https://doi.org/10.46344/JBINO.2021.v10i05.12

# USING ARTIFICIAL INTELLIGENCE FOR REPURPOSING OF DRUGS TO EFFECTIVELY SUPPRESS VIRAL REPLICATION PRODUCTIVITY UNDER THE CONDITIONS OF COVID-19

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## ABSTRACT

Drug repurposing using different technologies is the process of identifying new uses for approved or investigational drugs, and it is considered as a very effective strategy for drug discovery because it requires less time and cost to find a therapeutic agent compared to the de novo drug discovery process.The results obtained in the field of transcriptomics allowed to get detailed information on possible individual targets and pathways in which currently available drugs can be repurposed to treat COVID-19.We focused this study on a new and complementary approach to drugs using artificial intelligence and therapy aimed at effective suppression of the productivity of viral replication.Louisiana State University's DeepDrugTM Artificial Intelligence Computing System has identified the drugs that may be effective against SARS-CoV-2 based on how the drug's effects are similar to those of antiviral peptides.This mathematical representation was generated based on the following datasets: AVPdb, a dataset of 2683 AVPs, including 98 of SARS-CoV-1; HPIDB, a dataset of 981 HIV AVPs; hu.map, a dataset of 17.5 million protein interactions; Corum, a dataset of 4,274 mammalian protein complexes; STRING, a dataset of 4,584,628 proteins from 5,090 organisms; DrugBank, a dataset of 13,491 drugs; and BindingDB, a dataset of 846,857 drugs and 7,605 target proteins. As a result of our studies, it was found for the group after treatment the inhibition of SARS-CoV-2 by "poly-pills" relative to the control was 31% (1 μM), 4% (50 μM) and 59% (100 μM). For the group before and after treatment, the inhibition of SARS-CoV-2 by "poly-pills" was slightly increased and amounted to 48% (1 μM), 56% (50 μM) and 78% (100 μM). For both groups, the inhibition of SARS-CoV-2 by 100 μM "poly-pills" was statistically significant according to the data of single-factor ANOVA.Cytotoxicity experiments were performed in parallel using the same experimental conditions and incorporating human lung cell lines, and no cytotoxicity was observed at the concentration tested (up to 100 μM).The current study provided comprehensive artificial intelligence targeting and found suitable "life-saving" drugs for repurposing against COVID-19. We hypothesized the creation and use of "poly-pills", a combination of selected drugs for the treatment of COVID. This initiative is moving already sold and approved safe drugs for potential use in the treatment of COVID.

**Keywords**: COVID, artificial intelligence, viral replication, drugs.

**Introduction.**

Currently, there are still no treatment options available for the deadly contagious disease, Coronavirus Disease 2019 (COVID-19). Drug repurposing using different technologies is the process of identifying new uses for approved or investigational drugs, and it is considered as a very effective strategy for drug discovery because it requires less time and cost to find a therapeutic agent compared to the de novo drug discovery process.

For example, a number of drugs such as remdesivir, favipiravir, ribavirin, lopinavir, ritonavir, darunavir, arbidol, chloroquine, hydroxychloroquine, tocilizumab and interferons have shown an inhibitory effect against SARS-CoV2 in vitro, as well as in clinical conditions. These drugs act either through virus-related targets such as RNA genome, polypeptide packing and uptake pathways, or through host-related pathways involving angiotensin-converting enzyme-2 (ACE2) receptors and inflammatory pathways. Using basic knowledge of viral pathogenesis and pharmacodynamics of drugs, as well as using computational tools such as artificial intelligence (AI), many drugs are currently under development for repurposing.

The unprecedented pace of scientific research has led to the emergence of global proteomic datasets, which provides an opportunity to understand the mechanisms of interaction of the virus with host cell proteins, directly identifying interacting proteins and differentially expressed proteins.

The results obtained in the field of transcriptomics allowed to get detailed information on possible individual targets and pathways in which currently available drugs can be repurposed to treat COVID-19.

In the current scenario, drug repositioning can be seen as a new pathway of COVID-19 treatment.

*We focused this study* on a new and complementary approach to drugs using AI and therapy aimed at effective suppression of the productivity of viral replication.

**Materials and methods.**

*Drug associations using AI*

Louisiana State University's DeepDrugTM Artificial Intelligence Computing System has identified the drugs that may be effective against SARS-CoV-2 based on how the drug's effects are similar to those of antiviral peptides (AVPs).

AVPs are fragments of human proteins that respond to viral infection by impacting on key stages in the viral replication life cycle, including [1] binding the virus to the cell surface and its entry into endosomal compartments; [2] a virus releasing from endosomal compartments into the cytosol, and [3] processing of the viral protein and replication of the viral genome (replication) [4].

An artificial intelligence method was used to create a "fingerprint" for drugs with a similar AVP effect, which captures their properties and the context of a mathematical model and the

representation of all interactions of cellular proteins [5].

This mathematical representation was generated based on the following datasets: AVPdb, a dataset of 2683 AVPs, including 98 of SARS-CoV-1; HPIDB, a dataset of 981 HIV AVPs; hu.map, a dataset of 17.5 million protein interactions; Corum, a dataset of 4,274 mammalian protein complexes; STRING, a dataset of 4,584,628 proteins from 5,090 organisms; DrugBank, a dataset of 13,491 drugs; and BindingDB, a dataset of 846,857 drugs and 7,605 target proteins [6].

An artificial intelligence technology called the Siamese Network (SNet) was then used to compare the "fingerprints" of drugs with similar AVPs.

SNet predictions (comparisons) were based on drug similarity to the AVP fingerprint dataset. SNet made very specific predictions based on a small number of SARS-CoV-1 AVPs, which were selected and demonstrated the strongest antiviral effects. The overall structure of our proposed method-SNet is shown in Diagram 1.

*Drug-target interaction*

The approved drugs were collected from ChEMBL [7] and DrugBank [6]. Information on drug-target interaction was collected from DrugBank (v5.1) [6], STITCH (v5.0, confidence interval > 0.9) [8] and Cheng et al. [9].

*Cell culture*

Human lung cells, provided by the Ukrainian Association of Biobanks, Institute of Cellular Biorehabilitation, which showed a negative result for mycoplasma contamination prior to the study, were maintained in a humidified atmosphere at 37°C with 5% CO2 in Eagle's minimum necessary medium containing 20% FBS. The human cell lines used in this study were either not listed in the International Committee for the Authentication of Cell Lines database of cross-contaminated or misidentified cell lines, or were previously checked by karyotyping.

*Statistical analysis*

The statistical analysis performed is indicated in the figure captions. Differences were considered significant at P value <0.05.

**Research results.**

Based on a comprehensive analysis of SNet predictions for 4118 FDA-approved antiviral drugs, we identified two drugs, designated Drug 1 and Drug 2, which entered the top 99$^{th}$ percentile for each mechanism (Table 1).

Although several other tyrosine kinase inhibitors and antiviral agents have been identified as having a SNet-distance close to zero, drugs selected by us are currently unpatented (generic) drugs approved by Food and Drug Administration indicated for the treatment of human diseases.

Since the drugs chosen by us have a multidirectional effect, a hypothesis was put forward about the enhancement of the impact with their simultaneous use, which we designated as "poly-pills". Poly-pills were added to cells at the same time as the virus ("[drug] before and after") or after 1 hour incubation with the virus ("[drug] after") to assess whether the presence of the drug could prevent the

virus from entering the cell, which can be reported in the data as increased inhibition of SARS-CoV-2.

At the next stage of our study, in an in vitro study sponsored by Skymount, we tested our hypothesis and found out that the combined impact of the two poly-pills drugs inhibited SARS-CoV-2 in lung cells infected with SARS-CoV-2 (Fig. 1). SARS-CoV-2 was added to lung cells in 96-well plates (20 µl per well for 1 hour), and then poly-pills were added and the cells were incubated for 3 days (200 µl per well). SARS-CoV-2 and poly-pills were also simultaneously added to lung cells and incubated for 3 days. The SARS-CoV-2 virus isolate used in these in vitro experiments was the New York-PV091158 / 2020 strain.

As a result of our studies, it was found for the group after treatment the inhibition of SARS-CoV-2 by "poly-pills" relative to the control was 31% (1 µM), 4% (50 µM) and 59% (100 µM). For the group before and after treatment, the inhibition of SARS-CoV-2 by "poly-pills" was slightly increased and amounted to 48% (1 µM), 56% (50 µM) and 78% (100 µM). For both groups, the inhibition of SARS-CoV-2 by 100 µM "poly-pills" was statistically significant according to the data of single-factor ANOVA.

Cytotoxicity experiments were performed in parallel using the same experimental conditions and incorporating human lung cell lines, and no cytotoxicity was observed at the concentration tested (up to 100 µM).

**Discussion**

In our study, we used a new approach to drug repurposing to identify new induced SARS-CoV-2 pathways that could be impacted therapeutically. The use of AI included customized data integration techniques, network analysis, computer modeling, and machine learning.

The Siamese network, which takes features extracted using the Gabor-HoG descriptor, was used in our study. The proposed Siamese network is trained using adversarial learning [10, 11, 12]. Used in other fields such as criminology, it has shown to be highly effective in our research. The experimental results presented in this article show that the SiameseFinger achieves comparable features with modern methods.

Using the artificial intelligence technology SNet, to compare the "fingerprint" of drugs with similar AVPs, we have selected two drugs that can reduce the replication of the SARS-CoV-2 virus in cellular analyzes, which increases an interesting potential for their potential use for the prevention or treatment of COVID-19 as "poly-pills".

The mechanism by which drug 1 can show its potential therapeutic effect is primarily based on its anti-inflammatory and immunomodulatory effects. Tyrosine kinases play a very important role in maintaining cell homeostasis, adaptation to the external environment through various processes, such as cell proliferation and differentiation, migration, inflammation, and maintaining the integrity of the cell barrier [13]. As a result of viral infection, dysregulation of tyrosine kinase signaling contributes to a

hyperinflammatory condition that causes severe damage to various tissues and organs. Moreover, tyrosine kinase signaling is enhanced after viral infection, resulting in a variety of adverse physiological effects.

Inhibition of ABL2 with drug 2 can prevent SARS-CoV-2 from leaving infected cells and spreading to healthy cells. In addition, several studies have shown that tyrosine kinase signaling may be an important cellular process that enhances viral replication, and TKIs such as imatinib can reduce SARS-CoV-2 replication. Inhibition of tubulin polymerization, leading to disruption of transport, processing of the virus, as well as to a decrease in the replication of the viral genome [14].

However, the search for other therapeutic agents cannot be suspended pending results, because the need for new effective agents is enormous.

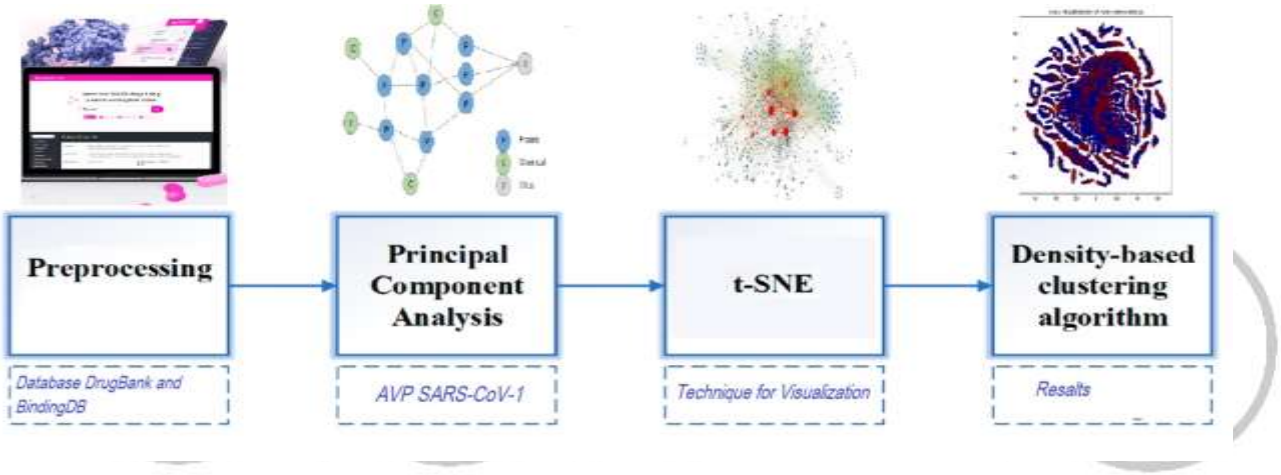


Diagram 1. Structure of method-SNet to compare "fingerprints" of drugs with similar AVPs.

Table 1. SNet Predictions for Entry, Fusion, and Replication.

| Drug | Entry Prediction [Ranking] (Percentile) | Fusion Prediction [Ranking] (Percentile) | Replication Prediction [Ranking] (Percentile) |
|---|---|---|---|
| Drug 1 | 0.1455 [20th] (99.51) | 0.0955 [9th] (99.78) | 0.2424 [27th] (99.34) |
| Drug 2 | 0.1072 [4th] | 0.0796 [2nd] | 0.2033 [10th] |

| | | | |
|---|---|---|---|
| | (99.90) | (99.95) | (99.76) |

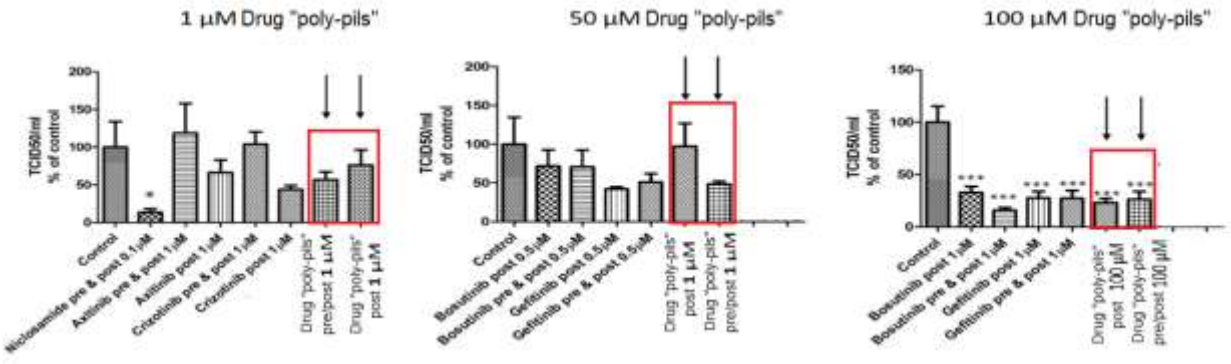


Figure 1. Inhibition of SARS-CoV-2 by lung cells by the "poly-pills" drug.

**Conclusion**

The current study provided comprehensive AI targeting and found suitable "life-saving" drugs for repurposing against COVID-19. We hypothesized the creation and use of "poly-pills", a combination of selected drugs for the treatment of COVID. This initiative is moving already sold and approved safe drugs for potential use in the treatment of COVID.

**Abbreviations**: COVID-19: Coronavirus Disease 2019; ACE2: angiotensin-converting enzyme-2; AI: artificial intelligence; AVPs: antiviral peptides; SNet: Siamese Network.

**Declarations**

Conflict of Interests

The authors declares that there is no conflict of interest.

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