Literature review for SARS-CoV-2 Drug Repurposing

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Abstract: Human coronaviruses (HCoVs) have long been considered as no significant pathogens causing common cold in healthy people. But in the 21st century, 2 highly pathogenic HCoVs which are Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) emerged from animal reservoirs to cause global epidemics with alarming morbidity and mortality. An other pathogenic HCoV, 2019 novel coronavirus (2019-nCoV) was discovered was seen at Wuhan, China in December 2019 and this pathogenic HCoV has caused serious illness and death. The proposed work discusses about the detailed literature review of the contribution made by different authors.

Index Terms – Covid, Corona Virus, Drug, repurposing

I. INTRODUCTION
The 2019 novel coronavirus (SARS-CoV-2) pandemic has resulted in more than a million deaths, high morbidities, and economic distress worldwide. The June 2020 Global Economic Prospects estimated a 5.2% downfall in the global gross domestic product (GDP) in 2020 that would lead to the worst economic slowdown in history after the Second World War. The pathogen that causes COVID-19 belongs to the Coronaviridae family, which is a family of enveloped positive-strand RNA viruses that affect mammals, birds, and amphibians. Coronaviruses are majorly grouped into four genera: alphacoronavirus, betacoronavirus, deltacoronavirus, and gammacoronavirus. Out of the seven known strains of human CoVs (HCoVs), the three betacoronaviruses, namely, middle east respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) produce severe symptoms. Although the 2003 SARS-CoV outbreak was controlled, it infected 8098 individuals and resulted in 774 deaths. SARS-CoV-2 being highly contagious, on 30 January 2020, the World Health Organization (WHO) declared it as a public emergency of international concern warning all the countries with vulnerable health care systems. The current treatment for COVID-19 is completely supportive and symptomatic as there are no specific known medicines.

Several research groups around the world are trying to develop a vaccine that would prevent and treat SARS-CoV-2. Looking at the current unpredictable trajectory of how the disease spreads and the life cycle of the virus, there is an urgent need to develop preventive strategies against it. There is an urgent need to identify medications that would treat and prevent novel diseases like the 2019 coronavirus disease (COVID-19). Given this strict timeline, a more realistic solution lies in drug repurposing or drug repositioning, which aims to identify new medical indications of approved drugs. Drug repurposing is a promising strategy to discover new medical indications of the existing approved drugs due to several advantages in terms of the costs, safety factors, and quick results compared to new drug design and discovery.

II. LITERATURE SURVEY

This project requires a rigorous literature survey. The below section gives the detailed literature review of the proposed topic.

Coronaviruses—drug discovery and therapeutic options: In humans, infections with the human coronavirus (HCoV) strains HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1 usually result in mild, self-limiting upper respiratory tract infections, such as the common cold. By contrast, the CoVs responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which were discovered in Hong Kong, China, in 2003, and in Saudi Arabia in 2012, respectively, have received global attention over the past 12 years owing to their ability to cause community and health-care-associated outbreaks of severe infections in human populations. These two viruses pose major challenges to clinical management because there are no
specific antiviral drugs available. This summarizes the epidemiology, virology, clinical features and current treatment strategies of SARS and MERS, and discusses the discovery and development of new virus-based and host-based therapeutic options for CoV infections. Genomes and structures of SARS-CoV and MERS-CoV. The typical coronavirus (CoV) genome is a single-stranded, non-segmented RNA genome, which is approximately 26–32 kb. It contains 5′-methylated caps and 3′-polyadenylated tails and is arranged in the order of 5′, replicate genes, genes encoding structural proteins (spike glycoprotein (S), envelope protein (E), membrane protein (M) and nucleocapsid protein (N)), polyadenylated tail and then the 3′ end.

**Coronavirus infections—more than just the common cold**: Human coronaviruses (HCoVs) have long been considered inconsequential pathogens, causing the “common cold” in otherwise healthy people. However, in the 21st century, 2 highly pathogenic HCoVs—severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)—emerged from animal reservoirs to cause global epidemics with alarming morbidity and mortality. In December 2019, yet another pathogenic HCoV, 2019 novel coronavirus (2019-nCoV), was recognized in Wuhan, China, and has caused serious illness and death. The ultimate scope and effect of this outbreak is unclear at present as the situation is rapidly evolving. Common symptoms of SARS included fever, cough, dyspnea, and occasionally watery diarrhea. Of infected patients, 20% to 30% required mechanical ventilation and 10% died, with higher fatality rates in older patients and those with medical comorbidities. Human-to-human transmission was documented, mostly in health care settings. This nosocomial spread may be explained by basic virology: the predominant human receptor for the SARS S glycoprotein, human angiotensin-converting enzyme 2 (ACE2), is found primarily in the lower respiratory tract, rather than in the upper airway. Receptor distribution may account for both the dearth of upper respiratory tract symptoms and the finding that peak viral shedding occurred late (=10 days) in illness when individuals were already hospitalized.

**Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China**: In December, 2019, a pneumonia associated with the 2019 novel coronavirus (2019-nCoV) emerged in Wuhan, China. Aiming to further clarify the epidemiological and clinical characteristics of 2019-nCoV pneumonia. This retrospective, single-centre study, has included all confirmed cases of 2019-nCoV in Wuhan Jinyintan Hospital from Jan 1 to Jan 20, 2020. Cases were confirmed by real-time RT-PCR and were analysed for epidemiological, demographic, clinical, and radiological features and laboratory data. Outcomes were followed up until Jan 25, 2020. Of the 99 patients with 2019-nCoV pneumonia, 49 (49%) had a history of exposure to the Huanan seafood market. The average age of the patients was 55 years (SD 13.1), including 67 men and 32 women. 2019-nCoV was detected in all patients by real-time RT-PCR. 50 (51%) patients had chronic diseases. Patients had clinical manifestations of fever (82 [83%] patients), cough (81 [82%] patients), shortness of breath (31 [31%] patients), muscle ache (11 [11%] patients), confusion (nine [9%] patients), headache (eight [8%] patients), sore throat (five [5%] patients), rhinorrhea (four [4%] patients), chest pain (two [2%] patients), diarrhea (two [2%] patients), and nausea and vomiting (one [1%] patient). According to imaging examination, 74 (75%) patients showed bilateral pneumonia, 14 (14%) patients showed multiple mottling and ground-glass opacity, and one (1%) patient had pneumothorax. 17 (17%) patients developed acute respiratory distress syndrome and, among them, 11 (11%) patients worsened in a short period of time and died of multiple organ failure. Human coronavirus is one of the main pathogens of respiratory infection. The two highly pathogenic viruses, SARS-CoV and MERS-CoV, cause severe respiratory syndrome in humans and four other human coronaviruses (HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-HKU1) induce mild upper respiratory disease. The 2019-nCoV infection was of clustering onset, is more likely to affect older males with comorbidities, and can result in severe and even fatal respiratory diseases such as acute respiratory distress syndrome. In general, characteristics of patients who died were in line with the MulBSTA score, an early warning model for predicting mortality in viral pneumonia. Further investigation is needed to explore the applicability of the MulBSTA score in predicting the risk of mortality in 2019-nCoV infection.

**Drug repurposing: progress, challenges and recommendations**: Given the high attrition rates, substantial costs and slow pace of new drug discovery and development, repurposing of “old” drugs to treat both common and rare diseases is increasingly becoming an attractive proposition because it involves the use of de-risked compounds, with potentially lower overall development costs and shorter development timelines. Various data-driven and experimental approaches have been suggested for the identification of repurposable drug candidates; however, there are also major technological and regulatory challenges that need to be addressed. This review presents approaches used for drug repurposing (also known as drug repositioning), discusses the challenges faced by the repurposing community and recommend innovative ways by which these challenges could be addressed to help realize the full potential of drug repurposing. Drug repurposing (also called drug repositioning, reprofiling or re-tasking) is a strategy for identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication.1 This strategy offers various advantages over developing an entirely new drug for a given indication.

**Machine learning-based prediction of drug–drug interactions by integrating drug phenotypic, therapeutic, chemical, and genomic properties**: Drug-drug interactions (DDIs) are an important consideration in both drug development and clinical application, especially for co-administered medications. While it is necessary to identify all possible DDIs during clinical trials, DDIs are frequently reported after the drugs are approved for clinical use, and they are a common cause of adverse drug reactions (ADR) and increasing healthcare costs. Computational prediction may assist in identifying potential DDIs during clinical trials. This proposes a heterogeneous network-assisted inference (HNAI) framework to assist with the prediction of DDIs. This work, first, constructed a comprehensive DDI network that contained 6946 unique DDI pairs connecting 721 approved drugs based on
DrugBank data. Next, calculated drug-drug pair similarities using four features: phenotypic similarity based on a comprehensive drug-ADR network, therapeutic similarity based on the drug Anatomical Therapeutic Chemical classification system, chemical structural similarity from SMILES data, and genomic similarity based on a large drug-target interaction network built using the DrugBank and Therapeutic Target Database. Finally, applied five predictive models in the HNAI framework: naive Bayes, decision tree, k-nearest neighbor, logistic regression, and support vector machine, respectively. Through machine learning-based integration of drug phenotypic, therapeutic, structural, and genomic similarities, this paper demonstrated that HNAI is promising for uncovering DDIs in drug development and postmarketing surveillance.

Modeling polypharmacy side effects with graph convolutional networks: The use of drug combinations, termed polypharmacy, is common to treat patients with complex diseases or co-existing conditions. However, a major consequence of polypharmacy is a much higher risk of adverse side effects for the patient. Polypharmacy side effects emerge because of drug-drug interactions, in which activity of one drug may change, favorably or unfavorably, if taken with another drug. The knowledge of drug interactions is often limited because these complex relationships are rare, and are usually not observed in relatively small clinical testing. Discovering polypharmacy side effects thus remains an important challenge with significant implications for patient mortality and morbidity. This article presents Decagon, an approach for modeling polypharmacy side effects. The approach constructs a multimodal graph of protein-protein interactions, drug-protein target interactions and the polypharmacy side effects, which are represented as drug-drug interactions, where each side effect is an edge of a different type. Decagon is developed specifically to handle such multimodal graphs with a large number of edge types. This approach develops a new graph convolutional neural network for multirelational link prediction in multimodal networks. Unlike approaches limited to predicting simple drug-drug interaction values, Decagon can predict the exact side effect, if any, through which a given drug combination manifests clinically.

III. LIMITATIONS OF THE EXISTING WORK AND MOTIVATION

The current treatment for COVID-19 is completely supportive and symptomatic as there are no specific known medicines. Several research groups around the world are trying to develop a vaccine that would prevent and treat SARS-CoV-2. Looking at the current unpredictable trajectory of how the disease spreads and the life cycle of the virus, there is an urgent need to develop preventive strategies against it. Given this strict timeline, a more realistic solution lies in drug repurposing or drug repositioning, which aims to identify new medical indications of approved drugs. Drug repurposing offers several advantages. It has a low risk of failure as the drug has already been approved with less unknown harmful adverse effects. It reduces the time frame for drug development as the drugs have passed all the pre-clinical trials and safety norms. Finally, compared to the discovery of a new drug, drug repurposing requires less economic investment and puts fewer lives of volunteers (particularly kids) involved in clinical trials at risk.

Drug repurposing involves identifying potential drugs and monitoring their in vivo efficacy and potency against the disease. The most critical step in this pipeline is identifying the right candidate drugs, for which experimental and computational approaches are usually considered. Recently, computational approaches are receiving attention due to the availability of large biological data. Efficient ways to handle big data has opened up many opportunities in the field of pharmacology. Zitnik, et al. elaborates several data-driven computational tools to integrate large volumes of heterogeneous data and solve problems in pharmacology such as drug-target interaction prediction (identify interactions between a drug and its target genes), drug repurposing, and drug-drug interaction or side effect prediction, to list a few. Hence this field is known as computational pharmacology. Many standard machine learning (ML) and deep learning (DL) techniques have been applied in computational pharmacology. Drug-drug interaction was formulated as a binary classification problem and solved using ML techniques like random forest, support vector machines (SVM), and naive bayes, and using DL models like deep multi-layer perceptrons and recurrent neural networks, to name a few. DL techniques often outperform standard ML techniques. However, these methods lack the ability to capture the structural information in the data, specifically the connections between 4 different biological entities (e.g., interactions between drugs and genes or between drugs and diseases). A natural and efficient way to represent such structural information is to construct a graph with nodes representing entities like drugs, genes, diseases, etc., and edges representing the complex interactions between these entities. Graph neural networks (GNNs) capture the structural information by accounting for the underlying graph structure while processing the data. Decagon, a GNN-based model designed for predicting the side effects of a pair of drugs has proved its capability by outperforming the non-graph based machine learning models in terms of its prediction performance. Similarly, drug repurposing has been studied using computational methods such as signature matching methods, molecular docking, and network-based approaches.

There exist several GNN variants such as graph convolutional networks (GCN), GraphSAGE , graph attention networks (GAT) and scalable inception graph neural network (SIGN) , to name a few. GCN is a vanilla flavored GNN based on above equation. GAT gives individual attention to the neighboring nodes instead of treating every node equally. To address the issue of scalability, GraphSAGE uses a neighbor sampling method, wherein instead of taking the entire neighborhood, random sampling of a subset of neighbor nodes is done. SIGN takes a different approach to solve the scalability issue and introduce a parallel architecture. The proposed Dr-COVID architecture is based on the SIGN approach due to its computational advantages.
IV OBJECTIVES

- The goal of drug repurposing is to identify potential drugs and monitoring their in vivo efficacy and potency against the disease. Drug repurposing offers several advantages.
- It has a low risk of failure as the drug has already been approved with less unknown harmful adverse effects.
- It reduces the time frame for drug development as the drugs have passed all the pre-clinical trials and safety norms.
- This work explores computational data-driven methods for drug repurposing and propose a dedicated graph neural network (GNN) based drug repurposing model, called Dr-COVID.
- This project proposes a model which constructs a four-layered heterogeneous graph to model the complex interactions between drugs, diseases, genes, and anatomies.
- This model elaborates several data-driven computational tools to integrate large volumes of heterogeneous data and solve problems in pharmacology such as drug-target interaction prediction (identify interactions between a drug and its target genes), drug repurposing, and drug-drug interaction or side effect prediction.
- Graph neural networks (GNNs) capture the structural information by accounting for the underlying graph structure while processing the data. GNN-based model outperforms non graph-based machine learning models.

VI. REFERENCES

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