DOI 10.18699/SBB-2022-198

Drug repurposing for COVID-19 therapy: challenges and opportunities

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Key words: SARS-CoV-2, COVID-19, virus-host interactions, drug repurposing, *in silico* prediction, *in vitro* validation, informational-computational platform

Motivation and Aim: Drug repositioning is the identification of new indications for the approved medicines [1]. The availability of information on pharmacological and toxicological characteristics provides conditions for rapid introduction of launched drugs for a new nosology. The need to respond quickly to the COVID-19 pandemic has spurred large-scale research in this direction. To identify new pharmacological effects of known drugs, *in silico* and *in vitro* studies are carried out [2]. Several large-scale experimental studies are devoted to *in vitro* screening for one or several targets from 1,400 to 12,000 drugs, making it possible to select some "candidates" for repositioning. In many cases, the results obtained for the same drugs in different test systems do not agree with each other. The observed contradictions could be explained by the absence of standardization of the assays developed by various researchers independently of each other and the lack of generally accepted reference drugs. Pre-selection of potentially active compounds based on *in silico* evaluations significantly increases the chances of success. The purpose of our research is the development of the Informational-Computational Platform (ICP) for drug repurposing aimed to COVID-19 treatment.
Methods and Algorithms: Informational modules of ICP integrates the current data about SARS-CoV-2 life cycle, virus-host interactions, mechanisms of pathological process at the early and later stages of the disease, most promising pharmacological targets, approved pharmaceuticals that may be analyzed as the candidates for repurposing. Computational modules of ICP includes the tools for (1) text mining to select the relevant information despite the “infodemic” [3], (2) network pharmacology to identify the promising molecular targets [4], (3) assessment of the chemical similarity using the distinct structures of the potent anticoronavirus agents as a query [5], (4) machine learning to predict wide biological activity profiles of the probable “candidates” [6]; (5) molecular modeling to estimate the plausibility of the “candidates” binding modes with the putative targets [7]. The general scheme of ICP is presented in Figure 1.
Results: The pilot ICP version is developed based on the information for the SARS-CoV-2 main protease (Mpro) inhibitors as the most studied anticoronavirus target. Currently it includes the available data on 1136 pharmaceutical substances considered as the potential Mpro inhibitors investigated *in silico* (1044 substances) and *in vitro* (304 substances). Database of World-Wide Approved Drugs including 4128 pharmaceutical substances is prepared for structural similarity assessment and application of machine learning methods. Structural similarity assessment is developed on the basis of MNA and QNA descriptors, which are successfully applied for analysis of structure-activity relationships with classification and regression approaches [5].

Prediction of anticoronavirus activity is carried out using machine learning method implemented in the computer program PASS [6]. Based on the available information, we selected the putative Mpro inhibitors for experimental testing, which could be presented in the following order: Disulfiram > Omeprazole > Silibinin > Saquinavir > Montelukast > Imatinib > Atazanavir > Dasatinib > Ciprofloxacin = Glycyrrhizic Acid > Dihydroquercetin > Narlaprevir = Teicoplanin = Bedaquiline = Doxazosin.

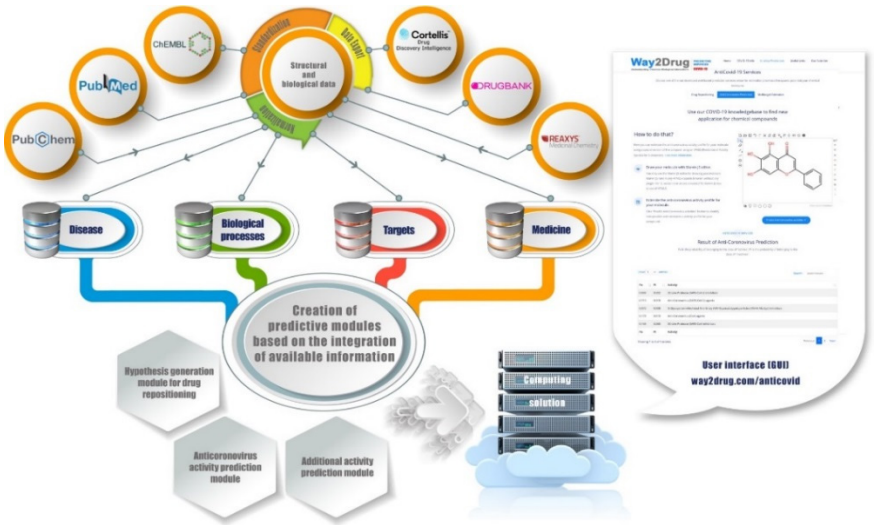

Fig. 1. Informational-computational platform for drug repurposing

Conclusion: We have developed a pilot version of ICP for drug repurposing to identify the most promising anticoronavirus drug-candidates and selected the most promising approved drugs as putative Mpro inhibitors. Some selected drug substances are currently tested by the Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products of the Russian Academy of Sciences.

Acknowledgements: This study is supported in the framework of the Program for Basic Research in the Russian Federation for a long-term period (2021–2030), project No. 122030100170-6.

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