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COVID-19 pandemic is not the time of trial and error

Correspondence

There is an urgent need for an effective medication against the novel coronavirus disease (COVID-19), as it has and continues to have not only significant clinical and non-clinical impacts but also substantial huge economic and psychosocial impacts that have paralyzed the entire world. The severe acute respiratory coronavirus 2 (SARS-CoV-2) uses the angiotensin-converting enzyme 2 (ACE2) receptor to infect humans with many pathological mechanisms that lead to a wide range of clinical presentations [1,2]. As a result, it has taken the lives of more than half a million people and has infected around 13.8 million people worldwide [3].

Scientists are the major players that strive for a potent cure in the globe [4]. The fastest route that scientists usually take is the drug repurposing, where the previously known drugs that their safety and pharmacokinetics were tested too are reconsidered for a possible new effect [5]. This method not only skips the time-consuming process of drug approval but also gives the chance of predicting the possible side effects of repurposed drugs and drug interactions. The swiftness of the computational or in-silico methods has made them appealing target methods for the drug repurposing world [6]. The computational drug repurposing methods have two main approaches; the target-based and the disease-based approaches [7]. The former one is based on detecting the drugs that suit the selected target based on a machine learning algorithm that predicts the drug-target interactions.

In contrast, the latter approach focuses on the characteristics of the different diseases as an aspect to look for the drugs that might be useful for a new disease. Computational drug repurposing has many types of algorithms, target modeling, and drug banks or data sets, which make it an appropriate method for diverse modalities [8]. If this method was the miracle that can rescue us from the COVID-19 disease, why are we still striving to obtain a convenient prescription?

Since the start of this pandemic, three eminent clinical studies have been published, but unfortunately, none of them came out with the expected positive results. In late December 2019, an ambiguous journey was started by COVID-19 in Wuhan, China. Bin et al. conducted a randomized controlled trial (RCT) of Lopinavir–Ritonavir in adults hospitalized with severe COVID-19. Indeed, this robust trial was performed accurately at the right time, but the results turned out to be against the use of Lopinavir–Ritonavir [9]. Subsequently, the same Chinese scientists started up another RCT, in which the effects of Remdesivir were questioned. Despite the promising effects of Remdesivir against the COVID-19, scientists were not able to announce it as a favorable drug due to the lack of statistical evidence. The major blame is put on the significant fall in the number of patients during this trial [10]. The next remarkable drug trial took place in different continents of the world. Mehra et al. handled a multinational observational study in which they investigated the influence of Hydroxychloroquine or Chloroquine beside a macrolide on the COVID-19 treatment. The consequences of this study were pessimistic, too; Hydroxychloroquine and Chloroquine showed no promises in the treatment of the COVID-19 infection [11].

What if there was a method that could rapidly predict the effects of the drugs against COVID-19? Then, we could have selected better candidates for our clinical studies, thus being closer to the drug that might possess tremendous results.

Indeed, such a method exists, but surprisingly, it was not used correctly. The computational drug discovery approach is an incredible method that can rapidly predict the interactions between the drug and the viral components. Our recent systemic review showed the discouraging effects that Ritonivir, Chloroquine, and Hydroxychloroquine might carry in addition to the probability of the potential therapeutic effects of Remdesmivir against COVID-19. To explain meticulously, Ritonavir was not able to form successful interactions with the coronavirus main proteinase (3CLpro) according to the molecular dynamics simulation, Chloroquine had no specific target with low docking scores, and Remdesmivir targeted both the viral RNA-dependent RNA polymerase (RdRp) and the 3CLpro with acceptable docking scores [12].

Studies using the computational drug discovery approaches began to publish in the early stages of the COVID-19 crisis, and this supports the anticipatory role of the computational approaches in determining the fate of the clinical studies. To exemplify the idea, if the fact of the possible positive impacts of Remdesivir and the fact of the potential ineffectiveness of Ritonavir were known previously, we could have chosen a more promising drug for our clinical trials, therefore saved time, spent less effort and money, and consequently obtained better outcomes.

This anticipatory role of the computational approaches for finding new indications of the previously known drugs is widely used in oncology, where there is an urgent need to find new anti-cancer drugs for resistant tumors. For instance, Ke and colleagues conducted a study where six compounds against the fibroblast growth factor receptor 3 (a biomarker of bladder cancer) were found in In-silico screening; one of these compounds showed efficacy in a xenograft mouse model, whereas another two substances demonstrated in vitro validation [13]. Moreover, Shi and colleagues introduced Adapalene and Fluspirilene as cyclin-dependent kinase 2 (CDK2) inhibitors in colon and liver cancers, respectively; these drugs were detected by in-silico screening and then validated in vitro and in vivo [14–16].

Hence, we would like to suggest some of the promising drugs that the computational drug repurposing has introduced, and can serve as potential candidates for the upcoming clinical trials. In our recent systematic review, we came across Atazanavir, Dolutegravir, and Efavirenz as multi-target drugs that target six viral proteins and Darunavir, Raltegravir, Ritonavir, and Grazoprevir as multi-target drugs that target five viral proteins [12]. What makes the multi-target therapeutic agents

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better than mono-target drugs is their greater predictive pharmacokinetics, better patient compliance, and reduced risk of drug interactions [17]. Concurrently hitting different targets is, in particular, advantageous for the individuals that express intrinsic or induced variability in drug response due to the alterations of crucial disease-relevant biological pathways and the activation of compensatory mechanisms [18,19].

In conclusion, it is incredibly critical to follow the results provided by fundamental, experimental, and computational methods in parallel with the clinical approaches [20]. The computational methods are rapid and cost-effective and can give a clear perspective of the desirable drugs, whereas, the clinical trials are the powerful tools that certify the use of the drugs. In this manner, computational drug repurposing is a promising predictor of the COVID-19 drug trials; thus, the combination of the computational methods and clinical trials delivers revolutionary influences on the drug discovery phenomena.

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Declaration of Competing Interest

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References

[1] Kiarash Saleki MB, Saghazadeh Amene, Rezaei Nima. The involvement of the central nervous system in patients with COVID-19. Rev Neurosci. 2020;31(4).
[2] Melika Lotfi NR. SARS-CoV-2: a comprehensive review from pathogenicity of the virus to clinical consequences. J Med Virol. 2020 online ahead of print.
[3] Organization WH. Situation Report-180 2020. Available from https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200718-covid-19-sitrep-180.pdf?sfvrsn=39b31718_2.
[4] Saghazadeh A, Rezaei N. Towards treatment planning of COVID-19: rationale and hypothesis for the use of multiple immunosuppressive agents: anti-antibodies, immunoglobulins, and corticosteroids. Int Immunopharmacol. 2020;84(106560):1–6.
[5] Lotfi M, Hamblin MR, Rezaei N. COVID-19: transmission, prevention, and potential therapeutic opportunities. Clin Chim Acta. 2020;508:254–66.
[6] Shim JSLJ. Recent advances in drug repositioning for the discovery of new anticancer drugs. Int J Biol Sci. 2014;10(7):654–63.
[7] Sanseau PKJ. Computational Methods for Drug Repurposing. Oxford University Press; 2011.
[8] Pushpakom SIF, Eyers PA, Escott KJ, Hopper S, Wells A, et al. Drug repurposing: progress, challenges, and recommendationsns. Nat Rev Drug Discov. 2019;18(1):41–58.
[9] Cao Bin. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe COVID-19 2020. Available from https://www.nejm.org/doi/full/10.1056/NEJMoa2001282.
[10] Wang Yeming. Remdismivir in Adults with Severe COVID-19: a Randomized, Double-Blind, Placebo-Controlled, Multicentre Trial 2020. Available from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext; 2020.
[11] Mehra Mandeep R. Hydroxychloroquine or Chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis 2020; 2020.
[12] Mohamed Kawthar. Computational Drug Discovery and repurposing for the treatment of COVID-19: a systematic review; 2020.
[13] Ke KLH, Yao H, Shi X, Dong C, Zhu Y, et al. In silico prediction and in vitro and in vivo validation of acaricide fluazuron as a potential inhibitor of FGFR3 and a candidate anti-cancer drug for bladder carcinoma. Chem Biol Drug Des. 2017;89:505–13.
[14] Huang C-Y HC-H, Chang P, Wu M-Y, Ng K-L. In silico identification of potential targets and drugs for non-small cell lung cancer. IET Syst Biol. 2018;8(2):56–66.
[15] Shi X-NN LH, Yao H, Liu X, Li L, Leung K-SS, et al. In silico identification and in vitro and in vivo validation of anti-psychotic drug fluspirilene as a potential CDK2 inhibitor and a candidate anti-cancer drug. PLoS One. 2015;10(7).
[16] Shi X-NN LH, Yao H, Liu X, Li L, Leung K-SS, et al. Adapalene inhibits the activity of cyclin-dependent kinase 2 in colorectal carcinoma. Mol Med Rep. 2015;12(5):6501–8.
[17] Alan T. Multi-target pharmacology: possibilities and limitations of the "skeleton key approach" from a medicinal chemist perspective. Front Pharmacol. 2015;6.
[18] Zimmermann GR LrJ, Keith CT. Multi-target therapeutics: when the whole is greater than the sum of the parts. Drug Discov Today. 2007;12(1-2):34–42.
[19] Xie LXL, Kinnings SL, Bourne PE. Novel computational approaches to polypharmacology as a means to define responses to individual drugs. Annu Rev Pharmacol Toxicol. 2012;52(1):361–79.
[20] Negar Moradian HDO, Sedikies Constantine, Hamblin Michael R, Camargo Jr Carlos A, et al. The urgent need for integrated science to fight COVID-19 pandemic and beyond. J Transl Med. 2020;18(1):205.

Kawthar Mohamed
Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
Systematic Review and Meta-Analysis Expert Group (SRMEG), Universal Scientific Education and Research Network (USERN), Tehran, Iran

Nima Rezaei
Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran
Corresponding author at: Children's Medical Center Hospital, Dr. Qarib St, Keshavarz Blvd, Tehran 14194, Iran.
E-mail address: rezaei_nima@tums.ac.ir

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