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**DRUG-INDUCED DERMATOPATHOLOGIES:
RATIONALITY AND SAFETY OF THEIR PHARMACOTHERAPY***O.Yu. Gorodnycha**Danylo Halytsky Lviv National Medical University**Department of Clinical Pharmacy, Pharmacotherapy and Medical Standardization, Lviv, Ukraine*

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The aim of the research: Pharmacotherapy assessment of drug-induced dermatopathologies by comparing real and good medical practice through the detection, identification and standardization of drug-related problems (DRP) and forming recommendations for the rational treatment of dermatological adverse drug reactions (ADR).

Materials and methods: The objects of research were Protocol Drug Order Form (PDOF) (n=139) of patients hospitalized to the allergy department of one stationary health facilities in Lviv during 2010-2013 with dermatological ADR. The mandatory criterion of including these objects to study was a clear indication of «causal» drugs undesirable consequences of which were skin changes: allergic dermatitis, flushing, erythema, urticaria, angioedema, pruritus and toxicoderma. Information resources for the study were: base standards of medical care in Ukraine (01.10.2014), the State Formulary of Drugs, II-V edition; data of evidence-based medicine; adapted to the national health system DRP classification of the European Network of Pharmaceutical Care (Pharmaceutical Care Network Europe) PCNE v5.01. The following methods were used: systemic approach, bibliographic, clinical-pharmaceutical, comparative analysis, modeling, standardization and statistical. Conflict of interests was none to declare.

Results: Pharmacotherapy assessment of dermatological ADRs by comparing real and good medical practice through the detection, identification and standardization of drug-related problems was conducted. The main DRPs were standardized in table format regarding dangerous drug combinations, improper duration of pharmacotherapy and drug dosing, route of administration etc.

Conclusions:

1. Conducted analysis of 139 PDOFs of patients with drug-induced dermatopathologies allowed us to identify and standardize 1416 DRP, the largest share of which are problems of national clinical practice (29,0%) and potential drug-drug interactions (27,1%). A significant number of DRP are dosing problems (19,9%) and the choice of drugs (17,5%). Technical problems and adverse events totaled 4,3% and 1,6% of all identified incorrectness respectively. The lowest number of DRP related to the drug's use (0,6%). All mentioned research confirms our hypothesis that the number of DRP may occur not only during pharmacotherapy of «primary» disease, but also during the medical treatment of drug-induced pathologies.
2. The results of our investigation clearly showed the necessity of recommendations for rationalizing dermatological ADRs treatment for prevention or minimization the risk of new complications of pharmacotherapy. The priority of increasing efficiency and safety of pharmacotherapy, on our opinion, is the prescribing drugs with taking into account the possibility of drug-drug interactions, data of evidence-based medicine, contraindications, proper drug dosage and duration of pharmacotherapy because these DRP were typical for drug-induced dermatopathologies treatment.

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CORRECTION OF MAGNESIUM DEFICIENCY IN PREGNANT WOMEN WITH ISTHMIC-CERVICAL INSUFFICIENCY

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The aim of the research: to study the features of pregnancy in women with isthmic-cervical insufficiency (ICI) during correction of magnesium deficiency.

Materials and methods: Observation group consisted of 50 women with magnesium deficiency (magnesium levels in the blood plasma of <0.80 mmol/l), who were diagnosed ICI at 13-15 weeks of pregnancy. The level of magnesium in the blood plasma was determined by using colorimetric analyzer Cobas 600 (c 501 module) and test systems Roche Diagnostics (Switzerland). The degree of ICI was determined by Shtember point scale. We assessed vaginal length of the cervix, its texture, location, condition of the cervical canal, situation of the presentive part of the fetus. Also ultrasound and Doppler methods were used to diagnose the condition of the cervix and the resistance index of the small artery of the cervix. Drugs of Magne B₆ (magnesium pidolate and magnesium lactate with pyridoxine) were prescribed to correct the magnesium deficiency, additionally the solution Magne-B₆ was used in the case of need. Statistical analysis of the results was carried out using modern methods of variation statistics with standard programs of statistical analysis Microsoft Exel 7.0. The difference between the parameters considered at $p < 0.05$.

Results: The level of magnesium in the blood plasma of pregnant women was $0,66 \pm 0,03$ mmol/l. In 74% of cases ultrasound research showed the decrease of reflectance of the cervix due to the presence of collagenopathy. The treatment of nutrient magnesium deficiency by combinations of magnesium pidolate and magnesium lactate with pyridoxine provided effective correction of hypomagnesaemia in pregnant women. Gradient of increase magnesium levels after 30-days treatment was $0,18 \pm 0,3$ mmol/l. Removal of magnesium deficiency led to stabilization of collagen structures of the cervix. As a result ultrasound research showed that in 43,2% cases the decrease of the ability of the ultrasonic ray to pass through the cervical tissue occurred. Also noteworthy is the fact that in these pregnant women the progression of ICI was not observed.

Conclusions:

1. Magnesium deficiency is a significant risk factor of complications of pregnancy, the development of ICI. Under the conditions of magnesium deficiency disorders of the metabolism of collagen and signs of undifferentiated connective tissue dysplasia can occur. Disorders of the formation of connective tissue of the cervix make its morphofunctional incompetence.
2. The use of organic salts of magnesium – magnesium pidolate and magnesium lactate in combination with magnesium protector pyridoxine provides effective correction of magnesium deficiency in pregnant women. It has positive effect on the formation of connective tissue of the cervix, improves its morphofunctional state, prevents the progression of ICI.

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INFLUENCE OF INFUSIONS OF MEDICINAL HERBAL MIXTURES ON THE DEVELOPMENT OF EXPERIMENTAL PERIODONTITIS

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The aim of the research: studying of therapeutic and preventive effects of infusions of medicinal herbal mixtures «Antiallergic» and «Gerbostom» based on the model of experimental periodontitis.

Materials and methods: The research was conducted in a biochemical laboratory of the State Establishment «The Institute of Dentistry of NAMS» (Odessa) on the model of periodontitis caused by application of 1% solution of phospholipase A₂ to rats' gums. In homogenates of gums (intact animals and groups with recreated pathology without treatment and with spraying of the infusions of new mixtures «Antiallergic» and «Gerbostom» in comparison with reference preparation «Aeucasob») the following markers of inflammation were determined: activity of acid phosphatase for identification of membrane-acting effect; activity of elastase for estimation of inflammation degree; content of malonicdialdehyde and catalase for determination of lipid peroxidation state; urease for estimation of pathogenic and conditionally pathogenic microflora levels; lysozyme for determination of state of antibacterial defense of the gum tissue.

Results: It was ascertained that the therapeutic and preventive effects of the infusions of the mixtures «Antiallergic» and «Gerbostom» on simulated dental pathology involve maintenance of antioxidant-prooxidant balance and antibacterial defense of the oral cavity as well as better prevention from inflammation in comparison with reference preparation.

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Conclusions:

1. It was determined that the infusions of the medicinal herbal mixtures «Antiallergic» and «Gerbostom» have anti-inflammatory, membrane-acting, antioxidant, antimicrobial effects on oral cavity tissue of rats.
2. The anti-disbiotic activity and parodontium protective action of the developed herbal remedies as well as the prospect of their using in preventive dentistry for treatment of inflammatory diseases were proven.

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**LABORATORY INDICATORS IN PATIENTS WITH TUBERCULOSIS
ACCORDING TO CYP2C19 GENOTYPE**

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The aim of the research: to detect the peculiarities of pulmonary tuberculosis course due to cytochrome-450 2C19 (*CYP2C19*) polymorphism according to cellular content and biochemical markers of the blood.

Materials and methods: 83 medical cards of patients with primary pulmonary tuberculosis were studied at the beginning and at the end of in-patient treatment in Odessa district dispensary in 2012. The *CYP2C19* genotype in TB-patients was detected at the beginning of the treatment according to J.A. Goldstein, J. Blaisdell (1996).

Results: The patients with genotype *2/*2 had the highest level of erythrocyte sedimentation rate, leukocytosis, the lowest lymphocytes amount both at the beginning and at the end of in-patient treatment. It revealed the most significant disturbances in peripheral blood cells in comparison with other groups. In addition, the highest level of aspartate aminotransferase and gamma glutamyltransferase was revealed in patients with *2/*2 genotype. It proved higher risk of hepatotoxicity in this category of patients in comparison with other *CYP2C19* genotypes. Data of peripheral blood in patients with genotype *1/*1 at the beginning and at the end of in-patient treatment did not differ significantly from those in patients with genotype *1/*2, although in formers the above mentioned pathological changes were less conspicuous.

Conclusion: Therefore, the detection of *CYP2C19* *2/*2 genotype can be useful for prognosis of tuberculosis treatment outcomes.

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**PECULIARITIES OF INTRAUTERINE TORCH-INFECTIONS IN CHILDREN
OF EARLY NEONATAL PERIOD**

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The aim of the research: to investigate the peculiarities of intrauterine TORCH-infections in children of early neonatal period.

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Materials and methods: statistical analysis of the Health Archives of Pathology Department of the Newborn children's hospital in Lviv in 2013. The statistical analysis of the results of research was carried out by standard methods (Borovykov, 2001).

Results: infectious diseases of the fetus and newborns still remain an open question in modern medicine. It can be accounted for the increased rate of women of child bearing age infected with pathogens which can cause fetal infections. These infections cause 10 to 61% of the early neonatal deaths among other fetal morbidities. There is a rather high level of early neonatal mortality consequences of TORCH-infections. In 2013, the Neonatal Pathology Unit admitted 660 children; 102 (15,4%) of the children were diagnosed with neonatal congenital malformations. Congenital abnormalities caused by intrauterine TORCH-infections make 2,9% of cases: 2/3 are cardiovascular congenital disturbances, 1/3 – urinary system disorders). Clinical examples of congenital malformations caused by TORCH-infections: congenital malformations of the urinary system – transverse dystopia right kidney, bilateral hydronephrosis. The diagnosis is confirmed by ultrasound examination on 18-19 weeks of gestation. Laboratory tests revealed TORCH-infections. Moreover, congenital cardiovascular disturbance was revealed on the background of TORCH-infecting from the mother who had suffered measles on 19-20 weeks of gestation. There were cases of infants with congenital abnormalities whose mothers suffered TORCH-infections at different periods of gestation. Therefore, intrauterine TORCH-infecting of children of early neonatal period causes congenital abnormalities. The rational solution to this problem should include early diagnostics and timely treatment of revealed pathologies.

Conclusions: There is a considerably high level of early neonatal mortality consequences of TORCH-infections. These infections cause from 10 to 61% of early neonatal deaths among other fetal morbidities. Infectious diseases of the fetus and newborns still remain an open question in modern medicine. Peculiarities of intrauterine TORCH-infections in children of early neonatal period depend on reproductive state of a mother, her immune defense, pregnancy and delivery courses, environmental factors, as well as immunity of a child of an early neonatal period. Congenital abnormalities caused by intrauterine TORCH-infections make 2,9% among 15,4 % of all revealed congenital pathologies in children. Early prenatal diagnostics and timely treatment of revealed abnormalities in women of fertile age can enable reducing of early neonatal death rate.

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КЛАСТЕРНИЙ АНАЛІЗ ЯК РАЦІОНАЛЬНИЙ СПОСІБ СЕГМЕНТАЦІЇ ФАРМАЦЕВТИЧНОГО РИНКУ ЗА ЦІНОВОЮ ОЗНАКОЮ

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Мета дослідження: 1) порівняти ефективність трьох методів *post-hoc* сегментації ринку: методу к-середніх, ієрархічного кластерного аналізу та методу вичерпного пошуку з використанням ціни як критерію групування; 2) охарактеризувати особливості ціни як критерію сегментації продукту та запропонувати методологію сегментації ринку, яка базується на ціні; 3) здійснити розподіл антигістамінних засобів, гепатопротекторів, сиропів від кашлю, спреїв і льодяників для лікування болю горла, засобів для лікування акне і вітамінів у розрізі трьох цінових сегментів як приклад сегментації продукту.

Матеріали та методи: У дослідженні використані роздрібні ціни на лікарські засоби у м. Берегово (Закарпатська область) та середні ціни, які були отримані на веб-сайті compendium.com.ua, станом на грудень 2012 року. Всього проаналізовано 147 лікарських засобів. В основі відбору фармакотерапевтичних груп лікарських засобів лежав принцип взаємозамінності ОТС-ліків, які можуть бути запропоновані пацієнтові в аптеці. З метою розподілу ліків на групи використовувались три методи: к-середніх, ієрархічного кластерного аналізу та вичерпного пошуку. Процедура кластеризації здійснювалась за допомогою програмного забезпечення R 3.0.1.

Результати: Проведено порівняння трьох можливих методів *post-hoc* сегментації ринку за ціною ознакою: методу к-середніх, ієрархічного кластерного аналізу та методу вичерпного пошуку. Розкрито сильні та слабкі сторони вказаних підходів та надані рекомендації для їх практичного застосування.

Висновки: Цінова сегментація є важливою та інформативною процедурою маркетингу. Серед трьох досліджуваних методів, методика вичерпного пошуку характеризується абсолютною точністю та найменшою тривалістю. Таким чином, цей метод є доцільним у тих випадках, коли немає потреби у всесторонньому глибокому розподілі та аналізі цін. Ієрархічний метод є більш цінним стосовно позиціонування товару відносно його внутрішньої вартості; він дає можливість графічно подати розподіл цін за допомогою спеціального графіка – дендрограми. Проте низька точність цього методу знижує його інформативність. В обох методах використовується логарифмічне значення ціни продукту. Доцільність використання саме такого

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значення обґрунтовується психофізичним законом Вебера і Фехнера. Розподіл антигістамінних засобів, гепатопротекторів, сиропів від кашлю, спреїв і льодяників для лікування болю горла, засобів для лікування акне і вітамінів в межах 3-ох цінових сегментів є модельним прикладом сегментації продукту. Запропоновані мануальні методи *post-hoc* сегментації ринку за ціновими категоріями можуть використовуватися у галузі менеджменту та маркетингу, а при умові використання відповідного програмного забезпечення надавати інформаційну підтримку прийняттю управлінських рішень.

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BIOORGANIC SYNTHESIS OF GLYCOSYLATED ANTHRAQUINONE DERIVATIVES PART 1. SYNTHESIS OF EMODIN DERIVATIVE

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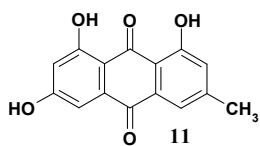
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The aim of the research: development of methods and obtaining by bioorganic synthesis of glycosylated emodin derivatives using the soil bacterium of the strain culture *Saccharothrix espanaensis*.

Materials and methods: monitoring the progress of the reactions and identification of compounds were carried out by TLC on plates «Merk Kizelgel-60F254» and «Silufol UV-254». Preparative chromatography was performed on silica gel brand «LS 5/40» (Merck). Spectra of ¹H and ¹³C NMR, COSY, HSQC, HMBC, 2D-NOESY, ROESY were recorded on a spectrophotometer «Varian XL-400», «BrukerAvance DRX 400», «JEOL Alpa», «Bruker WP-200», «Varian XL-200». Chromatography-mass spectra were recorded on «Agilent 1100». In determining the melting temperature correction for speaker connections column of mercury was undertaken.

Results: a strategy for bioorganic synthesis of glycosylated anthraquinones using soil bacterium strain culture *Saccharothrix espanaensis* has been developed. This culture is related to the actinomycetes – prokaryotic gram-positive microorganisms, which produce more than 90% of industrially important antibiotics. In addition, data regarding of emodin derivatives contained in aloe, buckthorn bark of and senna leaves, reveal *in vitro* and *in vivo* activity against selective neuroectodermal cancer cells, which prompted us as the original agents choose emodin 11.



It should be noted that it is only glycosylation by classical methods of organic synthesis requires a lot of steps in rather often meager output product with the required specificity and spatial orientation of products. Bioorganic synthesis was performed by standard methods for a 6-day incubation period. The extract at first of transformational products was analyzed by liquid chromatography-mass spectroscopy, and the formation of new glycosylated anthraquinones corroborated by comparing the UV spectra of initial and final products.

Conclusions: For the first time, glycosylated emodin derivatives were obtained by biosynthetic way using a strain of bacteria *Saccharothrix espanaensis*. The analysis of data LC / ESI-MS showed that during the biosynthesis of a mixture of three products with an overall yield of 87% and a ratio of 37%: 27%: 23% respectively, the structure of which was confirmed by NMR spectra (¹H, ¹³C, NMVS, H-COSY, ROESY).

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SYNTHESIS OF NOVEL 1,3,4-OXA(THIA)DIAZOLE-SUBSTITUTED (2,4-DIOXOTHIAZOLIDINE-5-YLIDENE)-ACETAMIDES AND EVALUATION OF THEIR BIOLOGICAL ACTIVITY

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The aim of the research: A considerable interest towards non-condensed thiazolidine and 1,3,4-oxa(thia)diazole derivatives is caused by a wide spectrum of pharmacological activity of these heterocycle systems as potential highly active compounds. The non-condensed oxa(thia)diazole derivatives with thiazolidine, benzimidazole or isatin fragments are known for their broad biological activity, including antitumor, antimycobacterial, antiinflammatory, antiviral, fungicidal, and antioxidant. Among mentioned compounds histone deacetylase inhibitors, tyrosine phosphatase inhibitors, HIV-1 integrase inhibitors, aminopeptidase N inhibitors and carbonic anhydrase inhibitors were identified. Therefore, the synthesis and evaluation of biological activity of new 1,3,4-oxa(thia)diazole-substituted thiazolidine-5-ylidene acetic acid amides is a promising direction of thiazolidine and oxa(thia)diazole derivatives investigation.

Materials and methods: Following the *N*-acylation and *N*- or *S*-alkylation reactions the new non-condensed compounds with thiazolidine and oxa(thia)diazole fragments were synthesized. Anticancer activity of synthesized compounds toward 60 human tumor cell lines panel (leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers) in National Cancer Institute was evaluated. The preliminary screening of antitrypanosomal activity has been performed against *Trypanosoma brucei brucei* at two concentrations of 10 µg/ml and 1 µg/ml.

Results: Based on the acylation reaction of 2-amino-5-aryl-1,3,4-oxadiazoles and 2-amino-5-mercapto (alkylthio)-1,3,4-thiadiazoles with (2,4-dioxothiazolidine-5-ylidene)-acetyl chloride the synthesis of novel non-condensed compounds with thiazolidine and 1,3,4-oxa(thia)diazole fragments was carried out. Further chemical modification of synthesized 2-(2,4-dioxothiazolidine-5-ylidene)-*N*-(5-aryl(mercapto)-1,3,4-oxa(thia)diazole-2-yl)-acetamides in position *N*3 of thiazolidine cycle was performed in alkylation reaction with *N*-arylchloroacetamides. The structure of obtained compounds was confirmed by NMR spectroscopy. In the ¹H NMR spectra of synthesized compounds the protons of methyl and methoxyl groups show singlets at δ~2.19-2.31 ppm and δ~3.83-3.99 ppm, correspondingly. The protons of the methylene group CH₂CO appear as a singlet at δ~3.92-3.99 ppm (**3c-f**), δ~4.02-4.31 ppm (**4a-d**, **6a-b**), and δ~4.47-4.59 ppm (**2a-e**). For the NH₂ protons of compounds **3c-f** one singlet at δ~7.17-7.20 ppm is observed and the CH proton in 5 position of thiazolidine cycle shows singlet at δ~7.14-7.38 ppm (**1a-c**, **2a-e**, **4a-d**, **5**). In the ¹H NMR spectra NH proton of mentioned compounds have been found as singlet or broad singlet at δ~9.46-10.53 ppm (**2a-e**, **3c-f**, **6a-b**), δ~12.73-12.84 ppm (**1a-c**) and δ~13.03-13.49 ppm (**4a-d**, **5**). Synthesized compounds **1a**, **1c**, **3a**, **3b**, **3d**, **3e**, and **3f** were submitted and evaluated at the single concentration of 10⁻⁵ M towards panel of approximately sixty cancer cell lines. Tested compounds displayed low antitumor activity with average values GP = 97,46-101,78%. A screening of antitrypanosomal activity of compounds **3a** and **3b** revealed the weak inhibitory of TBB.

Conclusions: Following the reaction of 2-amino-5-aryl-1,3,4-oxadiazoles and 2-amino-5-mercapto(alkylthio)-1,3,4-thiadiazoles with (2,4-dioxothiazolidine-5-ylidene)-acetyl chloride the synthesis of new 2-(2,4-dioxothiazolidine-5-ylidene)-*N*-(5-aryl(mercapto)-1,3,4-oxa(thia)diazole-2-yl)-acetamides have been performed. A screening of antitumor and antitrypanosomal activities of synthesized compound was carried out.

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