group by maintenance under conditions of constant darkness (0.00 light : 24.00 darkness). Toxic AKI (II-IV groups) was induced by daily administration of gentamicin at a dose of 80 mg/kg for 6 days. Animals from the III-IV groups were daily injected with melatonin at a dose of 5 mg/kg. 24 h after the last injection biochemical and histological examination was performed. For the statistical analysis SPSS 17.0 software was used.

Nephrotoxicity of gentamicin caused significant ($p<0.05$) functional changes and structural alterations of rat kidneys. Treatment with melatonin in conditions of gentamicin-induced kidney injury significantly limited the degree of damage to renal tissue and prevented a critical reduction in kidney function, confirming a protective effect of melatonin. At the same time, significant ($p<0.05$) differences between the indices of the III and IV group allow us to state, that treatment with exogenous melatonin on the background of endogenous melatonin deficiency was less effective in comparison to the administration of melatonin in conditions of pineal hyperfunction.

Melatonin ameliorates gentamicin-induced kidney injury by the limitation of histopathological changes in kidney tissue and preservation of kidney function. Pre-existing deficiency of endogenous melatonin decreases the resistance of kidneys to damaging action of the toxin and lessens the protective effect of the exogenous melatonin. Alternatively, in rats with increased pineal gland activity and melatonin production, co-treatment with exogenous melatonin more effectively protects the kidney from gentamicin-induced structural and functional changes and prevents the development of renal failure.

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EXPERIMENTAL SUBSTANTIATION OF MEDICAL APPLICATION OF THE NEW COMBINED OIL PHYTOEXTRACT WITH HEPATOTROPIC ACTION

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The range of oil-based medicines is relatively small but the potential of oil extracts is quite high, as vegetable oils are able to selectively extract biologically active substances from plant raw materials and are not toxic to the human body. Vegetable oils are known for their acceptable extractive properties, allow to obtain phytoextracts with a high content of active substances. In addition, the obtained oil extracts can be further used for introduction into other dosage forms without prior evaporation and drying. Therefore, the development of a new combined oil phytoextract with hepatotropic action from medicinal plant raw materials and the study of its toxicological properties and pharmacological activity is appropriate and relevant.

The aim of the research was to study the toxicological properties and pharmacological activity of a new combined oil phytoextract under the conditional name «Oleosyl» (oil extract of wild carrot seeds, chamomile flowers, corn columns with stigmas) on an experimental model of liver damage. For this purpose biological (determination of specific activity and safety) and mathematical (statistical processing of results and mathematical planning of the experiment) research methods were used.

Acute toxicity of «Oleosyl» was studied in accordance with the recommendations of the Ministry of Health of Ukraine. The experiments were performed on male rats weighing 300-320 g. Acute carbon tetrachloride hepatitis was induced by intragastric administration of 50% oil solution of carbon tetrachloride to rats at a dose of 0.7 ml / 100 g body weight.

The state of the extracellular liver function under the influence of oil phytoextract in the studied dose range was evaluated by the dynamics of biochemical indicators of bile (bile acids, cholesterol) and the estimated cholate-cholesterol coefficient (CCC) in comparison with animals of intact control group and reference samples. The level of choleretic activity of the phytoextract samples at different doses was evaluated by the total amount of bile released over 4 h and reflected as a percentage relative to the animals of the control group.

According to the obtained data on the indicator of acute toxicity «Oleosyl» belongs to the VI class of toxicity according to the classification of K.K. Sidorov - relatively harmless substances,

LD50 of which is more than 15000 mg / kg. Analysis of the obtained data revealed the hepatoprotective activity of «Oleosyl» when administered intragastrically at a dose of 0.5 ml / kg.

When assessing the choleretic and biliary activity of «Oleosyl» on the sum of active substances was more likely to be effective dose of 0.5 ml / 100 g, which was selected as conditionally therapeutic for further study of the pharmacodynamics of the phytoextract. The conducted studies illustrate the presence of a sufficient level of choleretic activity, namely, choleretic properties in «Oleosyl».

The specific activity and harmlessness of the new combined oil phytoextract «Oleosyl» are proved, as well as its hepatotropic effect: the herbal remedy reduces the development of functional and biochemical disorders in the liver in experimental animals in acute tetrachloromethane hepatitis.

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THE INFLUENCE OF SOME STATINS ON THE LEVELS OF PRO-INFLAMMATORY CYTOKINES AT GENTAMICIN-INDUCED ACUTE KIDNEY INJURY

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It is known that acute kidney injury (AKI) is associated with increased production of pro-inflammatory cytokines – interleukins (IL) 1β, 6 and tumour necrosis factor α (TNF-α), which initiate a cascade of inflammatory reactions with subsequent damage to nephrocytes (Ortega M.L., Fornoni A., 2010). At the same time, statins exhibit anti-inflammatory effects. Moreover, a number of studies consider statins as possible renoprotective agents.

Therefore, the goal of our study was to determine the influence of some statins on the levels of pro-inflammatory cytokines in blood plasma of rats with AKI (Zeleniuk V. G., Zamorskii I. I., 2019).

The experiments were conducted on 40 non-linear mature white male rats weighing 140-180 g. AKI was induced by daily intramuscular administration of 4% solution of gentamicin sulphate at a dose of 80 mg/kg for 6 days. Co-treatment with statins (atorvastatin, lovastatin, simvastatin at a dose of 20 mg/kg) was started from the first day of gentamicin administration. Statins were administered intragastrically in a form of 1% starch solution (1 ml of suspension per 100 g of body weight). The levels of cytokines (IL-1β, IL-6, TNF-α) in blood plasma were determined using immunoassay methods and Vector Best (RF) reagent set. A functional state of rat kidneys was evaluated in conditions of induced diuresis (enteral administration of water in the amount of 5% of the body weight). The statistical analysis was conducted using Mann-Whitney test and "Statistica 6.0" software.

It was established that on the 6th day of the AKI development a significant (more than 3-fold) increase in the levels of all studied pro-inflammatory cytokines in the group of animals with gentamicin nephropathy was observed comparing to the control group. It was accompanied by a profound renal dysfunction, in particular a decrease in the glomerular filtration rate (GFR) by 2.5 times, significant proteinuria (a 3-fold increase in urine protein level). Treatment with statins resulted in a significant reduction in the levels of studied cytokines in blood plasma of rats, but there were differences between effects of statins. Thus, the most pronounced reduction of the IL-1β levels by 3.1 times was observed in simvastatin-treated animals, while administration of atorvastatin and lovastatin showed less significant effect, decreasing this index by 2 and 1.5 times, respectively. Serum levels of IL-6 decreased by 2 times in the group of atorvastatin treated animals, by 1.5 in the group of lovastatin, and by 1.7 times in animals in the simvastatin group. The most significant reduction in the levels of TNF-α was observed in the group of simvastatin treatment – by 2.6 times, while the least was lovastatin (1.3-fold decrease). It can be concluded comparing the effects of drugs on the levels of pro-inflammatory cytokines, that treatment with simvastatin was the most effective in normalization of IL-1β and TNF-α levels, use of atorvastatin – IL-6 levels, while lovastatin had the least significant effect on the serum cytokine profile of the experimental animals.