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THE USE OF COMPUTER TECHNOLOGIES AT THE PRECLINICAL STAGE OF HEPATOTOXICITY ASSESSEMENT OF ANTIVIRAL DRUG RIAMILOVIR

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Abstract. Experimental data integrated with results of in silico studies allows to assess pharmacokinetic and pharmacodynamic parameters more carefully.

Computer technology permit to model the mechanism of action (molecular docking) and predict pharmacokinetic parameters (ADMET profile) based on the physicochemical properties of a small drug molecule. An experimental model (in vitro, in vivo) allows to evaluate the effects of a drug molecule on a biological model.

An example of the integration of computer technology and experimental research is a comprehensive approach to assessment of toxicity of the antiviral drug riamilovir. The aim of in vivo experiment was to simulate the chronic toxicity of riamilovir on non-linear guinea pigs (n = 20), the experiment lasted 8 weeks, animals were divided into 4 groups: the control group that didn't receive the drug, and the experimental groups received riamilovir in terms of the human equivalent dose (HED) 10 mg/kg, 20 mg/kg, 30 mg/kg. Liver histology samples showed macrovacuole steatosis in the experimental groups and decrease in cholesterol level in the group with HED = 20 mg/kg.

According to molecular docking data it was found that riamilovir is a potential inhibitor of the HSP90 protein [1], which is involved in lipid metabolism [2]. As a result of compiling the ADMET profile was detected that the subcellular location of riamilovir is inside the mitochondria. According to the literature, inhibition of the HSP90 protein leads to a decrease in cholesterol level and deformation of the mitochondrial architecture with a corresponding increase in the number of reactive oxygen species [3]. Oxidative stress is one of the pathogenetic mechanisms of the development of macrovacuole steatosis [4].

Thus, various types of studies complement each other and allow, based on the physicochemical properties of drug molecules, to interpret the data of experimental studies.

References

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