paracetamol.

MATERIALS AND METHODS: The scientific data has been collected from various sources such as PubMed, Ohio.edu, and Neuroscience news.

RESULTS: In recent researches, new effects of paracetamol have been reported. At the University of Ohio, USA, a series of studies have been conducted. Their results reveal that paracetamol can blunt physical and social pain by reducing activation in brain areas (i.e., anterior insula and anterior cingulate) by which it limits positive empathy that a person has for others. In addition, according to further researches, paracetamol can reduce empathy for another person's pain. Even more interesting effect discovered by the science team is that paracetamol alters the perception of risk. The study has shown that paracetamol has psychological effects that most people do not consider.

CONCLUSION: The eagerness to know more and more is what moves science forward. Though a lot is known about paracetamol, being curious and innovative will let new horizons ahead of us be conquered.

Keywords: *paracetamol, new effects, risk taking, positive empathy*