STUDY OF THE BIOFLAVONOID FUSTIN FOR ANTITUMOR, ANTI-INFLAMMATORY AND GASTRO-ENTERO-HEPATOPROTECTIVE ACTION IN EXPERIMENTAL PHARMACOLOGICAL MODELS

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ABSTRACT

Introduction: The research on biologically active compounds and the identification of new molecular targets are relevant to the development of drug therapy. The medicinal plant Cotinus coggygria has a high content of polyphenols, including fustin, which is unstudied in preclinical experiments.

Aim: Our aim was to explore the pharmacological activity of fustin in experimental models with human tumour cell lines and Wistar rats.

Materials and Methods: Fustin was isolated and purified from C. coggygria heartwood by HPLC and NMR spectroscopy. The in vitro anticancer potential was assessed on human cell lines from breast cancer (MCF7, MDA-MB-231), colon cancer (Colon 26), malignant skin melanoma (A375), and squamous cell skin carcinoma (A431). Gene expression analysis of the ability of fustin to affect the mechanisms of apoptosis, migration, and adhesion, and block the cell cycle was performed by qRT-PCR. The in vivo study of anti-inflammatory and organoprotective effects of fustin was conducted on rat models of carrageenan-induced acute paw inflammation, indomethacin-induced gastric ulceration, trinitrobenzene sulfonate-induced colitis, and paracetamol-induced hepatotoxicity by biochemical analyses, histopathological evaluation, and immunohistochemical tests.

Results and Conclusion: **Proapoptotic and anti-migratory activity of fustin on breast cancer cells was found. Its anticancer properties were associated with alterations in transcriptional levels of six genes involved in apoptosis, autophagy, and cell cycle control. Fustin suppressed the first phase of acute inflammation, similar to NSAIDs. It exerted a gastroprotective action and reduced the expression of NF-κB. Fustin ameliorated some histopathological parameters of colitis and hepatotoxicity. It was concluded that these effects were due to its antioxidant properties.**

Keywords: *smoke tree heartwood, Cotinus coggygria, fustin, cancer cell lines, Wistar rats*

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COMPARATIVE ANALYSIS OF GLOBALLY USED MEDICINAL PLANTS FOR TREATMENT AND PREVENTION OF COVID-19

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ABSTRACT

Introduction: The COVID-19 pandemic has highlighted the need for global collaboration among scientists and medical professionals

Aim: The objective of this study is to compare medicinal plants used by the Bulgarian population for prevention and treatment of COVID-19 to their use in other countries.

Materials and Methods: We researched medicinal plant usage during the pandemic among Bulgarian residents through an online survey. We compared the results with 14 other countries using a documentary approach.

Results: The analysis revealed a total of 260 medicinal plants cited for 21 different applications in preventing and treating COVID-19. The cited medicinal plants belong to 78 families, with most cited species from the Asteraceae family (31 species), Lamiaceae family (26), and Fabaceae family (11), collectively representing 30% of all reported medicinal plants.

The use of herbs is most widespread in Nepal, Thailand, Bulgaria, and Turkey, with Bulgaria ranking third in terms of the number of reported species (50). Among these, 31 species were also mentioned in foreign studies.

The greatest similarity in the cited species in our country is with those reported in Turkey (15), Algeria (14), and Colombia (13).

The most commonly used species include Allium cepa L., Allium sativum L., Matricaria chamomilla L., Mentha spp., Rosmarinus officinalis L., Nigella sativa L., Citrus × limon Osbeck, and Zingiber officinale Roscoe.

Conclusion: The analysis of used medicinal plants during the pandemic in Bulgaria and other countries reveals similarities in the species and differences in the categories of application. It can serve as a starting point for future scientific research and the development of methods for the treatment and prevention of COVID-19.

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

NUTRACEUTICALS IN DAILY LIFE

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ABSTRACT

Nutraceuticals (a borderline term between nutrition and medicine) have attracted an increasing interest due to their role in ensuring well-being and health since 1989. Nutraceuticals may be used to improve health, delay the aging process, prevent chronic diseases, increase life expectancy, or support the structure or function of the body. Nutraceuticals are concentrated and administered in the appropriate pharmaceutical form. Thus, for plant-based foods, a nutraceutical is the phytocomplex; and for foods of animal origin, a nutraceutical is represented by the group of secondary metabolites.

There are also limitations of formulations due to low solubility in water, thermal instability, sensitive gastric digestibility, and low bioavailibility. In this sense, oral delivery strategies for nutraceuticals include developed lipid-based nutraceutical release systems (liposomes, nanoemulsions, solid lipid nanoparticles (SLN), niosomes, self-emulsifying systems (SEDDS)) and 3D printing technology.

Although current European regulations (Regulation EC No. 1924/2006 of the European Parliament and of the Council, recently updated by EU Regulation 2015/2283) do not officially mention or recognize the term *nutraceutical*, different groups of experts proposed a different approach to the use and definition of nutraceuticals, a protocol for the development of new nutraceuticals taking into account safety, *in vitro* and *in vivo* efficacy, mechanism of action supporting any claims contained on labels, efficacy through clinical trials, assessment of possible unwanted side effects, and assessment of possible interactions with food, supplements, and medications.

Taking into account these recommendations, an *in vitro* study was developed to assess the hepatoprotective and antioxidant activity of some extracts based on *Prunus avium* (L.) syn. *Cerasus avium* (L.) Moench. var. *sylvestris* Ser. fruits pulp and red grape *Vitis vinifera* L. pomace Mamaia variety, and a novel combination of these extracts, for further use as a nutraceutical product. The preliminary results obtained indicated that this proposed extract combination is recommended for further testing and the development of new nutraceuticals with hepatoprotective potential.

Keywords: *nutraceuticals, efficacy, safety, regulation, fruits extracts, hepatoprotection*

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DEMONSTRATION OF A SUITABLE MEDICINAL PLANT AS A POTENTIAL PHYTOPRODUCT DEVELOPMENT FOR THE TREATMENT OF ALOPECIA

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ABSTRACT

Introduction: One of the greatest challenges facing humanity in the 21st century, the COVID pandemic, has led to an increase in the incidence of several dermatological diseases, including hair loss. Alopecia was observed in 60 percent of COVID-19 survivors.

Aim: The aim of this article is to demonstrate the potential and prospects in the application of a suitable medicinal plant as an alternative to conventional means in the fight against alopecia.

Materials and Methods: Conducting a search in national and international databases using keywords such as *COVID-19, alopecia, hair loss, hair loss phytotherapy*, etc. for studies published until 2022.

Results: We found that for a large number of representatives of the family Malvaceae, there is data on their application in dermatology and cosmetology. Available experimental data suggests that the oil extract of *Hibiscus rosa sinensis* L. flowers actively affects hair growth and may be an effective herbal alternative to minoxidil in the treatment of alopecia. This led us to a comparative analysis of the biochemical composition of *Hibiscus rosa sinensis* L. flowers with that of *Hibiscus esculentus* L. fruits. We found that substances of both plants contain the same bioactive compounds such as carotene, polyphenol, folic acid, riboflavin, niacin, vitamin C, and thiamine, which have been shown to stimulate the growth of thicker hair and lead to the extension of the anagen phase.

Conclusion: The results obtained will serve as a basis for future experimental studies of *Hibiscus esculentus* L. as a potential natural substitute for minoxidil with the aim of developing phytoproducts for the treatment of alopecia.

Keywords: *COVID-19, alopecia, hair loss, hair loss phytotherapy, medicinal plants*

HIGHLY EFFECTIVE ALUMOSILICATE-CYTOCHROME C COMPOSITE NANOPLATES FOR SELECTIVE TREATMENT OF SUPERFICIALLY LOCALIZED NEOPLASMS

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ABSTRACT

Introduction: In tumor cells apoptosis is blocked because of the inability of their mitochondria to release cytochrome C (cytC). Therefore, this process can be initiated by introduction of exogenous cytC, using the capability of the cancer cells to phagocytize extracellular colloid particles with submicron size. We use the mineral montmorillonite (MM) due to its high adsorption capacity determined by the huge size/thickness ratio. The inability of the normal cells (except from macrophages and neutrophils) to phagocyte colloid particles protects them and determines the selectivity of the composite cytC-MM nanoparticles.

Aim: The aim of this article is to investigate the physicochemical properties of cytC-MM nanoparticles as a function of cytC concentration in the suspension and their cytotoxicity.

Materials and Methods: Microelectrophoresis, static and electric light scattering were used to determine the electrophoretic mobility, mass increment of MM monoplates at cytC adsorption, adsorbed/free ratio, number of adsorbed cytC globules per one MM monoplate, and concentration of cytC-MM composite particles. Futhermore, we tested the cytotoxic effect of cytC-MM on colon cancer cell culture.

Results: Cytochrome C solution and MM suspension had no effect on the cancer cells. In contrast, the composite cytC-MM nanoparticles killed 97% of the cells after 96 h treatment. Interestingly, the cytotoxicity was found to depend nonlinearly on the concentration of cytC in the cytC-MM suspension, but linearly on the logarithm of this concentration.

Conclusion: The in vitro experiments demonstrate that cytC-MM composite nanoparticles have potential application in treatment of superficial neoplasms.

Keywords: *cytochrome C, cancer, apoptosis, cytotoxicity, nanoparticles, montmorillonite*

Acknowledgements: *The study was supported by the National Research Fund (Contract КП-06-Н69/4).*

IMPROVING OUTCOMES IN PEDIATRIC PATIENTS USING POWDERED PHARMACEUTICAL FORMS

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ABSTRACT

Introduction: The share of children aged 0–18 years in Bulgaria is 16.92% compared to 22.39% in EU. This specific population needs adequate and timely medical and pharmaceutical care. According to current projections, the number of children in Bulgaria is expected to follow a downward trend between now and 2025, which highlights the need for advanced, easy-to-use and patient-friendly therapeutic models to ensure better health outcomes.

Aim: The present study aims to review the pharmacokinetics and pharmacodynamics of pediatric patients, the application of different dosage forms, and to determine whether powder dosage forms would improve the compliance and health results.

Material and Methods: A literature review was performed using the keywords pediatric patients, pharmacokinetics, and powder dosage forms in the databases Scopus, ResearchGate, and Web of Science. Statistics were acquired from Eurostat, UNICEF, and the National Statistical Institute.

Results: Differences between adults and pediatric patients in the pharmacokinetic processes of absorption, distribution, metabolism and excretion were identified. Anatomical, physiological and biochemical changes that occur from birth affect pharmacokinetics/pharmacodynamics and, therefore, the bioavailability of drugs.

Powders as dosage forms are characterized by high stability, convenience in administration and transport, and low chance of incompatibility. They achieve a rapid effect and higher bioavailability.

Conclusion: The use of powder dosage forms in pediatrics appears to be a promising and relatively simple approach, which is aimed directly at younger patients. A satisfactory therapeutic effect is achieved. The aim is to continuously improve these drug forms and expand their applicability in both hospital and ambulatory settings.

Keywords: *pediatric patients, pharmacokinetics, powders*

EFFECT OF FORMULATION VARIABLES ON THE TEXTURAL CHARACTERISTICS OF POLOXAMER 407-BASED EMULGELS

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ABSTRACT

Introduction: Emulgels are biphasic semisolid formulations obtained by incorporating an emulsion into medium containing gelling agent(s). They are characterized by superior physical stability compared to emulsions, pleasant appearance, greaseless texture, and good spreading properties.

Aim: The aim of the study was to obtain an emulgel composition with suitable gelling and mechanical properties for cosmetic application. Therefore, the influence of composition constituents (emulsion oil/water phase ratio, gelling agent content) on the textural properties and stability of the developed emulgel bases was evaluated.

Materials and Methods: Emulgels were prepared by mixing o/w emulsions with Poloxamer 407-based hydrogels in 1:4 w/w ratios. The o/w emulsions containing different amounts of grape seed oil (10%/20%/30% w/w), emulsifiers (Span 80/Tween 80, total 40% w/w from the oil phase) and water were prepared using a magnetic stirrer (350 rpm) at 70°C for 10 minutes. Poloxamer-based hydrogels (22.5%, 25% w/w) were obtained by the classic "cold" method. The texture properties of emulgels (hardness, cohesiveness, adhesiveness) were assessed using texture analyzer. The spreadability was evaluated by the glass slide method. The stability of the formulations was determined by centrifugation test.

Results and Conclusion: Increasing both grape seed oil emulsion and gelling agent ratios decreased the spreadability of the formulations, likewise higher Poloxamer 407 content determined an increase in the firmness values. The formulation based on 20% emulsion and 22.5% Poloxamer 407 hydrogel was characterized by suitable spreading and mechanical properties for topical application, excellent physical stability, and was selected for further pharmaceutical development.

Keywords: *emulgel, grape seed oil, texture analysis, topical delivery*

QUALITY IDENTIFICATION OF METHYLENE BLUE DYE IN MOUTHWASH

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ABSTRACT

Introduction: Methylene blue, a thiazine dye, stands as a remarkable historical artifact in the world of chemistry. It represents the earliest synthesized antimalarial medication, first experimented with in the closing chapters of the nineteenth century. This intriguing compound possesses multifaceted properties, including antimicrobial and antiseptic attributes. Despite its extensive usage, the precise intricacies of its mode of action remain shrouded in mystery. In the contemporary landscape, methylene blue enjoys diverse applications, serving as a vital analytical reagent in the realm of microbiology. Moreover, it plays a pivotal role in the domain of medicine and pharmacy, where it finds employment as a treatment for methemoglobinemia. Notably, this versatile substance also finds its place in various oral hygiene products, harnessing its inherent antiseptic prowess.

Aim: The aim of the present work is to prove the presence of methylene blue in a commercial mouthwash product.

Materials and Methods: The analytical tools enlisted in this rigorous investigation comprise UV-VIS and IR spectroscopic techniques. Qualitative analytical reactions, featuring ascorbic acid and blue bottle experiment, were adroitly executed. TLC chromatographic analysis was also performed with a mobile phase of ethanol: chloroform: acetic acid (85:10:5). To further augment the study's depth, an MBRT (Methylene Blue Reductase Test) was meticulously administered to gauge the vitality of yeast within a bread yeast.

Results: In the UV-VIS spectra of the studied sample, three main absorption maxima are detected at λmax=664, 292, 264 nm. These values completely coincide with the UV-VIS spectrum of the standard. We also find a complete correspondence with a standard substance in the recorded IR spectrum. Regarding the TLC analysis, the Rf factor for both spots was 0.29. The qualitative analytical reactions were also positive. Solid blue staining of dead yeast cells was reported under the microscope, while living ones were not dyed and were observed to be colorless.

Conclusion: In conclusion, the mouthwash sample analyzed by us contained the dye described in the composition, methylene blue.

Keywords: *methylene blue, quality identification, mouthwash, UV-VIS spectroscopy*

OBSERVATIONS OVER THE TRAINEE PROGRAMME OF THE BULGARIAN SCIENTIFIC PHARMACEUTICAL LABORATORY FOR A NINE-YEAR PERIOD

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ABSTRACT

Introduction: Trainee programmes have a great influence over the education process during the university course, as well over the quality of higher education. As compounding of medications in Bulgarian pharmacies went out of fashion after 1989, the lack of qualified compounding pharmacists appeared quick after that. The university course has no capacity to cover most of the techniques and methods used in modern compounding. In addition, in the country there is no National Formulary, neither suppliers of API, excipients and books for pharmaceutical compounding. The business organisations have a task to run students' trainee programmes on their own.

Aim: The aim of this article is to provide direct observation report over the trainee programme for pharmacy students of the Bulgarian Scientific Pharmaceutical Laboratory (BSPL) to Erudita Pharmacy of Pediatrics for the period May 2015–August 2023.

Materials and Methods: The following files kept by BSPL: Register of the Trainees, Register of Initial Instructions, Register of Regular Instructions, Register of the Training Courses, Annual Training Programme, ISO documentation, Register of Work Incidents as well as Mentor's Evaluation Forms and Direct Interviews, were reviewed to draw the relations.

Conclusion: A period of approximately 4 years of training is required for a pharmacist to qualify as a compounding specialist.

Communication with the Ministry of Education in terms of the quality of secondary school education quality is needed.

Universities should consider paying the students' mentors, as well as the hosting organisations.

A more adequate Hosting Organization Selection Procedure (HOSP) should be developed in order to provide the needed level of competencies for the students.

Keywords: *pharmacy, education, practice, trainee programmes, business-to-academia network, quality*

ASPECTS OF STRESS IN A LEARNING AND PRACTICAL ENVIRONMENT AMONG MEDICAL STUDENTS

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ABSTRACT

Introduction: The increasing global prevalence of stress in society is a problem that major international organizations focus on annually. Professionally, it is recognized that people in the field of education and health are under the greatest stress. Various studies reveal alarmingly high levels of stress, except among health practitioners and medical students, highlighting the adverse effects on their physical and mental health due to the highly stressful environment in colleges and universities. Given the global shortage of health personnel and high dropout rates among trainees, the identification of stress factors and the development of stress management programs among health professionals and medical students is becoming an increasingly popular issue.

Aim: The aim of this study is to determine stressors among students from medical programs in the period of study.

Materials and Methods: In June 2022, a survey was conducted among 89 students enrolled in medical programs at different universities in Bulgaria, namely Sofia University "St. Kliment Ohridski" (n = 59), MU-Sofia (n = 20), MU-Plovdiv (n = 5), MU-Varna (n = 3), and MU-Pleven (n = 2). Of the 89 students, 41 studied medicine, 13—pharmacy, 27 were studying to be a nurse, 1 was enrolled in a dentistry program, and 2 majored in medical rehabilitation and ergotherapy. The survey was conducted using an anonymous electronic questionnaire. The survey data was analyzed using Microsoft Excel 2020 software products.

Results and Conclusion: The results of the survey demonstrate that daily activities during clinical practice, such as application of manipulations and integration into a functioning hospital environment, are part of the main stress factors among students. The presented alarming data emphasize the need for a more detailed study of the specific causes of stress in the learning process, as well as the development of mechanisms for its adequate management.

Keywords*: *stress, learning and practical environment, students from medical specialties

NARCOTIC SUBSTANCES AND THEIR IMPACT ON THE HEALTH AND MENTAL STATE OF ADOLESCENTS. PREVENTION OF DRUG USE

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ABSTRACT

Introduction: **Narcotics are one of the biggest challenges of our time. They are part of civilization, culture, and myths. Whether we accept their existence or not, they are present in our lives.**

Aim: **The purpose of the present study was to conduct a training for pedagogical specialists and provide theoretical knowledge and health information about narcotic substances: where they come from, what is the reason for their use among adolescents, the risks of their intake, detection of specific signs of their use, and prevention of their intake in order to maintain good physical and mental health.**

Materials and Methods: **Part of the process involved writing a leaflet titled Don't Let Drugs Turn You into a Stranger and distributing it through pedagogical specialists in schools in Bulgaria. It is developed to protect the physical and mental health of adolescents. This informational brochure is a joint initiative with the Ministry of Health and the Ministry of Education and Science.**

Results: **A program with UIN: 57660029 was held on the topic "Narcotics and Their Impact on the Physical and Mental Health of Adolescents. Prevention of Drug Use" in schools in the country. Pedagogical specialists were introduced to the main types of narcotic substances and their effects, their most common side effects, the main types of addictions, the legal framework, the reasons for drug use, signs of drug use, Bulgaria's National Drugs Strategy, sports as prevention, and educational video materials.**

Conclusion: **By going through the program, teaching staff increase their competence regarding narcotic substances, types of addictions and, above all, how to recognize the presence of a problem. Trained staff can distribute an electronic information leaflet to their students and their parents to highlight the risks. The multimillion dollar "army" of drug users is constantly growing, and, what is even more frightening—it is constantly getting younger.**

Keywords: *narcotics, prevention, risk, symptoms, education, pedagogical specialists*

ATTITUDE ON CAREER REALIZATION AMONG NURSING STUDENTS

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ABSTRACT

Introduction: The shortage of nurses is a problem of global scale, which also exists in our country. According to official data, in 2019, the working nurses in Bulgaria were 23,021, and at least another 35,000 staff were needed. In addition to the downward trend in the number of nurse practitioners, there is also an increase in the average age of workers, with an average age of 54 in Bulgaria. The presented problems are indicators of an outflow of professional nurses and mark the need to expand the opportunities for career development, as well as the development of mechanisms for promoting the profession in society and the labor market.

Aim: The purpose of this study is to investigate the attitude of nursing students toward their career realization and development in healthcare.

Materials and Methods: A survey of the motivational factors for choosing and practicing the nursing profession was conducted among 32 nursing students, Sofia University St. Kliment Ohridski, through an anonymous electronic questionnaire. The participants represent 45% of the students in the specialty at the time of the survey. The survey was conducted in April 2023. The Microsoft Excel 2020 software products were used to analyze the primary sociological information.

Results and Conclusion: The attitude towards career realization and development among future health professionals is of particular importance not only for the field of healthcare but also for the nursing community, as they have a key role in the continuity and development of nursing. The presented data show that the trend is changing in a positive direction, with the majority of future bachelors motivated to work and develop professionally in the field of healthcare.

Keywords: *attitude, career realization, nursing students*

CHALLENGES FOR PHARMACIES IN THE PROCESS OF PROCUREMENT OF MEDICINES DURING THE COVID-19 PANDEMIC

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ABSTRACT

Introduction: The process of procurement of medicines includes activities on provision, transportation, storage and dispensing medicines. Community pharmacies are the final step in the pharmaceutical supply chain before drugs reach the patient. They serve as an information link between patients, pharmaceutical manufacturers and distributors. The regulatory framework for community pharmacies varies across the country. During COVID-19, pharmacies faced several challenges related to providing medicines, dealing with shortages, ensuring equal medicines access, the rational use of medicines, and limiting the virus transmission.

Aim: The aim is to research the challenges of community pharmacies related to provision and dispensing medicines and providing pharmaceutical care during the pandemic.

Material and Methods: Literature published on the internet, normative documents on the issue, and a questionnaire specially developed for the purpose have been used.

Results and Conclusion: During the COVID-19 pandemic, pharmacies played an essential role in ensuring continued equitable access to medicines for the citizens and their rational use. They monitored sales, communicated with all stakeholders and implemented mechanisms to protect stocks. Different legislation changes which affected their work were introduced in some European countries. Attention was paid to eHealth and the rights of pharmacists to prescribe and dispense medicines. The medicine supply process includes innovative services that prevent the spread of COVID-19 and improve drug access. The role of the pharmacist in the overall patient health care is growing. In Bulgaria, pharmacists had eligibility only to renew chronic treatment prescriptions. The legal regulations limit their opportunity for quick reaction to the need for medicines at a time of shortage.

Keywords: *community pharmacy, COVID-19, drug/medicine procurement process, drug/medicine supply, drug/medicine shortage*

PHARMACEUTICAL CARE IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Introduction: **Pharmaceutical care in polycystic ovary syndrome (PCOS) involves the pharmacist delivering a variety of interventions to improve the patient's quality of life, providing effective advice on prescribed therapy and lifestyle changes, and communicating effectively to identify and prevent potential drug-related problems (DRPs).**

Aim: **The aim of our study is to propose a modeling approach to pharmaceutical care services in patients with PCOS by identifying the most common DRPs and possible interventions.**

Materials and Methods: **A literature review was performed followed by a detailed analysis to create an algorithm for pharmaceutical care for patients with PCOS.**

Results: **The most common DRPs associated with PCOS treatment are identified according to PCNE classification and commented in the scope of treatment patterns in Bulgaria. An algorithm for pharmaceutical care during the first and subsequent interactions with patients is proposed and possible interventions are discussed, aimed at improving the quality of life related to PCOS.**

Conclusion: **The role of pharmacists in the management of PCOS has to take into account the characteristics of the treatment, the patient's individual preferences, possible drug-related problems, and risks of self-medication.**

Keywords: *PCOS, pharmaceutical care, drug-related problems*

COMPARATIVE ANALYSIS OF AI MODELS FOR MEDICAL DIAGNOSIS: CHATGPT, CODY, AND DR. GUPTA

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ABSTRACT

Introduction: In early 2023, the advent of accessible artificial intelligence raised a fundamental question: Could AI accurately diagnose low- and medium-risk diseases based solely on patient-reported symptoms?

Aim: This inquiry propelled our current study, which aims to comparatively assess diagnostic capabilities among three AI models: ChatGPT, Cody, and Dr. Gupta.

Materials and Methods: Our research methodology encompassed a comprehensive review of Scopus and PubMed literature, revealing a promising landscape of AI's potential in medical diagnosis across specialties. This motivated our team to select ten diverse case reports, each featuring well-defined diagnoses, treatment plans, and positive outcomes. Patient-reported symptoms were input into ChatGPT, Cody, and Dr. Gupta, initiating diagnostic interactions.

Results and Conclusion: Impressively, ChatGPT achieved a 90% accuracy rate in its diagnoses, whereas Cody and Dr. Gupta yielded correct diagnoses at a 50% rate. Notably, these AI systems extended their roles beyond diagnosis, also offering therapeutic insights encompassing medications, interventions, and lifestyle adjustments. This study underscores AI's transformative impact on medical diagnosis and treatment recommendations, with ChatGPT emerging as a frontrunner with its high accuracy rate. As AI's role in healthcare evolves, this research illuminates the possibilities and challenges that lie ahead.

Keywords: *AI, medical diagnosis, comparative assessment, patient-reported symptoms, ChatGPT*

HPLC METHOD FOR SIMULTANEOUS DETERMINATION OF IBUPROFEN AND PRESERVATIVES IN GEL FORMULATION

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ABSTRACT

Introduction: Ibuprofen is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties. Methyl 4-hydroxybenzoate (methyl paraben) and propyl 4-hydroxybenzoate (propyl paraben) are well-known preservatives used primarily for their bactericidal and fungicidal activity.

Aim: The aim of this study was to elaborate a high-performance liquid chromatography method with UV detection for assay of nonsteroidal anti-inflammatory drug ibuprofen in gel formulation in the presence of both preservative compounds, methyl paraben and propyl paraben.

Materials and Methods: For chromatographic separation, C18 (250 mm x 4.6 mm, 5 µm) was successfully used. Excellent chromatographic behavior of analytes of interest was achieved, applying a mobile phase methanol, acetonitrile, and 2% sodium dihydrogen phosphate solution (20:70:10 v/v/v). A flow rate of 2.0 mL/min was performed at ambient temperature and detection was fixed at 240 nm. The analytical procedure presented was validated according to the requirements of the ICH Q2 (R2) guideline.

Results and Conclusion: Under the chromatographic conditions chosen, the obtained retention times were 2.32 min for methyl paraben, 3.18 min for propyl paraben, and 6.88 min for ibuprofen. The HPLC procedure presented was validated by means of the following parameters: linearity, specificity, precision, accuracy and limit of quantitation and limit of detection. The RP-HPLC method for the simultaneous determination of ibuprofen and both preservatives, methyl paraben and propyl paraben, in gel formulation was specific, rapid, and simple with good sensitivity and can be applied in routine quality control.

Keywords: *ibuprofen, methyl paraben, propyl paraben, RP-HPLC separation, validation*

TRAINING OF PHARMACISTS PREPARING SOLUTIONS OF CYTOTOXICS – A NECESSITY FOR A QUALITY PROCESS

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ABSTRACT

Introduction: According to the Bulgarian legislation, solutions of cytotoxics are prepared for direct administration centrally, in hospital pharmacies, only by master pharmacists and assistant pharmacists. In order to carry out this activity they need additional training related to the specifics of the process.

Aim: The aim of this article is to define the key mandatory areas to be targeted for specific training.

Materials and Methods: A number of international sources in this field have been studied and analyzed.

Results and Conclusion: Cytotoxics are classified as potent/hazardous drugs and multiple scientific data indicate that they can have negative effects on the health of personnel who work with them. This effect can be prevented by strict adherence to procedures associated with all stages of the dissolution process. At the same time, the preparation of medicines must be done in compliance with the aseptic technique to ensure the quality of the prepared product. Currently, there is no normative document in Bulgaria that specifies what exactly are the necessary competences for carrying out the activity of preparation of drugs for systemic treatment of malignant diseases. The development and approval of a specific training programme that all pharmacists are required to undergo before starting to dissolve cytotoxics will undoubtedly ensure equal access to the necessary basic knowledge and skills related to workplace protection and the quality of the prepared product regardless of their place of work.

Keywords: *cytotoxics, training, hazardous drugs, centralized preparation, hospital pharmacies, pharmacists*

PRECISION MEDICINE MEETS 3D PRINTING: THE FUTURE EXTEMPORANEOUS DRUG DOSAGE FORMS

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ABSTRACT

Introduction: In recent years, the high-speed development of information and technological resources in the world has led to a remarkable surge of interest in personalized medicine and new drug delivery methods. This interest is fueled by the potential of 3D drug printing to revolutionize how drugs are manufactured, customized, and administered, offering unprecedented opportunities to improve treatment efficiency and patient care.

Aim: This work aimed to examine the place of 3D printing techniques in the formulation of patient-specific dosage forms and the working principles of different printing techniques.

Materials and Methods: Available databases (ScienceDirect, Scopus, PubMed, and Web of Science) were reviewed for scientific publications addressing 3D printed drug products and the advantages and limitations of computer-aided design in pharmaceutical practice.

Results and Conclusion: Fused deposition modeling (FDM) is one of the most accessible and widely used 3D printing methods due to its simplicity and versatility. Based on extrusion, this computer-aided prototyping works with a wide range of thermoplastic materials, while stereolithography (SLA) uses liquid photopolymer resin as the printing material. The resin is solidified using precise UV light exposure. This curing process results in sharp and highly detailed layers with smooth transitions between them, but FDM cannot provide the same level of precision as SLA. Selective laser sintering (SLS), binder or inkjet jetting, multi-material printing, and 4D printing reduce the need for a one-size-fits-all approach to drug therapy. The choice of technique depends on the drug's properties, desired release profile, and intended application.

Keywords: *rapid prototyping, fused deposition modeling, stereolithography, laser-based selective laser sintering, computer-aided design, 4D printing*

Funding: *This work was founded by project BG05M2OP001-2.016-0025: Creation of a Multidisciplinary Educational Environment for Development of Specialists with Integral Competencies in Biomedicine and Health Care.*

A COMPARATIVE STUDY OF THE BIOLOGICAL EFFECTS OF NATURAL FOOD SOURCES OF SULFUR ON HUMAN INTESTINAL CELLS

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ABSTRACT

Introduction: Scientific data show that sulfur and inorganic sulfates from various foods, beverages, and drugs are almost entirely absorbed in the gastrointestinal tract. Our recent study revealed that the intake of sulfurous mineral water (SMW) improves the antioxidant status and reduces inflammation in the human body. In the available scientific literature, no data were found comparing the biological effects of SWM with other sulfur-containing foods and beverages or with their biologically active compounds.

However, the molecular mechanisms behind these effects remain unexplored. On the other hand, sulforaphane (SFN), the biologically active compound in broccoli, is one of the most studied organosulfides, mainly for its anti-cancer and anti-inflammatory properties.

Aim: The aim of the study was to compare the antioxidant and anti-inflammatory effects of SWM from the Varna basin with certain natural sulfur-containing compounds—allicin from garlic, sulforaphane from broccoli, and taurine contained in many foods.

Materials and Methods: Human intestinal epithelial cells (HIEC-6) were treated with various concentrations of various natural sources of organic sulfur: SMW or one of the studied sulfur-containing substances. The effect of SMW, sulforaphane, allicin, and taurine on the cell viability was studied with the MTT test. The effects of the SMW and the other sulfur-containing compounds on the expression of selected genes were investigated in a model of lipopolysaccharide (LPS)-induced inflammation. Salicylic acid (SA) was used as a referent anti-inflammatory compound.

Results: The results showed that pretreatment with organosulfides significantly reduced the transcription levels of proinflammatory genes in LPS-stimulated cells in a concentration-dependent manner. The effect of SMW was similar and comparable to the anti-inflammatory effects of SA.

Conclusion: In conclusion, the obtained results would contribute to enriching our knowledge about the biological effects of selected food sources of sulfur in human intestinal cells. The established anti-inflammatory effect of SMW is comparable to the effect of organosulfides as a dietary source of sulfur with implications for human health.

Keywords: *sulfurous mineral water, organosulfides, inflammation, human intestinal cells*

POTENTIAL ANTI-CANCER ACTIVITY OF ANETHOLE— A REVIEW

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ABSTRACT

Introduction: Cancer is the main cause of death all over the world. Lung, stomach, and liver cancers take up the largest part of causes of cancer death. To control cancer resistance to drugs, the involvement of natural substances with low toxicity is required. A potential candidate can be anethole, which is a natural monoterpene occurring in essential oils, such as anise and fennel.

Aim: The purpose of the present review was to summarize the available information about the anti-cancer activity of anethole and the targets affected.

Materials and Methods: Web-based databases such as Google Scholar, PubMed, and ScienceDirect were used for the review.

Results: In gastric cancer, anethole treatment resulted in a reduction of adenocarcinoma cells by inhibiting the cell cycle through mitochondrial pathways, down-regulating some oncogenes, and activating apoptosis. Cyclin D (oncoprotein) was destabilized by anethole, which was critical for oral cancer treatment, and autophagy was triggered as well. A synergistic effect was observed in the combination of anethole and doxorubicin in inducing cell death in triple-negative breast cancer cells. The monoterpene had an impact on prostate cancer cells by suppressing growth of PC-3 derived cancer stem cells, activating caspase-3 and 9, and elevating the Bax/Bcl-2 protein ratio. The pro-apoptotic potential of anethole in lung cancer was shown by the decrease of key proteins in PI3K-AKT and STAT3 signaling pathways as well as Ki67 expression and increased abundant DNA fragments.

Conclusion: The review highlighted the usefulness of anethole in the treatment of some types of cancers by regulating key signaling pathways.

Keywords: *anti-cancer, anethole, breast cancer, oral cancer*

REVIEWING DATA ON POTENTIAL FALSE POSITIVE ALCOHOL BREATHALYZER TEST RESULTS

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ABSTRACT

Introduction: Nowadays drivers are often confronted by breathalyzers. These devices detect the alcohol molecules in exhaled air. The effect of alcohol on the human brain is almost immediate and affects the person's ability to function normally.

Aim: The aim of our study is to identify the weaknesses in the testing procedure with the alcohol breathalyzers used in Bulgaria.

Materials and Methods: Seven scientific articles have been revised for this research. The Ministry of Internal Affairs in Bulgaria informed us about the devices authorized for use by the police officers. The basis of our study is a review of scientific articles and their data.

Results: The research presents four types of breathalyzers. We explained how they work. We focused on the gas-sensor breathalyzers. According to our sources, results can vary by about 20% from the actual alcohol concentration. We have found that factors and behaviors in our daily life, such as diets, various chemicals and not proper maintenance can influence the devices, thus leading to incorrect results.

Conclusion: A person can, without realizing it, cheat the alcohol test and get false results. Law enforcement authorities could be misled by these uncertain results to take inappropriate administrative sanctions for the sake of road safety.

Keywords: *breathalyzers, drivers, inaccuracy, blood alcohol concentration, breathalyzers with gas sensors, maintenance, road safety*

MAGNESIUM SUPPLEMENTATION: UNRAVELING THE DIFFERENT FORMS AND THEIR POTENTIAL APPLICATIONS

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ABSTRACT

Introduction: Magnesium is a key mineral for metabolic reactions, energy production, nervous transmission, and muscle function. It provides many health benefits. Deficiencies can lead to conditions such as diabetes, heart disease, osteoporosis, and migraines. Western societies are prone to magnesium deficiencies, despite it being present in common foods.

Aim: The aim of the study is to showcase and compare the different forms of magnesium supplements.

Materials and Methods: The data used has been curated from PubMed and Google Scholar to form an educated presentation of the different magnesium salts.

Results and Discussion: To address deficiencies, diverse magnesium supplement forms are available. Magnesium citrate, recognized for high bioavailability, effectively raises magnesium levels and aids with constipation. Magnesium oxide, less absorbed, helps ease digestive issues like heartburn. Magnesium chloride, well-absorbed orally, treats low magnesium levels, and topical use soothes muscle soreness. Gentle on digestion, magnesium lactate suits those needing high doses. Magnesium malate is absorbed well and may be less likely to cause laxative effects. It has a sour taste and is sometimes suggested for fibromyalgia. Magnesium taurate, containing taurine, may support blood sugar and blood pressure levels. Magnesium L-threonate shows potential for brain health, yet more research is required. Magnesium sulfate, or Epsom salt, dissolves for stress relief and muscle relaxation, with limited skin absorption data. Magnesium glycinate, easily absorbed, is favored for anxiety, depression, and insomnia. Lastly, magnesium orotate may benefit heart health, but cost-effectiveness varies.

Conclusion: While these magnesium supplements offer potential advantages, further research is needed to support claims. Consultation with healthcare professionals before supplementing is advised.

Keywords: *magnesium, supplementation, deficiency, magnesium salts, comparison*

NEW TREATMENT OPTIONS FOR MULTIDRUG-RESISTANT BACTERIA

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ABSTRACT

Introduction: The creation and introduction of antibiotics into clinical practice at the beginning of the XX century is undoubtedly one of the most significant achievements of medicine. Their improper and irrational use leads to the development of antibiotic resistance, which nowadays is a global threat to the health of the population. The fight against antibiotic resistance is a top WHO health priority. The need for effective treatment of diseases caused by multidrug-resistant bacteria requires the search for new methods. Different methods are used to develop new antibacterial molecules, which include: bacteriophages and their lytic enzymes, antifungal enzymes, antimicrobial peptides, nanoparticles, small molecule inhibitors and others.

Aim: The aim of this article is to examine two of the new methods for treatment of multidrug-resistant bacteria—nanoparticles and bacteriophages, which are gaining great popularity nowadays.

Materials and Methods: Through a documentary method, a literature review of scientific publications in various specialized databases (PubMed, WebMD, ScienceDirect) was done. The keywords used were: multidrug-resistant bacteria, antibiotics, nanoparticles, phage therapy.

Results: The two new methods examined show good clinical results and are suitable for use in medical practice. Nanoparticles and bacteriophages are effective not only when used separately, but also in combination with antibiotics—tetracyclines and cephalosporins, such as ciprofloxacin and cefixime.

Conclusion: The synergistic action of nanoparticles and bacteriophages with an antibiotic enhances its effect and leads to a decrease in the resistance of bacteria. In addition, phage therapy and nanoparticles used separately are successfully applied as substitutes for antibiotics.

Keywords: *antibiotic resistance, nanoparticles, bacteriophages*

A BRIEF OVERVIEW ON THE MANUFACTURING AND UTILIZATION OF ^{177}LU- DOTATATE

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ABSTRACT

Introduction: This overview consists of information about the ^{177}Lu- labeled radiopharmaceutical drug ^{177}Lu–DOTATATE. A description of basic steps of synthesis and uses for treating neuroendocrine tumors is presented.

Aim: With this paper we aim for a much more intuitive approach for understanding the concept of radiolabeling a biologically active molecule like DOTATATE. The simplified method explains basic concepts and helps one achieve a better understanding of the general principles of radiopharmaceuticals.

Materials and Methods: A binary chemical compound ($LuCl_3$) is used as a non-carrier source of the radioactive isotope. The radiolabeling of the DOTATE peptide occurs in an automated system. DOTATATE is bought pre-synthesized. The methods are of physico-chemical nature, and are also largely automated, in order to minimize the effect of ionizing radiation. Administration of the drug implies wearing protective gear, having trained personel and other safety protocols.

Results: The radionuclide integration in this biologically active molecule has successfully been implemented in the treatment of neuroendocrine tumors. Minor, but manageable side-effects occur.

Conclusion: The methods of administration and the treatment itself are effective and localized. It has shown promising results in the field of nuclear medicine. Most notably there is an increase of post-diagnosis lifespan.

Keywords: *lutetium, neuroendocrine, radiopharmaceutical, somatostatin, tumor*

PATIENT AWARENESS IN THE CHOICE OF DIETARY SUPPLEMENTS AND OTC MEDICINES

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ABSTRACT

Introduction: Over-the-counter (OTC) medicines and dietary supplements can be dispensed in a pharmacy/drugstore or purchased by the patient from an online retailer. These possibilities imply a higher patient awareness of this type of products in terms of intake, treatment, and avoidance of irrational use of medicines.

Aim: The aim of this article is to determine the level of patient awareness and the factors influencing the choice of dietary supplements and OTC products.

Materials and Methods: An online anonymous survey was conducted among 117 citizens on the territory of the Republic of Bulgaria, in the period August–September 2023. Historical, sociological, and graphical methods were used, and the results were processed using Microsoft Excel version 2016.

Results: The results of the study show that patients are relatively well informed and make difference between an OTC product and a dietary supplement. Patients' preferences for OTC and/or dietary supplements are related to influenza symptoms and prevention. Tablets are the most preferred dosage form. A significant proportion of respondents reports that they check information on the Internet or ask a pharmacist before buying products. Consumption of these types of products has increased during and after the pandemic, and patients are aware that excessive use can be dangerous to their health.

Keywords: *patient, awareness, choice, OTC, medicines, food supplements*

The study is related to a mobility project BG05M2OP001-2.016-0025, titled Creating a Multidisciplinary Educational Environment for Development of Specialists with Integral Competencies in Biomedicine and Health Care.

SPECIALIZED PHARMACEUTICAL SERVICES FOR PATIENTS WITH CARDIOVASCULAR DISEASES AND PATIENTS' ATTITUDE TOWARD PAYMENTS OF THIS SERVICES

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ABSTRACT

Introduction: Pharmaceutical care (PC) is an essential part of modern pharmaceutical practice. The highly qualified PC, including additional services, should be focused on monitoring and prevention of the diseases in high-risk patient populations and is crucial in the reduction of mortality caused by chronic, non-communicable diseases. Among them, cardiovascular diseases (CVDs) stand out as one of the leading global causes of death.

Aim: The aim of this article is to explore the attitudes of CVD patients towards paying for additional, specialized pharmaceutical services.

Materials and Methods: The study used an online questionnaire-based survey methodology and was conducted among a cohort of 79 individuals diagnosed with chronic CVDs during the period of July to August 2023.

Results: All the participants in our study reported that they have been diagnosed with a CVD for over a year. The results indicated that most of them were taking more than one prescription-only medicine (POM), and that the relative percentage of patients taking over-the-counter (OTC) medicines or food supplements was very low. These patients reported having access to both pharmacies and PC services. Notably, there was clear willingness among respondents to receive additional services and therapeutic education. However, the majority expressed reluctance to bear the cost of these supplementary services. Our survey participants emphasized the pivotal importance of prevention and the reduction of risk factors in mitigating the consequences of CVD and reducing overall mortality rates associated with the disease.

Keywords: pharmaceutical care, cardiovascular diseases (CVDs), *prevention, therapeutic training, willingness to pay*

FACTORS AFFECTING CONSUMER SELECTION OF COMMUNITY PHARMACIES

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ABSTRACT

Introduction: A pharmacy is a healthcare facility with free access for people. Patients are not restricted by law from visiting a specific site or pharmacist. This makes it possible to choose a pharmacy depending on their needs. Consumers preferences are influenced to varying degrees by a number of objective and subjective factors.

Aim: The aim of this article is to investigate factors influencing patients' choice of a pharmacy and make a comparative analysis for 2023 versus 2021.

Materials and Methods: To collect the data, an online anonymous survey was conducted among adult citizens on the territory of the Republic of Bulgaria in two stages, September–October 2021 and August–September 2023. Historical, documentary, sociological and graphic methods were used, the processing of the results was performed using Microsoft Excel, version 2016.

Results: In both years studied, patients reported two of the leading factors when choosing a pharmacy to be proximity to home and drug prices. In 2021, the pharmacist's attitude was one of the determining factors, while in 2023, the pharmacist's competence and consultation were leading in choosing a pharmacy. The tendency for patients to visit a pharmacy due to the dispensation of prescription medicinal products, followed by such without a doctor's prescription (OTC), was maintained in both studied periods.

Keywords: *community pharmacy, customers, selection, factors*

The study is related to a mobility project BG05M2OP001-2.016-0025, titled Creating a Multidisciplinary Educational Environment for Development of Specialists with Integral Competencies in Biomedicine and Health Care.

PERMEATION ENHANCERS OF NATURAL ORIGIN—RECENT APPLICATIONS AND ADVANCES

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ABSTRACT

Introduction: Transdermal delivery is a preferred, noninvasive method of drug administration, characterized by high patients' compliance, low first-pass metabolism, and low risk of side effects. However, the intrinsic barrier function of stratum corneum limits its exploitation by hindering the percutaneous permeation of topically applied drugs and restricts their absorption. The latter requires specific molecules, i.e., permeation enhancers, which promote drugs' passage through the skin by various chemically or physically mediated mechanisms. In recent years, permeation enhancers of natural origin have attracted great interest due to their advantages compared to chemical ones, such as superior tolerability profile, lower risk of skin irritations, and high effectiveness.

Aim: The study aimed to outline the feasibility of various natural compounds—essential oils, terpenes, and fatty acids as permeation enhancers, discussing their mechanisms of action, advantages, and limitations. Their current applications and advances have also been compiled.

Materials and Methods: The study was based on thorough research in the PubMed, ScienceDirect, and Web of Science databases, summarizing the recent (5 years) data.

Results and Conclusion: According to the outcomes from the reviewed reports, it can be concluded that natural origin permeation enhancers are capable of improving drugs' transport across stratum corneum in a comparative or even superior manner to the conventional approaches (use of dimethylsulfoxide, ethanol, non-ionic surfactants, urea, etc.). Furthermore, unlike their chemical counterparts, the natural compounds are biodegradable (volatile in the case of essential oils), an environmentally safe alternative and characterized by lower production cost.

Keywords: *essential oils, stratum corneum, terpenes, transdermal delivery*

METHODS FOR STABILIZATION OF EX-TEMPORE FORMS WITH TRETINOIN

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ABSTRACT

Introduction: Tretinoin is a vitamin A derivate, an element of the retinoid class of medications. Compounded in the form of various drug forms, applied topically or systemically, it is a valuable medication in treating mild, moderate, and severe acne, pre-malignant and malignant skin conditions, photoaging, management of acute promyelocytic leukemia. Tretinoin is quickly oxidizable, thermally unstable, and isomerizes fast when exposed to radiation, which presents technological difficulties when compounding.

Aim: The aim of this article is to show which are the factors that interfere with the stability of tretinoin, and to suggest ways to preserve the stability, thus to ensure the desired therapeutic effect for patients.

Materials and Methods: The materials and methods used in this study include a review of 18 scientific articles and experimental trials published by other authors.

Results and Conclusion: Tretinoin may retain its biological activity by a specific technology for compounding, which includes the use of antioxidants, with heating being avoided. It is necessary to maintain certain storage conditions—no exposure to (a) light and (b) temperature over 5°C. We have provided guidance on stabilizing the active substance via incorporating suitable excipients and/or changes in the technological approach.

Keywords: *tretinoin, retinoids, acne, leukemia, compounding, stability, vitamin A*

QUALITATIVE COMPARISON OF THE EFFECTS OF VALERIAN ROOT EXTRACT (EXTR. RADICIS VALERINAE, *VALERIANA OFFICINALIS L.*) ON HUMANS AND DOMESTIC CATS (*FELIS CATUS*)

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ABSTRACT

Introduction: *Valeriana officinalis L.* is a perennial herbaceous plant of the Caprifoliaceae family. In traditional folk medicine it is used for treatment of sleep disorders, anxiety, and mild to moderate form of depression. The underground part, the root, has a strong specific smell due to the high content of valepotriates. Valerian is known to contain more than 150 secondary metabolites, including: iridoids, sesquiterpenoids, lignans, their glycosides, flavonoids, and fatty acids.

Valerian roots are used as decoctus and various types of *Extractum radicis Valerianae* are often ingredients of tablets, capsules, tinctures, etc. There are also microencapsulated dosage forms that have an extended effect duration.

In veterinary medicine it is used due to its soothing effects.

Aim: The aim of this article is to evaluate the differences in the effects after administration of any form of valerian root extract on humans and domestic cats.

Materials and Methods: For our study, we used 20 scientific articles that described the effects of valerian root on humans and domestic cats. The methods we used were reading and comparing the action of the active ingredients of the plant on humans and cats.

Discussion: The *actinidine* in valerian extracts acts as a pheromone, so cats behave unpredictably after administration. Pharmacologically active substances of valerian roots are valproate, valeric acid and iridoids. Studies show that its essential oil has a sedative, antispasmodic, and analgesic effect. Valerian aqueous extract reduces anxiety without causing drowsiness. Valerian acid has the same effect and improves sleep disorders. Some studies discuss the pain reducing effects of valproates. Other sedative and calming substances of the plant include valerianone, flavonoids, and valeric acid.

Conclusion: In contrast to the data in human use, which indicate that the valerian extracts have calming, sedative and antidepressant effects, in domestic cats (*Felis catus*), literature data report deviation in behaviour.

Keywords: *valerian, roots, depression, domestic cats, pheromone, paradoxical behavior*

IDENTIFYING THE DISPLACEMENT VOLUME WHEN COMPOUNDING SUPPOSITORIES FROM TABLETS

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ABSTRACT

Introduction: Manual compounding of suppositories in pharmacies often requires identification of the displacement volume (DV) values for entirely different systems of incorporated powder—suppository base. Preparedness and dexterity of the pharmacist is of a great importance for the production speed and the pharmaceutical accuracy of the dose, thus for the safety and satisfaction of the patient. Identification of DV is a basic training task for trainee students.

Aim: The aim of this article is to identify the DV value for 2 different specimens of grinded drugs tablets in PEG suppository base.

Materials and Methods: Two different specimens of tablets have been manually dry grinded by porcelain pestle and mortar. The resulting powder specimen we took as a substance to include in a PEG suppository base.

In the experimental work, a method of preparation of suppositories by pouring was used. As forming package, we used single-use suppository form blisters containing 10 forms of 1 mL each.

Results: Experimental data was collected and processed in the Bulgarian Scientific Pharmaceutical Laboratory (BSPL). This included 12 different concentrations for each of the specimens, Specimen A and Specimen B, in the suppositories. The DV was calculated based on the retrieved data.

Conclusion: Knowing the real DV value for a concrete included powder–suppository base system is key to fast compounding of subsequent drugs inquiries.

Data collecting should be a permanent process in a pharmacy laboratory. Frequent retrospective re-identification of DV, based on collected data, may increase the repeatability of the results of the compounded suppositories.

Keywords: *suppositories, displacement volume, compounding, dispersion on results*

ADVANCEMENTS IN THE PHARMACEUTICAL COMPOUNDING TECHNOLOGY FOR CAPTOPRIL SOLUTIONS

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ABSTRACT

Introduction: Congenital heart conditions and neonatal hypertension pose significant challenges in pediatric cardiology. ACE inhibitors, including captopril, have emerged as a promising option for treatment. Captopril inhibits angiotensin II formation, leading to arterial dilation and reduced blood pressure. Despite the potential for hyperkalemia, captopril remains a recommended choice for managing congenital heart conditions and neonatal hypertension due to its efficacy and relatively low risk. Oral captopril solutions offer flexibility in concentration and taste, enhancing their patient-friendly profile.

Aim: This study focuses on the technology and methods employed in compounding captopril solutions. It emphasizes the importance of stability and safety during the compounding process within pharmacy laboratories. Strategies to counteract oxidation, a common issue in maintaining solution stability, are explored.

Materials and Methods: This review complies and analyzes existing literature, summarizing key findings. Captopril solutions are inherently unstable due to oxidation, resulting in dimer formation. Essential components for a stable solution include captopril pure substance, deionized water, stabilizers, and chelating agents. It is critical to avoid using captopril tablets, which may contain deactivating ions.

Conclusion: It is proved through multiple experiments that stabilizers like ascorbic acid and chelating agents such as EDTA play a dual role in slowing oxidation and eliminating deactivating ions such as magnesium and calcium ions.

Keywords: *captopril solution, compounding technology, stability*

PLANT-DERIVED SUBSTANCES FOR PAIN TREATMENT AND MANAGEMENT USED IN THE PAST

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ABSTRACT

Introduction: From the first recorded accounts, over 5000 years ago, various forms of natural products have been used to treat pain disorders. Plant extracts with a pronounced analgesic effect were described in ancient Egyptian, Roman, Arabic, and Greek manuscripts. The most impressive examples of such natural products are the opium poppy (Papaver somniferum) and the bark of the willow tree (Salix spp.). Nowadays the two of the most widely used classes of drugs for pain management (opioids and anti-inflammatory drugs) are also of plant origin.

Aim: The main goal of this study is to compose a problem-oriented retrospective analysis of pain relievers used in the past based on scientific reports.

Materials and Methods: A retrospective search of scientific publications published in the period 2013–2023 was conducted.

Results and Conclusion: The literature review shows a great potential of natural substances derived from herbs for pain relief. In addition, plant-derived bioactive compounds reveal a great potential for developing new compounds with desired pharmacological profiles (i.e., minimal side effects and non-addictive potential).

Keywords: *pain relief, natural products, natureceuticals, opioids, salicin*

ANALYTICALLY POSITIVE BUT CLINICALLY NEGATIVE RESULTS IN THE TOXICOCHEMICAL ANALYSIS OF SPECIMENS FROM PASSIVE CANNABIS SMOKERS

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ABSTRACT

Introduction: Cannabis is the most commonly used drug in the world. Given the increasing number of countries legalising its use, there is a higher risk of incrimination in drug testing without primary consumption. Such results are classified as analytically positive, but from a clinical point of view they are false. Since this is a serious health and legal problem, the aim of the present work was to clarify the possibilities of determining passive cannabis smokers.

Materials and Methods: For the purpose of the study, an analysis of Google Scholar, PubMed, and ScienceDirect databases was made.

Results: During the smoking process, up to 50% of Δ9-tetrahydrocannabinol (THC) is released into the environment as side smoke, which can be inhaled or deposited on hair, skin, and surrounding surfaces. Thus, an adequate amount of THC can be bioavailable and even may cause effects on behavior and psychomotor activity.

Based on years of clinical experience, health authorities have identified cut-off concentrations of various biomarkers indicating active cannabis use. In urine, the target analyte is the main metabolite 1-nor-9-carboxy-tetrahydrocannabinol (THC-COOH), as it is detectable for a long period of time. If it exceeds 50 ng/mL or 15 ng/mL in the screening and confirmatory methods, respectively, there is an active drug exposure. Blood levels of THC and THC-COOH above 2 ng/mL indicate regular cannabis use. The presence of THC-COOH in saliva and hair is also an argument for primary use of cannabis.

Conclusion: Modern toxicochemical tools allow distinguishing passive smokers from cannabis abusers without abrogating the personal responsibility of each individual to avoid passive exposure to THC.

Keywords: *cannabis, smoker, toxicochemical*

HEALTH RISKS ARISING FROM FOLLOWING A VEGETARIAN OR VEGAN DIET

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ABSTRACT

Introduction: According to data from the World Health Organization (WHO), alternative diets such as veganism and vegetarianism are gaining more and more popularity. At the same time, the low level of awareness among the public about the complications that could arise from improper diet control is worrying.

Aim: The aim of this study is to summarize the possible risks arising from alternative nutrition, as well as the ways of its safe application in healthy people and risk groups of patients.

Materials and Methods: Research articles and reports published in Google Scholar, PubMed and MDPI were reviewed. Data were also taken from the website of the WHO European Regional Office.

Results: Vegan and vegetarian diets are usually rich in folic acid, ω-6 fatty acids, vit E and vit C, carbohydrates, fiber, carotenoids, and magnesium. Some beneficial effects are observed—on cardiovascular and some kidney diseases, intestinal microbiome, and metabolism. On the other hand, a poorly balanced vegan diet can lead to serious deficiencies in proteins, fatty acids, iron, iodine, zinc, calcium and vitamins, especially vit B12 and vit D. Pregnancy and lactation could proceed under a similar nutritional regime as veganism/vegetarianism, but studies show that this is quite difficult to achieve and is a process that must be closely monitored by a specialist, according to the needs of the mother and the baby. For the same reasons, alternative feeding regimes are not recommended for children.

Conclusion: Veganism and vegetarianism appear to be applicable, but with caution, with adequate supplementation of deficient nutrients, which must be monitored by a specialist. It is most reasonable to consume a moderate amount of meat against a high intake of fruits, vegetables, dairy products, and fish.

Keywords: *vegans, diets, risks, pregnancy*

THE IMPACT OF ARTIFICIAL INTELLIGENCE IN PHARMACY

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ABSTRACT

Introduction: The pharmaceutical industry is a critical field that is vital in saving lives. As part of the pharmaceutical industry, pharmacists are qualified staff that can hardly be replaced, as they can participate in all stages, from the creation of a medicine to its dispensing in the pharmacy.

As time advances and technology improves, new methods enter the industry, leading to more accessible and better work. Along with the development of technology, artificial intelligence (AI) has entered all areas where people are significant.

Aim: The current study aims to establish the advantages and disadvantages of using artificial intelligence in the pharmacy sector and examine possible ways in which AI would contribute to the field of pharmacy in the future.

Materials and Methods: A documentary method was used to fulfill the purpose of the study. We used scientific articles from specialized databases such as PubMed, WebMD, ScienceDirect, and ResearchGate. The keywords used were artificial intelligence, pharmacy, and pharmaceutical industry.

Results and Conclusion: Artificial intelligence cannot wholly replace the pharmacist, but it can undoubtedly improve the work in the industry. The process from drug discovery to medication dispensation will change over time.

Keywords: *artificial intelligence, pharmacist, impact, technology, pharmaceutical industry*

MAGISTRAL FORMULATIONS OF 5-FLUOROURACIL

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ABSTRACT

Introduction: 5-fluorouracil (5-FU) is a well-known primary chemotherapy drug from the fluoropyrimidine group. It competitively inhibits the enzyme thymidylate synthase (TS), thereby creating thymine deficiency and leading to inhibition of deoxyribonucleic acid (DNA) synthesis and cytotoxicity. Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting factor of 5-fluorouracil and has a central role in its elimination patterns. 5-fluorouracil has several drug forms: it is administered intravenously (bolus or continuous infusion), orally, as a topical preparation and as eyedrops.

In Bulgaria, magistral forms of 5-FU are compounded mainly in the Bulgarian Scientific Pharmaceutical Laboratory (BSPL) to the Erudita Pharmacy of Pediatrics in Sofia. Two forms are offered: (a) 5% dermatic gel and (b) 1% eyedrops.

Aim: The purpose of this study is to introduce the magistral formulations of 5-FU in Bulgaria.

Materials and Methods: We have reviewed 3 publications from ScienceDirect on the work of 5-FU, PubMed and the Journal of Dermatological Treatment. The magistral ingredients in BSPL products include: 5-FU active substance, preservatives, gelling agents, solvents, pH correctors, and osmolarity agents.

Conclusion: The magistral forms of 5-FU offered in Bulgaria are only two, compounded in only one place—BSPL.

Keywords: *5-fluorouracil, dihydropyrimidine dehydrogenase, magistral formulations, 5-FU gel 5%, 5-FU collyr 1%, chemotherapy drug*

EXPLORING THE PHYSICS OF ^{18}F-FDG IN ONCOLOGY IMAGING

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ABSTRACT

Introduction: Fluorine-18 (^{18}F) is a radionuclide commonly incorporated in positron emission tomography (PET) radiotracers due to its short half-life, ease of access, and excellent imaging properties. ^{18}F-FDG (fluorodeoxyglucose) is a proven radiopharmaceutical widely used in PET/CT scans for in vivo cancer imaging. The enhanced glycolysis of tumor cells is a key difference used to tell them apart. Increased uptake of FDG by malignant cells results in a concentration of radioactive fluorine nuclei that undergo β^+ decay. The emitted positrons collide with nearby electrons in the cell and produce two γ-rays which are detected by the PET scanner. A sophisticated computer algorithm is then used to compile a 3D image illustrating the location of tumor cells.

Aim: The project aims to summarize the use of ^{18}F-based radiotracers such as FDG and show the underlying physics making PET scans possible.

Materials and Methods: The data resources of PubMed and Google Scholar were used for the purposes of this project.

Results and Conclusion: ^{18}F traced radiopharmaceuticals, such as FDG, are an indispensable tool used in medical imaging. They provide a safe and reliable way to monitor cancer patients.

Keywords: *radiopharmaceutical, fluorine-18 (^{18}F), PET scanner, location of tumor cells*

APPLICATION OF ULTRASOUND IN THE EXTRACTION OF BIOLOGICALLY ACTIVE SUBSTANCES

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ABSTRACT

Introduction: Many plants are a rich source of bioactive substances that serve to make various medicinal products. Before they are administered in the dosage forms, they must be extracted in a specific way.

There are various methods for extracting biologically active substances. The choice of method should ensure their maximum yield and high purity.

Brown algae are a rich source of various biologically active substances. The present study aimed to investigate the effects of different technological variables on the extraction efficiency of fucoidan from the brown alga *Ascophyllum nodosum*.

Their extraction using ultrasound is one of the most effective techniques that can also be used in industrial settings. Another advantage of this method is the possibility of working with lower temperatures and smaller amounts of extract.

The introduction of such techniques in industry would lead to a significant improvement in the quality and efficiency of the production of several pharmaceutical products and functional foods based on algal polysaccharides.

Aim: The objective of the present study was to investigate the effects of different process variables on the extraction efficiency of fucoidan from the brown alga *Ascophyllum nodosum* using ultrasound.

Materials and Methods: PubMed and Google Scholar resources were used for this review article

Results and Conclusion: The optimal conditions for the extraction of fucoidan from brown algae *Ascophyllum nodosum* are the application of ultrasound, 80°C temperature, and 30 min extraction.

Keywords: *brown algae Ascophyllum nodosum, biologically active substances, extraction, production of pharmaceutical products and functional foods*

SURVEY OF HEALTHCARE PROFESSIONALS' VIEWS ON THE ADOPTION AND PROSPECTS OF THE HEALTH RECORD

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ABSTRACT

Introduction: In recent years, the technological progress of mankind is taking a clearly noticeable upswing. As one of the fastest growing fields, healthcare is changing in line with progress. One example of this change is the digitalization of healthcare. One of the opportunities this presents is a patient health record, which gives healthcare professionals access to the health information they need to improve their practice.

Aim: The aim of the study is to analyze the healthcare professionals' views on the adoption and prospects of the digital health record.

Materials and Methods: Online anonymous survey was conducted among 114 healthcare specialists practicing on the territory of the Republic of Bulgaria

Results: According to the majority of respondents, health professionals, the digitalization of the healthcare system will make work easier. Experts support the need for strict regulations to ensure data security.

Respondents indicated that implementation is hindered primarily by funding for new implementations, a limited number of professionals willing to implement the system, and fears that digitalization will increase costs in their practices. Respondents indicated that the most important role in adopting the record is played by government institutions and healthcare professionals, and the biggest beneficiaries are patients and healthcare professionals.

For the successful introduction of health records in Bulgaria, it is essential to create the right environment for the transition to digital health solutions that will improve the quality of healthcare in the country.

Keywords: *health professionals, Electronic Health Records (HER), e-health*

EVALUATION OF ADHERENCE TO THERAPY IN PATIENTS WITH CHRONIC DISEASES

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ABSTRACT

Introduction: A chronic disease can be defined as an illness that persists over an extended period of time and involves a slow and irreversible progression of pathological changes in the body. They are a major cause of mortality and disability on a global scale. The degree of commitment to therapy plays a crucial role in defining the effectiveness of managing chronic diseases. This involves a patient's capacity and willingness to consistently adhere to prescribed treatment regimens over an extended period.

Aim: The aim of this article is to monitor the level of adherence to therapy in patients with chronic diseases.

Materials and Methods: A survey was conducted through an online questionnaire among 197 patients with chronic diseases, in the period of July–August 2023.

Results and Conclusion: The study found that patients visited their primary care physician at least twice a year and the pharmacy—at least once a month. Most of the respondents had no difficulty taking their medication and indicated that they read the leaflet before use. Patients emphasized that social support was extremely important for people with chronic illnesses. The four-item Morisky Medication Adherence Scale (MMAS) reported average adherence to therapy among the monitored patients. Understanding the reasons behind the adherence and non-adherence is crucial for developing tailored interventions that can improve patient compliance and health outcomes.

Keywords: *chronic diseases, adherence to therapy, therapeutic challenges, therapeutic monitoring, management of chronic diseases*

VIRTUAL CLINICAL TRIALS—BENEFITS AND CHALLENGES

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ABSTRACT

Introduction: In virtual clinical trials, patient recruitment takes place online, the informed consent process is obtained electronically, medications and necessary devices and supplies are delivered to the participant's home, and records are collected electronically.

Aim: The aim of the present work is to analyze the advantages of virtual clinical trials as well as the challenges in their implementation.

Materials and Methods: We conducted a literature review of terms used to describe clinical trials that utilize technology to center the trial around the participant, using MEDLINE as main search engine. The search strategy included the following terms: "digital clinical trials"; "virtual clinical trials"; "site-less clinical trials"; "remote patient centered trials"; "remote clinical trials", and "online clinical trials". In addition, some examples of virtual trials were studied.

Results: Various examples of virtual clinical trials are discussed, among which are ADAPTABLE, and platforms developed by UCB, Novartis, and Sanofi. In the examples analyzed, the main advantages of virtual clinical trials include higher degree of recruitment of participants, cost reduction in the initiation of many centers, increase in the frequency of information collection, and improvement in participant retention and safety understanding.

Conclusion: Virtual clinical trials will bring easier and faster recruitment of participants; availability of participants from different geographical areas, which has an extraordinary effect in terms of the external validity of the results; faster collection and analysis of data; more frequent collection of different results, and an increase the number of potential participants to follow up over a long period of time.

Keywords: *virtual clinical trials, good clinical practice, medicines, digitalization, computer technology*

DEVELOPMENT AND VALIDATION OF NOVEL AND RAPID RP-HPLC METHOD FOR SIMULTANEOUS ANALYSIS OF PARACETAMOL, BROMHEXINE, AND LEVOFLOXACIN

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ABSTRACT

Introduction: Paracetamol and bromhexine are some of the most used antipyretic and mucolytic drugs for the symptomatic treatment of cold. However, due to bacterial complications, the therapy should include the addition of antibiotics such as levofloxacin.

Aim: The aim of the current study is development with subsequent validation of the novel chromatography method for simultaneous analysis of paracetamol, bromhexine, and levofloxacin.

Materials and Methods: To achieve this purpose, Dionex UltiMate 3000 high-performance liquid chromatograph equipped with RP column Unisol® 5 µm C18 250 x 4.6 mm (Agela Technologies™) was selected. The applied mobile phase consisted of solvent A: phosphate buffer (pH=3):acetonitrile (20:80 v/v), and solvent B: phosphate buffer (pH=7):acetonitrile (70:30 v/v). The separation was based on gradient elution within 20 minutes. The diode array detector was set up at 243 nm for paracetamol and bromhexine, and 296 nm for levofloxacin. The flow rate started with 0.8 mL/min for 10 min, for 10.0–12.0 min it was increased to 1.0 mL/min, and finished with 1.0 mL/min for 13 mins. Subsequently, the developed method was validated according to the requirements of ICH Q2 (R2) guideline.

Results and Conclusion: The novel method was successfully applied for determination and quantitation of paracetamol, bromhexine, and levofloxacin in pharmaceutical products. Levofloxacin was eluted at 3.80 min, paracetamol—at 4.437, and bromhexine—at 19.457. The concentrations of all three products corresponded to the stated in the leaflet amounts. The obtained results demonstrated the developed method as suitable in further bioanalysis of the aforementioned molecules, using appropriate sample preparation.

Keywords: *paracetamol, bromhexine, levofloxacin, RP-HPLC analysis, gradient elution*

NOVEL PYRROLE-BASED AMIDES AS ANTIOXIDANTS AND MAO-B INHIBITORS

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ABSTRACT

Introduction: Alzheimer's disease (AD) is the most widespread neurodegenerative disorder with a significant impact on health systems. Considering the lack of efficient treatment, compounds with multitarget activities are usually designed as promising options to fill the evident gap.

Aim: The aim of the study was to find novel antioxidants and MAO-B inhibitors containing a pyrrole core motif.

Materials and Methods: The MAO-B effects were evaluated by the fluorimetric Amplex® UltraRed reagent. The scavenging rate of DPPH and ABTS radicals was carried out by reported classic protocols. The molecular docking simulations were performed with Glide and GOLD 5.3 on an AMD Ryzen 9 5950X 16 core CPU and 64 GB of installed RAM.

Results: In this study, two novel N-pyrrolyl carboxylic acids (4a and 5a) and eight corresponding amide derivatives (4a1-4a3 and 5a1-5a5) were synthesized and fully characterized. The title compounds were assessed for their radical scavenging properties (DPPH and ABTS) and MAO-B blocking potential. It was found that compound 5a2 could serve as a prominent lead structure for a future optimization as an antioxidant and MAO-B inhibitor. The major intermolecular interactions between 5a2 and the active site of MAO-B were examined through molecular docking studies. The analysis of the major interactions indicated the establishment of several unfavorable steric clashes. Thus, reducing the size of the core structure could drastically increase the MAO-B antagonizing potency of the title pyrrole-based compounds.

Conclusion: Overall, compound 5a2 was found to be the most prominent derivative as it displayed great antioxidant and MAO-B blocking effects.

Keywords: *pyrrole, amides, antioxidant, MAO-B, molecular docking*

ANTISENSE OLIGONUCLEOTIDES (ASO): THE NEXT FRONTIER FOR TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY (DMD)

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ABSTRACT

Introduction: **Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by progressive muscle degeneration due to the alterations of a protein called dystrophin. Antisense oligonucleotides (ASOs) are short, synthetic, single-stranded oligonucleotides that can alter RNA and reduce, restore, or modify protein expression through several distinct mechanisms. Three ASO-mediated therapies have received approval from the US FDA for the treatment of DMD**

Aim: **The aim of this article is to present ASO-mediated therapies for DMD from a pharmacology prospective, focusing on pharmacokinetics, pharmacodynamics, drug-drug interactions (DDI), adverse drug reactions (ADR), and proven efficacy in clinical trials**

Materials and Methods: **Review of the regulatory information by the marketing authorization holders and the published data from the clinical trials**

Results: **The medications are administered intravenously. They are metabolically stable, no metabolites are detected in plasma or urine with elimination half-life 3 to 4 hours. Eteplirsen is indicated for ~13% of patients with mutation of the DMD gene that is amenable to exon 51 skipping. Golodirsen is approved for ~8% of patients amenable to exon 53 skipping. Casimersen is designed to bind to exon 45 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing. Exon skipping is intended to allow for production of an internally truncated dystrophin. For golodirsen and casimersen kidney toxicity is common.**

Conclusion: **These medications are approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in DMD patients. They all have similar pharmacokinetics and low potential for DDI, but different ADR are reported.**

Keywords: *Antisense oligonucleotides (ASO), RNA, Duchenne muscular dystrophy (DMD), dystrophin*

COMPARATIVE ANALYSIS OF THE CURRENT MEDICAL DEVICE LANDSCAPE IN BULGARIA, ROMANIA, GREECE, TURKEY, AND SERBIA

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ABSTRACT

Introduction: Comparative analysis is a systematic approach to comparing two or more entities to identify their similarities and differences. It is a rigorous method that uses a variety of data sources and analytical techniques to draw conclusions about the entities being compared. Comparative analysis is often used in social sciences. The goal of comparative analysis is to gain a deeper understanding of the entities being compared by identifying the factors that contribute to their similarities and differences. This can help to develop theories about the entities being compared and to make predictions about their future behavior.

Aim: This study aims to conduct a comparative analysis of the latest information available in the Global Atlas for Medical Devices 2022 for the following Balkan countries: Bulgaria, Romania, Greece, Turkey, and Serbia. The specific objectives of the study are to: compare the number of medical devices in use in each country, compare the regulatory environment in each country, compare the economic impact of the medical device industry in each country.

Materials and Methods: The data for this study was obtained from the Global Atlas for Medical Devices 2022. The data for each country was extracted and analyzed using statistical software.

Results: The results of the study showed that there were significant differences in the number of medical devices in use, the regulatory environment, and the economic impact of the medical device industry in the five countries. Bulgaria had the lowest number of medical devices in use, followed by Romania, Greece, Turkey, and Serbia. Turkey had the most stringent regulatory environment, followed by Serbia, Greece, Romania, and Bulgaria. The economic impact of the medical device industry was highest in Turkey, followed by Greece, Serbia, Romania, and Bulgaria.

Conclusion: The results of this study suggest that there are significant differences in the medical device landscape in the five countries. These differences are likely due to several factors, including the size of the population, the level of economic development, and the regulatory environment. This study provides valuable insights into the medical device landscape in these five countries. The findings of this study can be used by policymakers, healthcare professionals, and industry stakeholders to improve the availability, quality, and affordability of medical devices in these countries

Keywords: *medical device, Balkan countries, comparative analysis, global atlas*

MYRTENAL-AMINO ADAMANTANE DERIVATIVES IN EXPERIMENTAL DEMENTIA

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ABSTRACT

Introduction: Alzheimer's disease (AD) is characterized by memory loss and other central nervous system (CNS) symptoms. Two newly synthesized myrtenal-amino adamantane conjugates (MACs) demonstrated CNS activity. Adamantane is a typical pharmacophore used in drug design, and myrtenal (M) has already shown neuroprotective effects in our previous research.

Aim: The aim of this study is to assess the neuroprotective capabilities of MACs (MAC-197 and MAC-198) in a rat dementia model.

Materials and Methods: Scopolamine (Scop) was administered intraperitoneally to Wistar rats for 11 days, along with MACs or M as a reference. The assessment of brain acetylcholine esterase (AChE) activity, noradrenaline, and serotonin levels followed a memory status behavioral test.

Results: Both M derivatives recovered Scop-damaged memory, demonstrating considerable AChE-inhibitory activity in the cerebral cortex, in contrast to M. Myrtenal-amino adamantane conjugates also changed the levels of noradrenaline and serotonin in the hippocampus.

Conclusion: The neuroprotective capabilities of MAC-197 and MAC-198 in a rat dementia model were discovered for the first time. They outperformed the natural M effects, making the two substances potential candidates for AD therapy.

Keywords: *neuroprotection, scopolamine dementia, acetylcholinesterase, brain monoamines, memory*

3,4,5-TRIMETHOXY-2-IODOXYBENZOIC ACID

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ABSTRACT

Introduction: 2-iodoxybenzoic acid (IBX) is a periodinane used as an oxidizer. It is particularly suitable for oxidizing alcohols to aldehydes. 2-iodoxybenzoic acid is prepared by a known method from 2-iodobenzoic acid, potassium bromate, and sulfuric acid.

Aim: The aim of our work was to synthesize an analog of IBX using the starting material—3,4,5-trimethoxy-2-iodobenzoic acid. In the present work, we describe two procedures for the synthesis of 3,4,5-trimethoxy-2-iodoxybenzoic acid (T-IBX) with the $KBrO_3/H_2SO_4$ system and with the commercially available Oxone®.

Materials and Methods:

***Procedure 1:* In an attempt to synthesize an IBX derivative involving Oxone®, we used a procedure reported by other authors.**

***Procedure 2:* $KBrO_3$ is dissolved in a pre-cooled sulfuric acid solution. The iodine compound is dissolved in NaOH solution and added to the $KBrO_3/H_2SO_4$ system. The reaction takes place in a water bath with heating to 60°C and stirring for 1 hour.**

Results and Discussion: We found that the parent compound, 3,4,5-trimethoxy-2-iodobenzoic acid, exhibited atypical behavior. When we used 1.1 equiv. Oxone® for the synthesis of T-IBX, we obtained a product that dissolved when washed with acetone. This result has not been observed by other authors. We conducted several experiments, changing the synthesis parameters: amount of water 1 or 1.5 mL and temperature 45 or 60°C. Using Oxone® and with the applied conditions, we isolated small amounts of the product, which after washing and recrystallization were lost, and IR analysis did not prove that the target compound was obtained. Using the $KBrO_3/H_2SO_4$ system, instead of the expected IBX analog, we obtained 2,6-dibromo-3,4,5-trimethoxybenzoic acid.

Conclusion: The aim of the experiment, namely the preparation of the IBX analog, T-IBX, from 3,4,5-trimethoxy-2-iodobenzoic acid with the applied reaction systems $KBrO_3/H_2SO_4$ and Oxone® was not achieved. A thorough investigation of the causes leading to the observed atypical results is needed. Our future efforts will be focused on establishing the appropriate parameters and reagents for the reaction to proceed.

Keywords: *3,4,5-trimethoxy-2-iodobenzoic acid, Oxone®, IBX analog*

FAT SOLUBLE VITAMINS AND ANTIOXIDANTS IN BLOSSOMS AND LEAVES OF *PELARGONIUM ROSEUM*

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ABSTRACT

Introduction: The rose geranium (Pelargonium roseum) is an edible plant widespread and cultivated in all Bulgarian areas. It is known for its different applications in culinary, traditional medicine and perfumery. Pelargonium roseum is used for flavoring products like canned foods, sweets, salads, and drinks; their essential oil are also applied in fragrance compositions and cosmetic products; for relief of gastrointestinal and respiratory problems. Its diverse use is due to the wealth of biologically active substances. The major focus in the scientific literature is on the medicinal application of leaf lipid extract of rose geranium to prevent and treat a number of diseases, such as hyperglycemia, cancer, heart disease, as well as its antibacterial and antioxidant properties.

There is a lack of studies on the benefits of direct consumption of geranium leaves and flowers. Therefore, the present research aims to determine the fat soluble vitamins and antioxidants in fresh parts of Pelargonium roseum.

Materials and Methods: Qualitative and quantitative analysis was performed on fresh samples of rose geranium by reverse phase HPLC with UV/Vis/FL detectors.

Results: As a result of the conducted research, the content of fat-soluble biologically active substances (ergocalciferol, alpha-tocopherol, phylloquinone, astaxantine, and beta-carotene) in fresh leaves and flowers of home-grown Pelargonium roseum was established. The comparison of the quantitative data shows a higher content of the analytes in the leaves of the plant, except for phylloquinone, in which flowers are richer.

Conclusion: The obtained data characterize the green parts of the rose geranium plant as a very good source of the studied biologically active substances.

Keywords: *Pelargonium roseum, fat-soluble vitamins, antioxidant, HPLC*

COMPARISON STUDY ON ANTIOXIDANT ACTIVITY AND PHENOLIC COMPOSITION IN FRESH JUICE AND WINE FROM THE NORTH-EAST BULGARIAN BLACK SEA AREA

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ABSTRACT

Introduction: Polyphenolic compounds are prominent secondary metabolites found abundantly in grape berries, known for their robust antioxidant properties and potential health benefits. During the winemaking process, the majority of these polyphenols are transferred to the wine. While genetic factors regulate some polyphenol classes, the terroir and environmental conditions significantly influence the final content.

Aim: The aim of this article is to compare the phenolic composition and antioxidant activity of wine and hand-pressed juice of three different varieties of grapes organically grown in the North-East Black Sea area.

Materials and Methods: Grapes and wines (Merlot, Cabernet Sauvignon, Zelas) were kindly provided by a local producer. Juice was prepared by hand-squeezing. Total polyphenolic, flavonoid, anthocyanin, and tannin content were assayed spectrophotometrically. HPLC with PDA and QDa detectors was employed to analyze 11 phenolic acids, 6 flavonoids, and resveratrol. The antioxidant activity was evaluated using ABTS, DPPH and FRAP assays.

Results: In grape juice all studied parameters were significantly lower than in wine ($p < 0.0001$). Zelas juice revealed the lowest levels of all studied compounds, which correlated with the lowest antioxidant activity.

In wine, total polyphenols and anthocyanins strongly correlate ($r^2 = 0.98$) with the antioxidant activity. Furthermore, a positive correlation between antioxidant activity and the content of selected phenolics: resveratrol ($r^2 = 0.998$, $p = 0.028$), quercetin ($r^2 = 0.990$, $p = 0.062$), myricetin ($r^2 = 0.978$, $p = 0.095$), epicatechin ($r^2 = 0.999$, $p = 0.0002$), syringic ($r^2 = 0.992$, $p = 0.018$), chlorogenic ($r^2 = 0.989$, $p = 0.067$), caffeic ($r^2 = 0.996$, $p = 0.038$), and salicylic acid ($r^2 = 0.980$, $p = 0.09$), was found.

Conclusion: Our findings provide valuable information regarding phenolic composition and antioxidant activity of grape products from the North-East Bulgarian Black sea region.

Keywords: *grapes, wine, phenolic compounds, antioxidant activity, LC-MS*

NEW INSIGHTS OF THE ADIPONECTIN PARADOX

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ABSTRACT

Introduction: Adiponectin is a peptide hormone produced primarily by adipose tissue. Numerous studies prove its anti-atherogenic and anti-inflammatory effects. Hypoadiponectinemia has been identified as one of the risk factors for atherosclerosis and diabetes in humans. However, some clinical studies, including meta-analyses, have reported an association between high adiponectin levels and mortality. Unfortunately, when high adiponectin levels do not have health benefits, this is referred to as the adiponectin paradox.

Aim: The aim of the current item was to investigate new possible causes of the adiponectin paradox.

Materials and Methods: A search with keywords in scientific databases was conducted to collect current data.

Results and Discussion: Circulating adiponectin levels are influenced by various factors, both endogenous, such as genetic, hormonal, inflammatory, and exogenous, such as nutritional and medicational. One possible explanation for the decrease in adiponectin levels in malignancy is that the prolonged inflammatory status of the cancer patient results in increased cytokines that suppress adiponectin synthesis. Another possibility is the overloading of endoplasmic reticulum due to low-grade inflammation associated with obesity. The regulation of adiponectin levels in response to vascular impairment differs between non-obese and obese patients, suggesting that the regulation of adiponectin levels is impaired by fat accumulation. Dysfunctional adiponectin signaling can cause a loss of membrane-bound T-cadherin and a gradual further decline in adiponectin signal transduction.

Conclusion: In recent years, numerous studies of the „adiponectin paradox“ have been conducted, generating various hypotheses. Anyway, the complete clarification of the concept of the „adiponectin paradox“ remains a challenge for the future investigations.

Keywords: *adiponectin paradox, obesity, inflammation*

PRELIMINARY EVALUATION OF THE ADMET PROPERTIES OF A SERIES OF PYRROLE-BASED SCHIFF BASES

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ABSTRACT

Introduction: The favorable pharmacokinetic behavior of one active substance is of great importance for its future consideration as potential drug. The webserver admetSAR implements the state-of-the-art machine methods to build predictive models covering major ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties for new drug discovery.

Aim: The aim of this article is to conduct a preliminary *in silico* assessment of ADMET properties, as well as a prediction study of the ability of a newly synthetized series of pyrrole-based Schiff bases to cross the blood-brain barrier (BBM). The enzyme inhibitory potential against CYP3A4, CYP2D6, CYP1A2 was also studied.

Materials and Methods: ADMET property evaluation of the compounds was performed using the admetSAR open access web-based server. Their permeability properties and the ability to cross the blood-brain barrier were predicted and measured by using a PAMPA assay.

Results and Conclusion: The possibility to ensure acceptable bioavailability, successful transportation to the cellular targets through several membranes, and the optimal metabolism and elimination are important issues in the development of potential new drugs. Moreover, an essential part of the xenobiotic metabolism is their biotransformation by the liver CYP450 enzyme system. Thus, in the present work, a prediction was made of the probability that the series of investigated pyrrole-based Schiff bases exhibit substrate and/or inhibitory effects against the most important for drug metabolism CYP families, such as CYP3A4, CYP2D6, and CYP1A2.

Based on the performed ADMET and PAMPA studies, we found the series of pyrrole-based Schiff bases as the perspective for future *in vitro* and *in vivo* studies.

Keywords: *in silico, ADMET properties, PAMPA test, CYP450 isoenzymes*

THE SUPERHERBS OF BULGARIA

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ABSTRACT

Introduction: Traditional medicine, with its centuries-old history, is a widespread practice across the globe, which has been passed down through generations and continues to play a significant role in many societies. Ethnobotanical studies are essential for understanding the traditional knowledge and practices related to plant use within a specific culture or region. Despite the globalization of modern society, there is specificity in traditional medical practices in different countries. Bulgaria boasts a rich tradition of herbal medicine, deeply rooted in its culture and history, and herbs are often used both for their potential therapeutic benefits and their cultural significance in the region.

Aim: The primary objective of this study is to establish the most popular herbs in Bulgaria used in traditional medicine.

Materials and Methods: Systematic reviews and original articles in several databases, including Scopus and Web of Science, were retrieved. The ethnobotanical studies conducted among the Bulgarian population were evaluated.

Results: The findings of the study demonstrate that Bulgarian traditional medicine is rich in its utilization of a diverse array of plant species for addressing a wide spectrum of health conditions. Despite this extensive plant diversity, Bulgarians predominantly lean towards a select few herbs for their medicinal needs. Furthermore, the study identifies three specific medicinal plants that stand out as unmistakable superherbs—thyme, chamomile, and St. John's wort.

Conclusion: Further research is needed on the cultural, historical, and pharmacological factors that turn these medicinal plants into superherbs.

Keywords: *ethnobotanical research, most popular herbs, traditional medicine*

PLASMA ADIPONECTIN AND LEPTIN MRNA LEVELS IN COLORECTAL CANCER PATIENTS IN RELATION TO BODY MASS INDEX AND GLUCOSE LEVELS

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ABSTRACT

Introduction: Studies of the link between obesity and colorectal cancer (CRC) have begun to generate data suggesting a link between adipose tissue dysfunction, abnormal regulation of adipokines in obesity, and the initiation and progression of CRC. mRNA from tumors is detected in plasma and research is focused on its potential as a biomarker.

Aim: The aim of this study was to analyze adiponectin and leptin mRNA levels in CRC patients in comparison with individuals with no neoplasm (control group).

Material and Methods: Eighty patients were included in this study. mRNA levels of respective genes were analyzed using $2^{-\Delta\Delta Ct}$ method. The relationship between relative mRNA levels and body mass index (BMI) and plasma glucose levels was analyzed.

Results: Adiponectin and leptin plasma mRNA levels were higher by 48% ($p < 0.001$) and 28% ($p < 0.05$), respectively, in CRC patients with normal BMI (< 25), and by 97% ($p < 0.001$) and 60% ($p < 0.01$), respectively, in those with obesity (BMI > 25) as compared to the controls. In CRC patients with plasma glucose levels within the reference range, adiponectin and leptin mRNA levels were 88% ($p < 0.001$) and 47% ($p < 0.01$) higher that the control group and in hyperglycemic individuals they were 35% ($p < 0.05$) and 33% ($p < 0.05$) higher.

Conclusion: In conclusion, plasma mRNA levels of adiponectin and leptin appear to be promising biomarkers in CRC and are in relationship with obesity and blood glucose levels.

Keywords: c*olorectal cancer, adiponectin, leptin, obesity, hyperglycemia*

Acknowledgements: *This study was supported by the Science Fund, Medical University of Varna, Bulgaria, Grant No 19034.*

A REVIEW OF THE MOST COMMONLY USED LINKERS IN CREATING HYBRID MOLECULES

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ABSTRACT

Introduction: Antimicrobial resistance is a global health problem. Multidrug-resistant pathogens can be untreatable with conventional antibiotics. The discovery of new molecules, including hybrid ones, with antibacterial properties would greatly contribute to addressing this problem. In medicinal chemistry, the term linker is used to describe a part of a molecule that connects two other parts together.

Aim: The purpose of this study was to review the available data about the most commonly used linkers in organic synthesis.

Materials and Methods: A literature review in databases such as PubMed, Scopus, and Google Scholar was conducted.

Results: The most commonly used linker is a methylene group. Hydrocarbon linkers containing a double or triple carbon-carbon bond are also common. The second most common linker is an amide group. Several studies have shown that amide-bond formation is one of the most popular reactions used in organic synthesis. Ether linkers are usually prepared by palladium-catalyzed coupling of phenols. Ester linkers are obtained by standard esterification or transesterification. Of the aromatic linkers, the most popular are 1,3- and 1,4-substituted phenols, 1,2,4-oxadiazole, and 1,3,4-thiadiazole. Piperazine, piperidine, pyrrolidine, and azetidine are the most commonly used aliphatic cyclic linkers. Hydrazones are a versatile linker for connecting various classes of organic compounds.

Conclusion: A large number of linkers can be used in the process of creating hybrid molecules—a modern method of obtaining molecules with improved pharmacological and therapeutic properties. Which linker will be used in the synthesis process depends entirely on the available functional groups in the parent compounds.

Keywords: *linkers, organic synthesis, hybrid molecules*

REGULATION AND CONTROL OF THE UNREGULATED USE OF CANNABIS AND CANNABIDIOL IN NOVEL FOODS

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ABSTRACT

Aim: The aim of this article is to study the regulation and control of the unregulated use of cannabis and of cannabidiol (CBD) in novel foods.

Results: The control of Cannabis sativa is subject to the Psychotropic Substances Convention, which includes delta-9-tetrahydrocannabinol (THC), and the Narcotic Drugs Convention, which includes the illicit products: herbal and liquid cannabis, resin, extracts and tinctures of flowering or fruiting tops containing the addictive psychoactive phytocannabinoid THC. Approved by the FDA for use in chemotherapy are Marinol capsules (THC) and Cesamet capsules, containing the synthetic THC derivative Nabilone. There is no harmonized European Union legislation on the use of cannabis and CBD, which antagonizes the THC psychotropic effect. Legitimate products include seeds, oil, extracts, and seed tinctures of the industrial cannabis chemotype, containing primarily CBD and less than 0.2% THC. Sativex oral spray (THC/CBD = 1:1) is approved for muscle spasticity in multiple sclerosis. Cannabidiol was not used as a food ingredient in the European Union before 15.05.1997 and is a new food according to Regulation 2015/2283. Flour; protein powder and cannabis seed oil are not new food. Cannabidiol as Epidiolex is FDA approved for epilepsy forms Lennox-Gastaut and Dravet.

Conclusion: The need for increased control and legal restrictions on the unregulated cultivation and distribution of cannabis is due to increasing use, lack of a standardized product, toxic effects and illegitimate production of a chemotype containing small quantities of CBD and more than 0.2% THC (EC 327/2002). The development and regulation of CBD products as new foods is based on the anti-inflammatory, anticonvulsant, and analgesic effects of CBD.

Keywords: *cannabidiol, novel foods, regulation, control, cannabis*

NEW NON-CODING RNAS AS POTENTIAL THERAPEUTIC TARGETS IN COLORECTAL CANCER

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ABSTRACT

Introduction: Dysregulation of non-coding RNAs (ncRNAs) is part of the development of colorectal cancer (CRC). The identification of ncRNAs as therapy targets is the focus of contemporary research. Among the ncRNAs, miRNAs are the most studied.

Aim: The aim was to identify new miRNAs as potential therapeutic targets using the capabilities of RNA sequencing and base data for predicting miRNA-mRNA interactions.

Materials and Methods: RNA was extracted from CRC patients and healthy controls. NovaSeq SE50 and bioinformatics analysis were conducted by Novogene. A qPCR assay was used to validate differential expression found by RNA sequencing. TargetScan and miRDB were used to predict regulatory targets of miRNAs.

Results: RNA sequencing identified 142 miRNAs (44 upregulated, 98 downregulated) to be differentially expressed in tumor and normal colon tissue. Six downregulated and four upregulated miRNAs were validated. According to prediction analysis, three of the upregulated miRNAs, miR-1269a, miR-29c-3p, and miR-4512, target FOXO1 or FOXO3 genes. In terms of cancer biology, FOXO proteins act downstream of several oncogenic pathways such as PI3K–AKT, ERK, and NF-κB-IKKβ. The fourth selected for validation, miR-10401-3p, was identified as targeting WNT9B. Wnt9b is a protein involved in the Wnt pathway, which plays a significant role in the initiation and progression of CRC. However, Wnt9b is not extensively studied in CRC.

Conclusion: Our analyses provide a good basis to investigate the effects of the miR-10401-3p/WNT9B axis and offer the possibility to explore functional proof of the role of miR-10401-3p as a potential therapeutic target for CRC.

Keywords: *ncRNAs, miRNA, colorectal cancer*

DO STATINS ENHANCE CALCIUM ACCUMULATION IN THE ARTERIAL WALL BY INHIBITING VITAMIN K-DEPENDENT PROTEINS IN CARDIOVASCULAR DISEASE PATIENTS?

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ABSTRACT

Introduction: Statins are effective in lowering LDL cholesterol and are widely used for primary and secondary prevention in people with cardiovascular disease (CVD). Recently, a possible association between statin use and vascular calcification (VC) has been discussed intensively. Considering that vitamin K-dependent Gla proteins are endogenic inhibitors of VC, the question whether a connection could be established between statin-associated calcification and vitamin K dysfunction arises.

Aim: The aim of this article is to determine possible relationships between statin exposure, coronary artery calcification (CAC) and certain vitamin K-dependent proteins in patients with CVD.

Materials and Methods: A total of 98 inpatients were enrolled in this study—47 with moderate-to-high risk for CVD (controls), 32 with paroxysmal and persistent atrial fibrillation, and 19 with heart failure (CVD group). Both groups were stratified as statin users and non-users. Coronary artery calcification was assessed by multi-slice computed tomography. Circulating ucMGP, Gla-rich protein, uncarboxylated (ucOC) and carboxylated (cOC) osteocalcin were determined by commercial ELISA kits.

Results: Circulating ucMGP and GRP did not differ between statin users and non-users, while ucOC and ucOC/cOC were significantly elevated in statin users, indicating vitamin K deficiency. Positive correlation between ucOC and CAC was found in the entire population and among statin users, but not in non-users. No association was found between ucMGP or GRP and CAC. Positive association was indicated between statins and VC. Both the presence of CVD and statin use are independently and significantly associated with VC.

Conclusion: Statins may enhance arterial wall calcium accumulation by inhibiting vitamin K-dependent proteins and their functions involved in vascular protection.

Keywords: *statins, vitamin K-dependent Gla proteins, vascular calcification, CVD*

PERIPHERAL BLOOD MONONUCLEAR CELLS MATRIX GLA-PROTEIN EXPRESSION IN RELATION TO CVD RISK FACTORS

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ABSTRACT

Introduction: Matrix Gla protein (MGP) is a local calcification inhibitor with a role in preventing calcification of soft tissues and the vascular wall local mineralization. In cardiovascular disease (CVD) research, MGP isoforms are suggested as inhibitors of vascular calcification.

Aim: The present study aimed to assess the expression of MGP in peripheral blood mononuclear cells (PBMC) in patients with CVD and to correlate it with coronary artery calcium score (CACS) and CVD risk factors, such as dyslipidemia and obesity.

Materials and Methods: Matrix Gla protein expression was measured in 87 individuals using real-time qPCR. Subgrouping was performed according etiologic and metabolic CVD risk factors.

Results: Decreased MGP expression was observed in all subgroups with high CVD risk and statistical significance was detected in abdominally obese hypertensive individuals and in those with dyslipidemia. MGP expression was significantly lower in patients with elevated levels of total cholesterol and LDL cholesterol. A positive correlation between MGP expression and the number of cigarettes per day in patients with coronary calcium and in the CVD group was found. Matrix Gla protein expression correlated negatively with atrial hypertension duration in the group without coronary calcium deposits.

Conclusion: The current study supports the hypothesis that MGP expression in PBMC is related to CVD pathology and lipid metabolism dysregulation.

Keywords: *cardiovascular disease, gene expression, matrix Gla protein, peripheral blood mononuclear cells*

A LITERATURE REVIEW ON THE CLINICAL APPLICATION OF BIOACTIVE GLASSES AS DRUG DELIVERY SYSTEMS

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ABSTRACT

Introduction: In the field of tissue engineering, there is a growing interest in the development of scaffolds based on inorganic materials with the ability to act as a carrier for the local delivery of bioactive molecules and therapeutic drugs. The main advantage of local delivery of drugs is an increase in their concentration in the desired place, a depot with a sustained release, as well as avoidance of the excretion by renal filtration. Bioactive glasses are promising materials for tissue engineering due to their important properties such as biocompatibility, biodegradability, osteoconductivity, as well as osteogenic and angiogenic potential.

Aim: Considering a number of studies carried out in recent years, we aimed to analyze the different chemical compositions of bioactive glasses used as a carrier for bioactive molecules and therapeutic drugs.

Results and Conclusion: The analyzed literature shows that the use of bioactive glasses as a carrier for various bioactive molecules and therapeutic drugs is a successful approach for the treatment of osteomyelitis through the delivery of antibiotic preparations, as well as the healing of critical bone defects with the participation of growth factors and peptides. As a future task, we can set methods to obtain alternative compositions of bioactive glass for specific applications. This is particularly relevant when, in addition to the positive effects of the ion-releasing ability of bioactive glasses, the possibilities of delivering a local drug or growth factor to fight and suppress infections or improve bone regeneration are added.

Keywords: *tissue engineering, bioactive glass, drug-delivery systems, regeneration*

CONTAMINATED SEAFOOD: A NEW POTENTIAL SOURCE OF *TOXOPLASMA GONDII* TRANSMISSION TO HUMANS

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ABSTRACT

Introduction: In 2019, the European Food Safety Authority (EFSA) report found that foodborne transmission accounts for 40–60% of *T. gondii* infections. Recent reports indicate positive samples of meat, fish, raw mollusks and shellfish, honey, and potable water, and *T. gondii* was included in category III of zoonotic agents to monitor.

Seafood, such as oysters, clams, mussels, and fish have been identified as potential sources of infections due to their ability to filter and concentrate the parasite's oocysts. This bioaccumulation has been proven experimentally and has been reported in wild and cultivated bivalves.

Aim: The main goal of this study is to assess whether Black Sea mussels (*Mytilus galloprovincialis*), collected from the Varna coastal area, could be a risk factor of foodborne toxoplasmosis for human consumers.

Materials and Methods: A problem-oriented retrospective search of scientific publications published in the period 2008–2020 was conducted.

Results and Conclusion: The literature review shows high prevalence of *T. gondii* oocysts in a lot of different types of seafood. Based on the information from Global Water Pathogen Project, Part III, 2017, several countries reported high prevalence of *T. gondii* oocysts in seafood. Up to this moment there is no information about the levels of contamination with oocysts in the North Black Sea coast region. Further analysis should be done to establish parasite burden of *T. gondii* in Black Sea mussels (*Mytilus galloprovicialis*) from Varna coastal area.

Keywords: *toxoplasmosis, Toxoplasma gondii oocysts, seafood, Black Sea mussels*

STUDIES CONDUCTED ON THE PREVALENCE OF *TRICHOMONAS TENAX* IN THE POPULATION AFFECTED BY PERIODONTAL DISEASE— A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: ***Trichomonas tenax*** **is a flagellated unicellular eukaryotic organism that is involved in the composition of the human oral microflora. In the literature its prevalence is reported in individuals with poor oral hygiene. Furthermore, it is considered as a potential participant in the pathogenesis of inflammatory diseases of the periodontium.**

Aim: The aim of this article is to systematize and make an international comparison regarding the number of available studies about the prevalence of ***Trichomonas tenax*** **in the population affected by periodontal disease.**

Materials and Methods: Several systematic reviews and original articles in English in Scopus, ResearchGate, PubMed, and other databases were reviewed. The articles analyzed had a publication time range of 2000 to 20 July 2023. They were found using the following keywords: ***Trichomonas tenax, Trichomonas buccalis, periodontal disease, oral protozoa.***

Results: We found 61 studies about the distribution of ***Trichomonas tenax*****. The countries with the highest number of studies were Iran, Poland, and Iraq.**

Conclusion: Interest in ***Trichomonas tenax*** **has grown considerably since 2000. There are a number of studies that have identified it in oral specimens of patients with periodontitis using various diagnostic methods. Its role in the inflammatory process should not be overlooked, hence** *Trichomonas tenax* **should be discussed in the diagnosis and treatment of these patients.**

Keywords: *Trichomonas tenax, periodontal disease, oral health, oral microbiome, gingivitis*

IS THERE AN ASSOCIATION BETWEEN VITAMIN D STATUS AND SPERM QUALITY?

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ABSTRACT

Introduction: Male fertility disorders have increased greatly due to various genetic and lifestyle factors (obesity, sedentary life, harmful habits, stress, etc.). The presence of vitamin D metabolizing enzymes and a vitamin D receptor (VDR) inside spermatozoa is a reason to hypothesize that vitamin D may play an important role during spermatogenesis and the adequate maturation of spermatozoa.

Aim: The study aimed to determine the effect and relationship between intracellular sperm 1,25-dihydroxycholecalciferol levels, and two genes of interest related to vitamin D metabolism (1-α-hydroxylase and VDR) about sperm quality.

Materials and Methods: Seventy volunteers aged 25–45 were involved in the study. According to spermogram analysis, participants were stratified into normozoospermic control group and non-normozoospermic target group (decreased sperm count and/or motility and/or morphology). 1,25-dihydroxycholecalciferol in spermatozoa was determined by an enzyme-linked immunosorbent assay (ELISA) method. mRNA expression of VDR and 1-α hydroxylase was evaluated by qPCR.

Results: Intracellular sperm 1,25-dihydroxycholecalciferol was higher in the control group compared to the target group. The mRNA levels of 1-α-hydroxylase were significantly higher in the control group, while VDR expression was significantly higher in the target group.

Conclusion: Higher expression of 1-α-hydroxylase likely leads to higher intracellular levels of 1,25-dihydroxycholecalciferol, which could exert some beneficial effects on sperm quality parameters. The higher VDR expression in non-normozoospermic men may be a compensatory mechanism related to lower intracellular sperm 1,25-dihydroxycholecalciferol.

Keywords: *vitamin D, sperm quality, VDR, male fertility*

ELABORATION OF ALL-NATURAL ANTIPLAQUE CHEWING GUM

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ABSTRACT

Introduction: Dental plaque is one of the major culprits of tooth decay and periodontal diseases. Since synthetic antiplaque agents can cause various adverse reactions, successful prevention could be sought in natural compounds with proven antibacterial properties, such as thymol. In addition, facilitated mechanical biofilm removal could be achieved by employing chewing gum as a vehicle. However, the latter comprise mainly non-degradable synthetic gum bases and are among the most serious plastic pollutants. Therefore, utilizing only natural constituents in chewing gum would also benefit the environment.

Aim: This study aims to develop a biodegradable thymol chewing gum with favorable consistency to prevent dental plaque formation.

Materials and Methods: Seven chewing gum bases were formulated using mastic gum and beeswax in different proportions (from 30:70 to 90:10) and obtained via the hot melting technique. They were loaded with thymol (0.05%, *w/w*), and menthol and *Stevia rebaudiana* extract were added as flavoring agents. To determine the superior model, the mechanical properties of the chewing gums were evaluated.

Results and Conclusion: All gum bases were uniform and yellowish, with a characteristic mastic scent. They presented acceptable firmness, cohesiveness, brittleness, and elasticity; however, those containing less than 70% mastic gum were excluded from the study due to their significantly higher adhesiveness. After the addition of thymol and the taste corrigents, desirable textural characteristics were only observed in the model comprising 80% resin; thus, the latter was selected for further investigations.

Keywords: *biodegradable gum base, dental plaque, mastic, thymol*

START SHOT: A DIETARY SUPPLEMENT TO OVERCOME THE SYMPTOMS OF ALCOHOL INTOXICATION

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ABSTRACT

Introduction: The right selection of active ingredients and a well-considered marketing strategy are crucial for reaching the highly competitive and constantly evolving market of dietary supplements. We offer a novel dietary supplement intended to reduce the side effects and facilitate recovery after alcohol intoxication.

Materials and Methods: A research-based combination of four active ingredients was rationalized to fight alcohol intoxication on several accounts:

1. anti-inflammatory properties and pain and stiffness relief effects of curcumin (50 mg);

2. improvement of curcumin's oral bioavailability by piperine (0.3 mg);

3. energizing properties provided by matcha (167 mg)

4. antioxidant protection provided by ascorbic acid (100 mg) (along with curcumin and matcha).

Effervescent granules were obtained by the wet granulation technique. The organoleptic properties of the product were optimized with the aid of natural sweeteners and essential oils. The granules were subjected to all pharmacopoeial tests. A comprehensive marketing strategy, combining social media outreach and aggressive tactics, was developed.

Results: Fast-dissolving effervescent granules (1–2 min) with excellent rheological characteristics, 0.75 mm average diameter, and a refreshing sweet-sour taste were produced. The marketing strategy of the product, given the name Start Shot, included social media presence, partnerships with health and wellness influencers, data-driven advertising, aggressive marketing, and customer engagement tactics.

Conclusions: Start Shot effervescent granules were developed for hangover prevention and fast body recovery after alcohol consumption. The supplement is intended to be applied ideally several hours before alcohol intake as a single dose dissolved in 200 mL cold water. As a dietary supplement with no direct competition on the market, Start Shot possesses the potential for successful placement in pharmacies, drugstores, and nightclubs.

Keywords: *alcohol intoxication, hangover prevention, curcumin, piperine, effervescent granules*

GUIDELINES FOR AUTHORS

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Discussion: must review the relevant literature on the subject and discuss the findings of the current study in ther differences and similarities.

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Pages should be single-spaced, Times New Roman should be used throughout, sized at 12 pt. Captions should be used within the body of the manuscript to outline important points. The text of the manuscript should be submitted in Microsoft Word .doc/.docx format.

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References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References (www.nlm.nih.gov/bsd/uniform_requirements.html) webpage and detailed in the NLM's Citing Medicine, 2nd edition (www.ncbi.nlm.nih.gov/books/NBK7256/). These resources are regularly updated as new media develops, and currently include guidance for print documents (journal articles, books or other monographs); unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet (url, DOI, database).

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Journal article

Iwamoto Y, Koide H, Ogita K, Nishizuka Y. The protein kinase C family for the regulation of cellular functions. Biomed Rev. 1992;1:1-6.

Journal article with more than 6 authors

Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

Book

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Book chapter

Thornton T. On the interface problem in philosophy of psychiatry. In: Broome MR, Bortolotti L, editors. Psychiatry as Cognitive Neuroscience: Philosophical Perspectives. Oxford: Oxford University Press; 2009. p. 121-137.

URL

American Medical Association [Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2 screens]. Available from: http://www.ama-assn.org/ama/pub/category/1736.html

DOI, PMID

Zhang M, Holman CD, Price SD, Sanfilippo FM, Preen DB, Bulsara MK. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. BMJ. 2009 Jan 7;338:a2752. doi: 10.1136/bmj.a2752. PubMed PMID: 19129307; PubMed Central PMCID: PMC2615549

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Each figure should be accompanied by a title and an explanatory legend. The title should be part of the legend and not lettered onto the figure itself. Legends should be concise.

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Use abbreviations if a term appears three or more times. Spell out all abbreviations at first occurrence, and then introduce them by placing the abbreviation in parentheses. The metric system should be used for all volumes, lengths, weights, etc. Temperatures should be expressed in degrees Celsius (centigrade). Units should conform to the International System of Units (SI).

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