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Authors: Francis Edem Agamah[1], Thomas H.A. Ederveen[2], Michelle Skelton[1], Darren P. Martin[1], Emile R. Chimusa[3], Peter A.C. 't Hoen 't Hoen[2]
Affiliations: computational biology division, department of integrative biomedical sciences, institute of infectious disease and molecular medicine, faculty of health sciences, university of cape town, cape town, south africa[1], department of medical biosciences, radboud university medical center nijmegen, the netherlands[2], department of applied science, faculty of health and life sciences, northumbria university, newcastle, tyne and wear, ne1 8st, uk[3]
Orcid ids: 0000-0002-2980-1392[1]
Contact e-mail: francisagamahh@gmail.com
Journal: DrugRxiv
Review statement: The manuscript is currently under review and should be treated with discretion.
Links to data: https://github.com/francis-agamah/Network-based-multi-omics-disease-drug-associations_drugs-for-COVID-19-disease-p
Manuscript submission date: 16 April 2024
Keywords: multi-omics, drug repurposing, random walk, COVID-19, networks

Network-based multi-omics-disease-drug associations reveal drug repurposing candidates for COVID-19 disease phases

Francis E. Agamah[1], Thomas H.A. Ederveen[2], Michelle Skelton[1], Darren P. Martin[1], Emile R. Chimusa[3*], Peter A.C. 't Hoen[2*]

[1]Computational Biology Division, Department of Integrative Biomedical Sciences, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.
[2]Department of Medical BioSciences, Radboud University Medical Center Nijmegen, The Netherlands.
[3]Department of Applied Science, Faculty of Health and Life Sciences, Northumbria University, Newcastle, Tyne and Wear, NE1 8ST, UK.

*joint corresponding authors
Address correspondence to:

Peter A.C. 't Hoen, PhD
Medical BioSciences department
Radboud University Medical Center Nijmegen, The Netherlands
PO Box 9101, 6500 HB Nijmegen, The Netherlands
E-mail: Peter-Bram.tHoen@radboudumc.nl
Telephone: +31 (0) 243619390

Emile R. Chimusa, MSc, PhD
Department of Applied Sciences,
Faculty of Health and Life Sciences,
Northumbria University, Newcastle,
Tyne and Wear, NE1 8ST, UKE
E-mail: emile.chimusa@northumbria.ac.uk
Tel: +44 (0)191 227 3831

Abstract

Background: The development and roll-out of vaccines, and the use of various drugs have contributed to controlling the COVID-19 pandemic. Nevertheless, challenges such as the inequitable distribution of vaccines, the influence of emerging viral lineages and immune evasive variants on vaccine efficacy, and the inadequate immune defense in subgroups of the population continue to motivate the development of new drugs to combat the disease.

Aim: In this study, we sought to identify, prioritize, and characterize drug repurposing candidates appropriate for treating mild, moderate, or severe COVID-19 using a network-based integrative approach that systematically integrates drug-related data and multi-omics datasets.

Methods: We leveraged drug data, and multi-omics data, and used a random walk restart algorithm to explore an integrated knowledge graph comprised of three sub-graphs: (i) a COVID-19 knowledge graph, (ii) a drug repurposing knowledge graph, and (iii) a COVID-19 disease-state specific omics graph.

Results: We prioritized twenty FDA-approved agents as potential candidate drugs for mild, moderate, and severe COVID-19 disease phases. Specifically, drugs that could stimulate immune cell recruitment and activation including histamine, curcumin, and paclitaxel have potential utility in mild disease states to mitigate disease progression. Drugs like omacetaxine, crizotinib, and vorinostat that exhibit antiviral properties and have the potential to inhibit viral replication can be considered for mild to moderate COVID-19 disease states. Also, given the association between antioxidant deficiency and high inflammatory factors that trigger cytokine storms, antioxidants like glutathione can be considered for moderate disease states. Drugs that exhibit potent anti-inflammatory effects like (i) anti-inflammatory drugs (sarilumab and tocilizumab), (ii) corticosteroids (dexamethasone and hydrocortisone), and (iii) immunosuppressives (sirolimus and cyclosporine) are potential candidates for moderate to severe disease states that trigger a hyperinflammatory cascade of COVID-19.

Conclusion: Our study demonstrates that the multi-omics data-driven integrative analysis within the drug data enables prioritizing drug candidates for COVID-19 disease phases, offering a comprehensive basis for therapeutic strategies that can be brought to market quickly given their established safety profiles. Importantly, the multi-

omics data-driven integrative analysis within the drug data approach implemented here can be used to prioritize drug repurposing candidates appropriate for other diseases.

Keywords: multi-omics, drug repurposing, random walk, COVID-19, networks

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the highly contagious and virulent coronavirus responsible for the global outbreak of coronavirus disease 2019 (COVID-19). Between 2020 and 2023 COVID-19 imposed an unprecedented burden on global public health systems and by December 2023, had been responsible for at least seven hundred and seventy million reported cases and close to seven million reported deaths [1].

The pandemic's containment and the restoration of societal normalcy have been achieved through two key routes: (1) the development and widespread use of SARS-CoV-2 vaccines, and (2) the gradual increase in natural infection-acquired immunity. While progress has been made, critical hurdles remain, notably the need for equitable vaccine distribution and effective treatment options for those unvaccinated or immunocompromised [2]. Furthermore, there are also some concerns surrounding vaccine efficacy against a backdrop of waning immunity [2, 3] and the emergence of immune evasive viral strains [4, 5]. It is now a widely held view that COVID-19 is likely to transform into another endemic human coronavirus, possibly with seasonal epidemic waves [6]. Irrespective of the number of infections that occur or the intensively with which vaccines are used, it remains uncertain whether true herd immunity of the sorts achieved with measles and rubella will ever be achieved for COVID-19.

While data is currently being collected and analysed to understand how newly evolved SARS-CoV-2 variants might impact the effectiveness of vaccines and the severity of future COVID-19 infection waves, there remains a demand for both host-directed and pathogen-directed drugs that could be utilized to treat the mild, moderate, and severe manifestations of the disease.

In light of this, multiple existing drugs have been sought to treat or control SARS-CoV-2 infection [7]. An example is *ritonavir-boosted nirmatrelvir* (*paxlovid*) (DrugBank: DB16691), a protease inhibitor used for the treatment of mild to moderate COVID-19 in adults who are at high risk of developing severe symptoms [8]. Additionally, *remdesivir* (Veklury) (DrugBank: DB14761), an adenosine triphosphate analogue

targeting the conserved viral RNA-dependent RNA polymerase (RdRp), shortens the recovery time for adults hospitalized with COVID-19 infection and pneumonia, while also mitigating disease severity and associated mortality [9-11]. Other virus-directed antiviral drugs like *favipiravir* (DrugBank: DB12466), *molnupiravir* (DrugBank: DB15661), and *ritonavir* (DrugBank: DB00503), may also potentially improve the health outcomes of COVID-19 patients [12]. Furthermore, a host-directed drug such as *dexamethasone* (DrugBank: DB01234), an anti-inflammatory corticosteroid, has demonstrated its effectiveness in reducing mortality among severely infected patients. It achieves this by modulating inflammation-mediated lung injury, preventing in some cases progression to respiratory failure and death [13, 14]. Another host-directed drug, *aspirin* (DrugBank: DB00945) [15], decreases the risk of complications, and mortality in hospitalized COVID-19-infected patients [15-17].

While these drugs are mainly utilized for severe COVID-19 cases, some virus-directed monoclonal antibodies (e.g., *bebtelovimab, casirivimab*) received emergency-use authorization at various stages of the pandemic for managing mild to moderate COVID-19 [18]. Additionally, other monoclonal antibodies including the combination of *bebtelovimab, casirivimab,* and *imdevimab* (CAS/IMDEV), and the combination of *bamlanivimab* and *etesevimab* (BAM/ETE) have been useful for managing mild to moderate COVID-19 in adults [18]. These monoclonal antibodies inhibit viral entry into host cells by preventing viral attachment to human *ACE2* receptors.

Host-targeted monoclonal antibodies such as *tocilizumab* (DrugBank: DB06273) and *sarilumab* (DrugBank: DB11767), [19-22], which modulate aberrant immune responses to infection by binding to the host *IL6* receptor (*IL6R*), have also been granted emergency use authorization. Specifically, these IL6R-binding monoclonals are used for treating hospitalized adults and peadiatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation [22].

Although existing drugs have been recommended for managing COVID-19, concerns have arisen about post-hospitalization effects and the appropriateness of using these drugs in different COVID-19 disease phases [23-25]. COVID-19 exhibits a wide spectrum of symptoms and severities, necessitating a nuanced approach to treatment. Personalized medicine, where the right drug is administered to the right patient group

at the right disease phase, could revolutionize COVID-19 treatment strategies. Hence, it would be useful to identify effective drugs that are specific to different phases of the disease, and which could also be potentially applicable to combatting any future emergence of other coronaviruses.

Given that the development of new medications is a time-consuming process, the repurposing of existing medications for other indications may prove to be a viable alternative. However, most studies that have implemented computational methods to identify drug repurposing candidates for COVID-19 have so far leveraged disease-gene associations, protein-protein interaction, and drug-target data but less consideration is given to the interactions between other biomedical and molecular features specific to different COVID-19 disease phases, such as recorded in large scale multi-omics profiling efforts [26-29]. Applying computational multi-omics data-driven within drug data approaches to the repurposing of existing medications is, in fact, a potentially and highly efficient means of drug discovery since the pharmacological properties, formulations, and toxicities of such agents are already known [26-32]. In this study, we explore the utility of incorporating disease-state specific omics-graph along with drug-related data to identify drug repurposing candidates for mild, moderate, or severe COVID-19 disease states. We employ multiXrank [33], a random walk with restart (RWR) algorithm that can combine multiple heterogeneous networks and allows for universal multi-layer network exploration. We demonstrate that this integrative multi-omics network-based approach with drug data has the potential to repurpose drugs in different disease states and can be applied to other diseases.

Materials and Methods

Study design and procedures

The methodology employed in this study **(Figure 1)** encompasses five main steps: (1) curation and pre-processing of data related to the action of drugs and to the molecular omics profiles associated with the different phases of the disease; (2) multi-layer network-based random walk analysis; (3) predicting drug repurposing candidates; (4) drug prediction robustness analysis; and (5) validation of predicted candidate drugs.

Drug repurposing knowledge graph, COVID-19 knowledge graph, and disease-state specific omics-graphs

We utilized an existing drug repurposing knowledge graph constructed by Ioannidis *et al.*, [32]. The Drug Repurposing Knowledge Graph (DRKG) is a biological knowledge graph relating genes, compounds, diseases, biological processes, side effects, and symptoms as of 2020 when it was constructed. The DRKG includes information from six existing databases: (1) Global Network of Biomedical Relationships (GNBR) [34], (2) STRING [35], (3) IntAct [36], (4) Hetionet [37], (5) DrugBank [38] and, (6) Drug-Gene Interaction database (DGIdb) [39]. The DRKG includes 97,238 entities classified into 13 different node types (**Table 1**) and consists of 5,874,261 triplets belonging to 107 edge types (**Supplementary Table 1**). We leveraged the gene-pathway and gene-biological process edge types (**Supplementary Table 1**) in the DRKG to construct pairwise interaction between biological processes and pathways based on the semantic relation that biological processes and pathways that share similar disease-related genes are indirectly associated. This was achieved by exploring the associations between genes, biological processes, and pathways to investigate the biological processes and pathways enriched among the disease-associated genes. We then paired pathways and biological processes sharing common genes.

We additionally considered the COVID-19 knowledge graph (COVID-19 KG) built by Hsieh *et al.*, in 2021 [30]. This COVID-KG is notable for its integration of drug data from the Comparative Toxicogenomics Database (CTDbase), specifically data available as of 2021 [40], along with protein-protein interactions involving SARS-CoV-2 and host proteins from a study by Gordon *et al.*, [41]. In addition to the virus-host interaction data, we also included SARS-CoV-2 and host protein interactions from IntAct database [36]. The SARS-CoV-2 and host protein interactions data extracted from IntAct were derived from several studies that examined protein-protein interactions between SARS-CoV-2 and humans. Following the merge of the COVID-KG and virus-human protein interaction data, the resulting graph represents the interactions between entities belonging to 5 different node types (**Table 2**) and consists of 33,621 triplets belonging to 5 edge types (**Supplementary Table 2**).
Furthermore, we considered disease-state specific omics-graphs (DSOG) constructed from our previous study, Agamah *et al.*, [42] for downstream analysis. The DSOG were

constructed by integrating harmonized proteomics, transcriptomics, metabolomics, and lipidomics datasets retrieved from Overmyer *et al.*, [43] and Su *et al.*, [44] together with a unified knowledge graph, assembled by merging protein-protein interactome, metabolite-metabolite interactome, transcript-transcript, and lipid-lipid interactome curated from literature and databases [42]. The DSOG consisted of four node types (i.e., protein, transcript, metabolite, lipid) and nine edge types (i.e., protein-protein, transcript-transcript, metabolite-metabolite, lipid-lipid, protein-transcript, protein-metabolite, transcript-metabolite, protein-lipid, and transcript-lipid).

The process used to construct the graphs is described in Agamah *et al.*, [42]. In summary, the World Health Organization (WHO) Ordinal Scale (WOS) was used as a disease severity reference to harmonize COVID-19 patient metadata across the Overmyer *et al.*, [43] and Su *et al.*, [44] studies. This harmonized metadata was then used to categorize the multi-omics data into mild, moderate, and severe COVID-19 disease phases. Subsequently, a correlation network approach was implemented to construct co-expression networks for proteomics, transcriptomics, metabolomics, and lipidomics data for each disease state. The co-expression networks generated were integrated/merged based on the disease state and omics data type to construct disease-state specific omics-graphs.
Overall, these above data sources were used to construct a unified and integrated knowledge graph comprised of three sub-graphs including COVID-19 KG, DRKG, and the DSOG from which we conducted an in-depth quality check (see the section below), prioritize, characterize, and repurpose specific drugs for the mild, moderate, and severe state of COVID-19.

Data pre-processing, quality control, and filtering

We observed differences in the gene and drug identifiers across the DRKG and COVID-19 KG. To achieve consistency in the identifiers across the datasets, we mapped gene identifiers to gene symbols using the UniProt database resource [45], and drug identifiers to drug names using the DrugBank database [38]. To identify clinically approved drugs with known safety profiles and pharmacokinetic properties, we filtered/cleaned the drug-related data by maintaining (1) drug-drug interactions between FDA-approved drug candidates, (2) drug-protein/gene interactions between

FDA-approved drug candidates and proteins/genes, (3) biological process/pathways-chemical interactions between biological processes/pathways and FDA approved chemicals. As our investigation is centered around identifying potential repurposable drugs for COVID-19, we took additional measures to refine our analysis. To prioritize approved drugs with known safety profiles for COVID-19, we specifically removed interactions involving drugs that have been studied (based on literature evidence) and found to lack therapeutic effectiveness in treating COVID-19, as is the case with quinolones like chloroquine and hydroxychloroquine [46, 47]. Moreover, we omitted certain endogenous substances including hormones such as progesterone, testosterone, and melatonin, as well as alcohol (ethanol), various compounds like cholesterol, and cocaine, and gases such as oxygen, and hydrogen from our analysis.

Random walk with restart network analysis

The random walk method is a technique for detecting the spread of biological information through networks. The concept behind the random walk method is such that a hypothetical particle exploring the network structure takes discrete steps (walks) in some direction from a seed node [48]. The walk explores different layers based on the premise that nodes related lie close to each other in the network [48]. To perform random walk with restart (RWR) network analyses, we utilized multiXrank [33], a RWR on a multilayer network algorithm, to explore the disease-state specific omics-graphs, COVID-KG and DRKG. Whereas the multiXrank algorithm enables random walk analysis on multiple large multidimensional datasets in a multilayer network framework, other methods are limited in the combination and heterogeneity of networks that they can handle [49]. In brief, the first step of the algorithm is to create adjacency matrices for the input graphs, followed by computing different transition probabilities of the random walk with restart on the graphs. The probabilities are estimated based on the concept that an imaginary particle starts a random walk from the seed node to other nodes in the network. These different transition probabilities describe the walks within a graph and the jumps between graphs. A higher probability score (close to 1) suggests a higher likelihood of walking or jumping between graphs. We made specific adjustments to the algorithm's configuration script based on the input datasets. While the global restart probability was set at 0.7, the intra-layer jump probability and the probability to restart in a specific layer were set to 0.5 and 1,

respectively. Other parameters such as inter-layer jump probability were fine-tuned to align with the number of input graph layers. We set parameters in the algorithm to control the behaviour of the algorithm to achieve desired outcomes.

As a result of this analysis, we obtained multi-layered graphs that detailed the exploration of seed nodes across various omics layers and drug data, along with a ranked list of features in each graph layer.

RWR analysis on DRKG, COVID-19 KG, and DSOG

We performed an initial analysis focused on identifying drugs that can be repurposed for COVID-19 without accounting for omics profiles. Thus, we employed DRKG and COVID-19 KG as the input data sources in the RWR algorithm to predict candidate drugs for COVID-19. The algorithm accepts as layers, monoplex graphs, and/or a combination of monoplex graphs (multiplex). Specifically, in our analysis, edge-types with the same node entities including the drug-drug and gene-gene interactions each served as a monoplex and were interconnected by edge-types with different node entities including the gene-drug, pathway-gene, phenotype (biological process)-gene, phenotype (biological process)-drug, and SARS-CoV-2-host gene interactions (**Supplementary Table 1** and **Supplementary Table 2**).

In subsequent analysis to predict potential drugs for different COVID-19 disease states, we utilized DRKG, COVID-19 KG, and DSOG as input data. Herein, the input data included the proteomics, transcriptomics, metabolomics, and lipidomics disease-state graphs which also served as individual monoplex layers. Similar to the analysis on DRKG and COVID-19, graphs with edges-types of the same node entities were interconnected by graphs with edge-types of different node entities including the protein-transcript, protein-metabolite, transcript-metabolite, protein-lipid, and transcript-lipid interactions from the DSOG which were not utilized in the previous analysis.

Prediction of drugs using the RWR algorithm is based on a network exploration process where simulated particles walk iteratively from one node to one of its neighbours with some probability. In this process, the walk is restricted to restart from seed nodes to prevent the random walker from being trapped in dead-ends [48].

Selection of seeds for RWR based on a hypothesis- and data-driven approach

To select seed nodes for the analysis, we implemented two approaches: (1) a hypothesis-driven approach where we selected seeds based on their impact on disease severity to test the hypothesis of their differential associations with mild, moderate, and severe COVID-19 disease states**,** and (2) a data-driven approach where we selected, after merging the different co-expression networks, the features with the highest node integrated centrality score in each omics layer as seeds. The hypothesis-driven has the advantage of bringing the question being investigated into focus by designing the model with a specific biological hypothesis in mind and exploring variations across disease phases, whereas the data-driven approach, enables a more unbiased and informed model [50, 51]. Although hypothesis- and data-driven modelling approaches are not mutually exclusive, it is worth noting that this diversity is beneficial: most model-building tools and models have a specific and clear role, however at the same time, combining hypothesis- and data-driven approaches in an interoperable way, provide an immense impact on our understanding of the disease phases as modelling and integrating data at different biological scales [50, 51].

Interleukin-6 (*IL-6*) and interleukin 6 receptor **(***IL-6R*) features were used as hypothesis-driven seeds for the random walk analysis because of the evidence for their significant role in the pathology of SARS-CoV-2 and COVID-19 [52-54]. *IL-6* is a cytokine, a type of signalling molecule involved in various inflammatory and immune responses. The inflammatory response plays a critical role in COVID-19, with an excessive inflammatory response leading to a “cytokine storm” increasing the severity of COVID-19. Since *IL-6* interacts with cells via *IL-6R,* it has been hypothesized that inhibition of *IL-6R* might reduce the likelihood of cytokine storms developing, ameliorate the symptoms of severe COVID-19, and reduce mortality [49]. In this context, we, therefore, used *IL-6* and *IL-6R* as hypothesis-driven seeds in a RWR analysis that we refer to as our “hypothesis-driven approach”.

For a random walk with restart using data-driven seeds, we selected seeds following the approach described in our previous study [42]. Specifically, we selected, after merging the different co-expression networks, the features with the highest integrated centrality score in each omics layer [42]. The features were ranked by leveraging the

node degree, closeness, betweenness, and eigenvector centrality metrics to compute an integrated score (see **Supplementary data equation 1**). These centrality metrics provide insight into the importance of a node. For instance, the closeness metric measures how close a node is to all other nodes in the network. A lower closeness centrality score indicates the node is on average closer to other nodes, potentially making it a faster "information hub." The degree metric measures the number of connections (edges) a node has with other nodes. A higher degree signifies the node has more direct connections, suggesting it might be more influential or receive more information flow. The betweenness metric captures how often a node lies on the shortest path between other pairs of nodes in the network. A higher betweenness score suggests the node acts as a crucial bridge for information flow within the network. The eigenvector metric considers goes beyond the number of connections and considers the "importance" of a node's neighbours. Nodes with high eigenvector centrality are considered influential due to their connections to other influential nodes. By integrating these diverse perspectives, the calculated score provides a comprehensive understanding of a node's relative importance within the network structure and its potential role in information flow and communication. Herein, RWR analysis using the data-driven seeds is referred to as our “data-driven approach”.

Ranking candidate drugs for COVID-19 disease states

The RWR approach has the benefit of capturing the global topology of a graph and representing a measure of proximity from all the nodes to the seed(s) based on the graph topology [55]. The measure of proximity between nodes is a relevant measure quantifying how closely connected a node is with the seeds and can be used to rank nodes [48, 55, 56]. In this study, nodes within each layer were ranked based on their measure of proximity to the seed nodes. The measure of proximity was the geometric mean of the node’s proximity to the seeds [48].

Results

Predicting candidate drugs using existing knowledge graphs and hypothesis-driven seeds.

To predict potential COVID-19 drugs, we systematically analysed the DRKG and COVID-19 KG excluding disease-state specific omics-graphs by implementing a random walk with restart analysis (**Materials and Methods**). The random walk with restart is an approach that allows for the exploration of the disease-state specific omics-graphs, COVID-19 KG, and DRKG to identify patterns and prioritize features within the network. The algorithm, multiXrank, conducts multiple random walks over the graphs, each originating from the seed nodes. These walks iteratively traverse from one node to a neighbouring node at random, thus simulating a pattern that results in a multi-layered graph. In our hypothesis-driven approach, we selected, *IL-6* and *IL-6R* as seeds given their established roles as aggravators of the disease. The random walk process restricts the restarts from seed nodes (*IL-6* and *IL-6R)* during network exploration. The RWR analysis revealed a multi-layered graph describing the random walks from the seed nodes (**Figure 2**) and a set of potential therapeutics (**Table 3**) for the treatment of COVID-19. These included immunosuppressants, vital minerals, anticancer agents, antivirals, antibiotics, angiotensin receptor blockers, and corticosteroids (as detailed in **Table 3**). Notable among these are presently recommended drugs for treating the disease such as tocilizumab [22, 57, 58], dexamethasone [13, 14], and losartan [59, 60]. Furthermore, our analysis pinpointed additional potential pharmaceutical options, such as *cannabidol* and *doxorubicin* [61-63]. While these have yet to be definitively endorsed for COVID-19 treatment, prior research indicates their potential candidacy based on their efficacy and merits for further experimental validations [61, 64]. **Figure 2** shows a multi-layered graph generated from the RWR analysis highlighting interactions involving highly ranked drug candidates and other features such as *IL2, IL1B, HCK,* and *TYK2*.

Predicting candidate drugs using existing knowledge graphs, disease-state specific omics-graphs, and hypothesis-driven seeds

To discover potential candidate drugs that could be used to specifically treat the disease in either its mild, moderate, or severe phases, we employed the RWR method in a network-based approach utilizing the knowledge graphs (DRKG and COVID-19

KG), alongside the disease-state specific omics-graphs encompassing transcriptomics, proteomics, metabolomics, and lipidomics data (**Materials and Methods**). The outcome of the RWR analysis is a ranked list of potential drugs and a multi-layered graph describing the random walks from the seed nodes (*IL-6* and *IL-6R*). Across different analyses of the mild, moderate, and severe disease states we consistently identified the same sets of drugs (**Table 4**) that could potentially be impactful during COVID-19 treatment. Notably, our analysis revealed that drugs known to suppress the immune response and reduce inflammation, including those promoting interleukin-6 (IL-6) production, consistently ranked high across all investigated disease states (**Table 4**). This observation aligns with expectations, considering our choice of *IL-6* and *IL-6R* as seeds: both are pivotal biomarkers identified in multiple studies as displaying expression levels that are positively associated with severe disease states [65, 66]. These biomarkers are prominently expressed during cytokine storms that are characteristic of severe COVID-19 cases [66].

We observed differences between the multi-layered graphs generated by the RWR analysis on the mild, moderate, and severe disease states**.** Specifically, these differences were observed in the levels of connectivity between molecular features and the drug repurposing candidates. We therefore performed network topology analysis on the multi-layered graphs generated from the RWR analysis to explore the differences between these graphs and how that can provide more insights into the use of predicted drugs across mild, moderate, and severe disease states. First, we evaluated the degree, betweenness, and closeness measures of the drug repurposing candidates and observed relatively similar scores (**Table 5**). The node degree indicates the number of connections a drug has, revealing its involvement in broader disease processes. Higher degrees might suggest broader applicability across multiple diseases. The betweenness centrality measures a drug's "traffic control" role, indicating how often it lies on the shortest paths between other nodes. High betweenness suggests a potential "bridge" molecule connecting different disease pathways. The closeness centrality reflects how quickly information can reach other disease elements or nodes from a candidate drug. High closeness suggests a central position within the disease network, potentially making it a good starting point for treatment. For instance, cyclosporine had a higher degree of 6 in the multi-layered graph generated by RWR analysis on the moderate disease state as compared degree

of 5 in the multi-layered graph generated by RWR analysis on the mild disease state and a degree of 4 in the multi-layered graph generated by RWR analysis on the severe disease state with a corresponding high betweenness score of 0.0014 and closeness score of 0.4832 suggesting it might have potential utility for moderate disease state. Similarly, mycophenolic acid had a higher degree of 5 in the multi-layered graph generated by RWR for moderate disease state as compared to a degree of 4 in both multi-layered graph generated by RWR analysis on the mild and multi-layered graph generated by RWR analysis on the severe disease state with a corresponding high betweenness score of 0.009 and closeness score of 0.4739 also suggests it might have potential utility for moderate disease state.

Next, we evaluated the contribution of other molecular features in the networks. To begin with, beyond the central influence of top-ranked drugs (*dexamethasone, tocilizumab,* and *sarilumab*) in the multi-layered graph generated from the RWR analysis on the mild disease state (**Figure 3A**), three key inflammatory-related features: C-C Motif Chemokine Ligand 2 (*CCL2*), C-C Motif Chemokine Ligand 4 (*CCL4*), and Negative Elongation Factor Complex Member C/D (*NELFCD*) formed distinct subnetworks, acting as crucial hubs that connected seed nodes and promising candidates for drug repurposing. In mild COVID-19 cases, *CCL2* helps recruit monocytes and macrophages, which are essential for fighting the virus as compared to excessive immune cell recruitment in severe disease states [67, 68]. Also, *CCL4* levels in mild disease states help recruit necessary immune cells to fight the virus [69]. Thus, using drug repurposing candidates that could influence the recruitment of immune cells in mild disease states could be more appropriate, acknowledging the fact that the development of clinical COVID-19 involves cell activation such as dysfunctional mast cell activation [70]. From the predicted drugs, histamine is a biogenic amine known to attract and activate immune cells, particularly mast cells, basophils, neutrophils, and certain T cells, through specific histamine receptors [71]. Histamine can stimulate mast cell degranulation, leading to the release of *CCL4* and *CCL2* among other inflammatory mediators [72, 73]. This suggests a potential indirect link between histamine and these chemokines in inflammatory processes. Paclitaxel is known to modulate the immune system in various ways, including; (1) promoting the migration of T cells and other immune cells into tumours, (2) enhancing the activity of antigen-presenting cells, vital for activating T cells, and (3) modulating the expression

of immune-related genes that influence inflammation and immune responses. Paclitaxel induces the release of cytokines like *TNF*, and *IL-6* and chemokines like *CCL2*, and might, therefore, help control viral infection by stimulating immune cell recruitment and boosting immune responses [74]. Metformin might enhance the activity of certain immune cells like macrophages and natural killer cells potentially aiding in viral clearance [75, 76]. Metformin activates AMPK, a cellular energy sensor that regulates various metabolic and inflammatory processes [77]. AMPK activation can downregulate pro-inflammatory signalling pathways and reduce the production of inflammatory mediators like *TNF* and *IL-6* [78].
The *NELFCD*, as part of NELF, regulates RNA polymerase II pausing, potentially influencing viral RNA synthesis during viral genome replication [79]. This suggests that drugs with the potential to inhibit SARS-CoV-2 replication could be appropriate for repurposing. Such drugs would include, for example, dactinomycin which is, besides having immune-modulatory properties also inhibits viral genome replication [80, 81].

Analysis of the multi-layered graph generated by the RWR analysis during predictions for moderate disease state identified *NELFCD*, Nuclear Factor Kappa B Subunit 1 (*NFKB1*), and interleukin 10 (*IL-10*) as hubs influencing the network based on their high connectivity, forming both direct and indirect pathways between the seed nodes and the top candidates for drug repurposing **(Figure 3B)**. *NFKB1* activates genes encoding pro-inflammatory cytokines, chemokines, and adhesion molecules, orchestrating the body's initial response to viral infection and enhancing the severity of COVID-19 symptoms [82, 83]. Thus, moderating *NFKB1* activity could mitigate cytokine storms and improve outcomes. Corticosteroids like *dexamethasone* can be used in severe COVID-19 to suppress *NFKB1* activity and reduce inflammation. It is, however, important to note that while dampening *NFKB1* can be beneficial, completely suppressing it could impair the body's ability to fight the virus. Thus, finding the right balance remains crucial. *IL-10* is a natural anti-inflammatory cytokine, acting as a brake on the immune response. It helps control excessive inflammation, as disease severity progresses, particularly in moderate disease states, to prevent tissue damage. However, overactive *IL-10* production in moderate COVID-19 cases can dampen the immune system's ability to fight the virus, potentially prolonging the infection and allowing persistent viral replication. From our results (**Figure 3B**), drugs with the potential to modulate *IL-10* activity could be beneficial during moderate

disease states to balance the suppression of excessive inflammation with optimal immune functioning. For instance, *sirolimus* inhibits the mammalian target of the rapamycin (mTOR) pathway, which can indirectly suppress *IL-10* production by limiting *STAT3* signalling [84, 85]. Also, it can dampen the activation of certain immune cells like T cells, which may indirectly decrease *IL-10* production. Additionally, *sirolimus* promotes the differentiation and expansion of regulatory T cells (Tregs), a subset of T cells that naturally suppress inflammation and can promote *IL-10* production as part of their suppressive function [86].

In the multi-layered graph generated by the RWR analysis during predictions for severe disease state **(Figure 3C),** we observed key inflammation-related features like C-X-C Motif Chemokine ligand 1 (*CXCL1*), C-C Motif Chemokine ligands 4 (*CCL4*), and Janus Kinase 2 (*JAK2*) to establish subnetworks which included both direct and indirect interactions with the seed nodes and top-ranked drug candidates **(Figure 3C).** *JAK2*, a signalling molecule inside immune cells, expresses both inflammatory and anti-inflammatory effects during COVID-19. For its inflammatory role, *JAK2* activates certain signalling pathways including Janus kinase 2/signal transducer and activator of transcription 3 (*JAK2/STAT3*) pathway that trigger inflammatory responses in the lungs, which may help fight viral infections [87]. In its anti-inflammatory role, *JAK2* also activates pathways promoting tissue repair and regeneration. Thus, drug repurposing candidates with the potential to influence *JAK2* signalling, may represent an effective therapeutic strategy for controlling the disease [88]. For instance, *IL-6* binds to soluble and transmembrane *IL-6R* and the resultant complex induces homodimerization of gp130, leading to activation of JAK2 [89]. This suggests that *sarilumab* and *tocilizumab* targeting the *IL-6* receptor, indirectly activate *JAK2* downstream by limiting the IL-6-mediated signalling pathway [89, 90]. *Sirolimus* targeting a mTOR pathway connected to *JAK2* can be appropriate. Increased levels of *CXCL1* and *CCL4* have been associated with severe disease and hyperinflammatory states, suggesting a potential role in COVID-19 disease progression [68, 91]. In general, the drug repurposing candidates (**Table 4**) with anti-inflammatory activities, immunomodulatory activities, and viral replication inhibitory activities have the best potential to manage excessive inflammation and limit viral persistence during the severe disease state. We further observed from shortest path analysis how these molecular features act as mediators

connecting the drug repurposing candidates to the seed nodes across mild, moderate, and severe disease states (**Supplementary File 4**).

Predicting candidate drugs using existing knowledge graphs, disease-state specific omics-graphs, and data-driven seeds

To investigate the prediction of drugs that might be differentially applicable to treating different COVID-19 disease states, we used a data-driven approach to identify seeds by computing an integrated node centrality metric score leveraging the node degree, closeness, betweenness, and eigenvector centrality metrics (**see Materials and Methods**).

In the transcriptomics layer, we identified *Signal Transducer And Activator Of Transcription 1* (*STAT1*) as a seed node. *STAT1* is known to be involved in immune responses and antiviral activity [68] and is reported to be upregulated in mild and severe COVID-19 cases, with the phosphorylation of the gene associated with both the upregulation of *ACE2* expression and the development of severe disease states [92, 93]. In the proteomic layer, *Superoxide Dismutase 2* (*SOD2*) was identified as a seed node. *SOD2* is an essential antioxidant enzyme that protects cells from superoxide radical anions which are known to be significantly under-expressed in the plasma [94] and lung cells of severe COVID-19 patients [95]. In the metabolomics layer, *3-hydroxyoctanoate* was identified as a seed node. This metabolite is generated during medium-chain fatty acid oxidation and serves as a marker for primary defects in beta-hydroxy fatty acid metabolism. It is also affiliated with essential pathways such as those responsible for macrophage activation and platelet aggregation, with increases in 3-hydroxyoctanoate concentrations being associated with asymptomatic COVID-19 infections [96]. In the lipidomics layer, we identified "*unknown_mz_815.61548_+_RT_27.063"*, an uncharacterized lipid associated with disease severity as a seed node.

Using these seed nodes for RWR analysis across the various disease states, we identified several potential drug repurposing candidates (**Table 6**) including "natural compounds" (such as *glutathione* and *curcumin*) and inhibitors of signal transduction pathways of protein kinases and cell proliferation (tyrosine, histone deacetylase, and

methyltransferase). The results revealed the same drug repurposing candidates across the various disease states (**Table 6**). However, network topology analysis revealed differences between the multi-layered graphs generated by the RWR analysis (**Figure 4A-C**). Specifically, these differences were observed in the connectivity of the drug repurposing candidates with corresponding node degree, betweenness centrality, and closeness centrality scores (**Table 7**). This provides more insights into the most appropriate drug repurposing candidates for the different disease states. For instance, *curcumin* had a higher degree of 1,076 in the multi-layered graph generated by the RWR analysis on mild disease state as compared to a degree of 4 in the multi-layered graph generated by the RWR analysis on moderate disease state and a degree of 2 in the multi-layered graphs generated by the RWR analysis on severe disease state. *Podofilox* had a higher degree of 478 in the multi-layered graph generated by the RWR analysis on severe disease state as compared to a degree of 2 for both multi-layered graphs generated by the RWR analysis on mild and moderate disease states. Therefore, whereas *curcumin* is an appropriate drug repurposing candidate with potential utility during mild COVID-19, *podofilox* is an appropriate drug repurposing candidate with potential utility during severe COVID-19. Furthermore, *vinblastine's* high degree of 1,905 in the multi-layered graph generated by the RWR analysis on moderate disease state and a degree of 1,378 in the multi-layered graph generated by the RWR analysis on severe disease state as compared to a degree of 4 in the multi-layered graph from the RWR analysis on mild disease state. This suggests that *vinblastine* might be most effective in tackling advanced disease stages. Also, *crizotinib's* high degree of 1,919 in the multi-layered graph generated by the RWR analysis on mild disease state and a degree of 1,947 in the multi-layered graph generated by the RWR analysis on moderate state as compared to a degree of 2 in the multi-layered graph from the RWR analysis on severe disease state indicates it might be most appropriate for treatment of the mild and moderate stages of COVID-19 (**Table 7**). Similarly, *glutathione's* high degree of 212 in the multi-layered graph generated by the RWR analysis on mild disease state and a degree of 234 in the multi-layered graph generated by the RWR analysis on moderate disease state as compared to a degree of 118 in the multi-layered graph from the RWR analysis on severe disease state suggests it can be a promising drug repurposing candidate for the mild and moderate disease states. Noticeably, nodes with higher degree scores (**Table 7**) have higher betweenness and closeness scores revealing

how often these nodes lie on the shortest paths between other nodes in the network and mediate how quickly information can reach other disease-related features from a candidate drug (**Supplementary File 5**). Such nodes have high relevance within biological systems and, besides their specific biological activities, might also facilitate communication and synergy between biological pathways, making them key targets for the management of the disease.

Analysis of the multi-layered graphs generated by the RWR analysis revealed several features that establish subnetworks (**Figure 4**). Specifically, we observed the *CCL4* to establish subnetwork in the mild disease state and Hepatocyte Growth Factor (*HGF*) to establish subnetworks in both moderate and severe disease states. *HGF* expresses anti-inflammatory properties and plays a complex and multifaceted role in the battle against COVID-19 [97]. While it initially acts as a crucial player in lung tissue repair following viral damage, its activity can also contribute to excessive inflammation if not properly regulated [97]. *HGF* can activate certain signalling pathways that promote inflammation in moderate to severe cases. On the other hand, up-regulation of *HGF* represents a robust counter-regulatory mechanism employed by the host immune response to counteract pro-inflammatory cytokines.

Drug prediction robustness analysis

The three highest-ranked candidate drugs yielded by both the hypothesis-driven approach (*dexamethasone, sarilumab, tocilizumab*) and the data-driven approach (*glutathione, crizotinib*, and *curcumin*) are all known to be efficacious in controlling moderate to severe COVID-19. However, the high rankings of these drugs (based on measures of proximity) are expected simply because their efficacy during moderate to severe COVID-19 treatment has been comprehensively reported on in the literature up to 2021. These reports are reflected in the COVID-19 KG layers of our networks.
In this section, we removed direct interactions between the top three predicted potential drug candidates identified using the hypothesis-driven and data-driven approaches, and other features (such as drugs, proteins, and transcripts) to assess the influence of these interactions and features on the drug predictions. We assessed the robustness of the drug predictions in both the hypothesis-driven and data-driven approaches by repeating the RWR analysis (as described in the materials and

methods) after individually and collectively removing direct interactions associated with the three highest-ranked candidate drugs and examining changes in the drug rankings.

These analyses yielded a relatively consistent trend (**Supplementary Files 1** and **2**): drugs such as *sirolimus*, *histamine*, *cyclosporine,* and *vorinostat* that initially ranked below the drugs that were removed tended to achieve higher rankings following the removal of the initial top-ranked drug candidates. The measure of proximity of the drugs that attained elevated rankings varied from one drug removal experiment to the next, but generally increased relative to the measure of proximity that the drugs obtained in the absence of any exclusions (**Supplementary Files 1** and **2**).
Further, the drug removal analyses revealed additional candidate drugs that were not apparent in the absence of drug removal. For instance, with the hypothesis-driven approach, when we removed *dexamethasone* and *tocilizumab* simultaneously for each disease state, drugs like *dinoprostone*, and *perhexiline* emerged among the top drug candidates across the mild, moderate, and severe disease states (**Supplementary File 1**). Similarly, when we removed sarilumab, we observed *ketamine, acetylsalicylic acid* (aspirin), and *menadione* in the top 20. Concurring with the individual drug removal, when *dexamethasone, tocilizumab*, and *sarilumab* were collectively removed, we observed *dinoprostone*, *perhexiline*, *menadione*, iron, and *ketamine* all entered the top 20 for the disease states.

When we excluded the top-ranked drug candidates that were revealed by the data-driven approach (*glutathione, crizotinib,* and *curcumin*) we observed similar ranking score changes to those seen with the drug candidates identified by the hypothesis-driven approach. For example, when *glutathione* was removed, the measure of proximity of both *lL-glutamine* and *carglumic acid* dropped substantially (from 0.0000945 and 0.0000942 to 0.0000022 and 0.0000594) resulting in lower rankings whereas thimerosal disappeared completely (**Supplementary File 2**). This observation could be partly because (1) *thimerosal* interacted with nodes that established connections with *glutathione* and *crizotinib*, and (2) *thimerosal* established direct interactions with *glutathione* and *crizotinib*.
When *glutathione, crizotinib*, and *curcumin* were collectively removed, several notable drug candidates surfaced among the top hits, including *penicillamine, pregabalin,*

dexamethasone, *midostaurin,* and *treprostinil* (**Supplementary File 2**). Similar to when *crizotinib* and *curcumin* were individually removed, the measure of proximity of *l-glutamine* and *carglumic acid* increased from 0.0000945 and 0.0000942 to 0.0001621 and 0.0001629 for *crizotinib* removal, and from 0.0000945 and 0.0000942 to 0.0001306 and 0.0001308 for *curcumin* removal respectively (**Supplementary File 2**).

In silico validation of top hit candidate drugs

To validate the COVID-19 drug predictions, we aimed to investigate how enriched the potential candidate drugs are as anti-COVID drugs in other databases. Specifically, we conducted RWR analyses using hypothesis-driven seeds on drug data extracted from DrugCombDB (version 2.0), a drug resource database [98]. We implemented these analyses to investigate whether we were able to predict known efficacious COVID-19 drugs (**Table 4**). Among the top-ranked drugs (**Supplementary File 3**) revealed by these analyses were *dexamethasone* (rank 1), *simvastatin* (rank 7), *cyclosporine* (rank 8), *hydrocortisone* (rank 9), *paclitaxel* (rank 11), *indomethacin* (rank 15), and *methotrexate* (rank 16).

Discussion

In this work, we employed computational analyses for the prediction of drug repurposing candidates tailored for disease-state-specific COVID-19 treatment. Leveraging a combination of knowledge graphs (DRKG and COVID-19 KG), along with COVID-19 disease-phase specific omics-graphs generated from experimental proteomics, transcriptomics, metabolomics, and lipidomics data, enabled the identification of various drug repurposing candidates that could potentially be useable as treatments for specific COVID-19 disease states. We implemented multiXrank, a random walk algorithm capable of handling multiple multi-layered graphs and integrated drug data to predict candidate drugs for the mild, moderate, and severe COVID-19 disease states. The analysis resulted in the generation of multi-layered graphs that described the exploration of seed nodes across different disease-state specific omics-graphs.

Although the hypothesis-driven and data-driven methodologies differed, the findings from both approaches have contributed to prioritizing potential drug repurposing candidates for mild, moderate, and severe COVID-19. The hypothesis-driven approach revealed mostly drugs known to suppress the immune response and reduce inflammation, including those promoting interleukin-6 (*IL-6*) production. In contrast, the data-driven approach revealed more diverse drugs including "natural compounds" (such as *glutathione* and *curcumin*) and inhibitors of signal transduction pathways of protein kinases and cell proliferation (tyrosine, histone deacetylase, and methyltransferase). The random walk analysis using both the hypothesis-driven and data-driven approaches yielded distinct multi-layered graphs (**Figure 3 and Figure 4**) characterized by different hubs and interactions with the candidate drugs, highlighting the unique perspectives offered by each method. With these differences, a consistent finding emerged from both approaches: cross-layer interactions between omics features and drug repurposing candidates play a role in the dynamics of the drugs at the different disease states.

Some of the drugs identified through both hypothesis-driven and data-driven approaches are being or have already been, tested in various clinical trials to assess their efficacy and effectiveness in the treatment of COVID-19. For instance, from the hypothesis-driven approach, corticosteroids such as *dexamethasone* and *hydrocortisone* have demonstrated an association with lower 28-day all-cause mortality in critically ill patients with COVID-19 [99]. Also, *mycophenolic acid* which has been investigated and validated to reduce mortality and hospital stays in patients with moderate to severe COVID-19 [100], and *indomethacin* which has been found in clinical trials to be safe and effective for treating mild and moderate COVID-19 cases [64], and the diabetes medication, *metformin*, which exhibits potential in reducing prolonged illness by inhibiting virus replication when administered during the acute phase of COVID-19 [101]. From the data-driven approach antihelminthic drug *mebendazole*, enhanced innate immune responses and restored inflammation to normal levels in symptomatic non-hospitalized COVID-19 patients during a recent clinical trial [102]. Also, *etoposide* has been investigated for its potential to treat severe disease, albeit with observed adverse events that warrant further investigation [103].

In general, immunosuppressive drugs might have a beneficial effect in the moderate to severe phase of COVID-19 because it is in this phase when dysregulated pro-inflammatory immune responses can precipitate tissue damage and result in acute respiratory distress syndrome, organ failure, and mortality [104]. On the other hand, drugs predicted using the data-driven approach either had antioxidant properties (such as glutathione, and curcumin), or were inhibitors of tyrosine kinase, histone deacetylase, methyltransferase, and protein synthesis (**Table 6**). The antioxidants can protect immune system cells and those directly targeted by SARS-CoV-2 from oxidative stress. For example, *glutathione* is an antioxidant assumed to have a vital role in maintaining the balance of reactive oxygen species (ROS), and aids in diverse cellular processes including immune responses [105, 106]. Notably, oxidative stress reflects an imbalance between ROS generation and antioxidation mechanisms [107] and plays an important role in COVID-19 onset, progression, and severity [108-110], possibly by exacerbating inflammation and tissue damage [111]. This therefore suggests that *glutathione'*s capability to counteract ROS and diminish oxidative stress holds promise for mitigating some of the adverse effects inflicted by the virus [105]. *Glutathione* and *SOD2* bring unique strengths such that their combined efforts provide a multi-layered defence against oxidative stress and its harmful consequences. By neutralizing superoxide radicals, *SOD2* sets the stage for glutathione to efficiently handle other free radicals and detoxify the cell. Also, given the aggressive inflammatory response and the production of cytokines occurring during severe COVID-19 disease states, some known inhibitors of receptor tyrosine kinases and cell proliferation, such as *crizotinib* and *vorinostat*, have been investigated as COVID-19 treatments [112, 113]. For instance, a recent study has shown that histone deacetylase inhibitors modulate immune responses in stimulated monocytes [113], whereas tyrosine kinase inhibitors have the potential to reverse pulmonary insufficiency because of their anti-inflammatory activities, cytokine suppression activities, or antifibrotic activities [112].

Overall, the prioritized drug repurposing candidates (**Table 3, Table 4,** and **Table 6**) exhibit the potential to target a multitude of specific biological pathways and gene ontology processes that are associated with COVID-19 outcomes. Among these candidates are those that have shown promise in treating other diseases or conditions such as cancer, malaria, viral infections, and obstructive pulmonary disease. For

instance, *glutathione* shows activity against HIV, influenza A, and hepatitis C by inhibiting viral replication and modulating immune response [114]. *Curcumin* shows activity against HIV, influenza A, hepatitis C, and Dengue virus by inhibiting viral entry and replication [115]. *Vorinostat* shows activity against HIV by inhibiting viral replication and disrupting HIV-1 latency in patients on antiretroviral therapy [116]. Consequently, there is the possibility of repurposing these to combat COVID-19 and other virus-induced conditions.

The approach implemented in this study is relevant to identifying drugs that warrant further exploration. It is important to mention that some of the drugs that were highly ranked in our hypothesis-driven and data-driven analyses as potential COVID-19 treatments have not, to our knowledge, been tested before in the context of COVID-19 treatment. These included *podofilox*, *calcipotriol*, *vinblastine*, *etoposide*, and *carglumic acid* identified from the data-driven approach, and *paclitaxel* identified from the hypothesis-driven approach. The shortest path analysis revealed molecular features that were close to the drugs (**Supplementary Files 4** and **5**). Considering the drugs generated from the data-driven approach, *podofilox* for example inhibits topoisomerase I by stabilizing the covalent complex formed between the enzyme and a broken DNA strand [117]. This prevents religation, causing DNA damage and eventually cell death [117]. *Podofilox* is known to down-regulate SOD2 expression in cancer cells and indirectly modulate *SOD2* activity, impacting reactive oxygen species levels and influencing cell survival and death. The reactive oxygen species' impact on COVID-19 progression [108-110] suggests that *podofilox* may have a potential role in COVID-19 treatment. Also, *etoposide* possesses an immunosuppressive effect. While suppressing certain immune cells, *etoposide* may also selectively eliminate abnormal or activated T cells involved in the inflammatory process [118]. This can be beneficial in some inflammatory conditions, potentially mitigating immune-mediated damage. Additionally, *etoposide* has the potential to influence the production of certain cytokines and signalling molecules involved in immune communication [119]. In the context of COVID-19, this could have both pro-inflammatory and anti-inflammatory effects. *Vinblastine* can modulate the production of certain cytokines, signalling molecules that orchestrate immune responses [120].

Furthermore, the analysis conducted indicated that ritonavir, an HIV protease inhibitor utilized in combination with nirmatrelvir in the potent COVID-19 treatment paxlovid, was assigned a lower ranking in our data-driven analysis. This may be attributed to the characteristics of the exploited knowledge graphs that contained limited information about the impacts of *ritonavir* on the transcriptomics, proteomics, lipidomics, and metabolomics of human cells. As a result, the topology of the networks that we used was biased in favour of ranking better-researched compounds like *dexamethasone* and *tocilizumab*. In our analysis, we did not identify *nirmatrelvir* among the ranked drug candidates either. This observation is partly attributed to the choice of seeds for the RWR analyses and also to the fact we focus here on the omics networks from the host because *nirmatrelvir* targets the viral genome, (polyprotein 1ab), and could, therefore, not be captured by the network exploration.

This analysis, drawing on diverse datasets, has provided valuable insights that contribute to ongoing efforts to combat endemic COVID-19 and the long-term health consequences of repeated SARS-CoV-2 infections. While some of the identified drugs have been implemented in disease management, several promising candidates are yet to be investigated for COVID-19 disease treatment. The predictions provide a starting point for further experimental validation and clinical investigations. Ensuring the safety and efficacy of new COVID-19 drugs requires rigorous experimental and clinical testing and validation. *In vitro* analyses and clinical trials must be conducted to determine the cytotoxicity, optimal dosages, administration protocols, and potential interactions with other medications. These experiments would ultimately be needed to provide actual proof that many of the less well-studied drug repurposing candidates that we have identified could indeed be used to effectively treat COVID-19. Importantly, the algorithmic framework implemented in this study can be translated to other diseases to investigate relevant drug repurposing candidates and to explore the dynamics among drugs and multi-omics features in a multi-layered network.

Limitations

Considering the limitations of the DRKG and COVID-19 KG data, which predate large-scale drug evaluations, incorporating more recent drug information is crucial for future studies. While this study identified potential drugs for acute COVID-19 treatment, it

did not address Long COVID or the impact of comorbidities and disease severity. Thus, future investigations should explicitly explore treatment options for Long COVID Furthermore, our drug prediction analysis did not account for COVID-19 comorbidities and recommends further studies to refine drug prediction analysis specific for mild, moderate, or severe COVID-19-infected patients experiencing other infections. To maximize the potential of our approach, future work should incorporate drug synergy analysis. By systematically evaluating how the therapeutic activities of different drugs might combine, we can identify and prioritize the most promising combination therapies for further testing and development in the fight against COVID-19.

Conclusion

This chapter explored an integrative multi-layered network approach to identify drugs for repurposing against COVID-19 disease phases. We analysed multi-omics data (proteomics, transcriptomics, metabolomics, and lipidomics) and drug-related data (drug repurposing knowledge graph and COVID-19 knowledge graph) using RWR technique. Notably, we conducted RWR analyses in both hypothesis-driven and data-driven manners, incorporating information specific to disease severity levels (mild, moderate, severe) via dedicated disease-state specific omics-graphs. Our multi-layered network approach successfully identified potential drug candidates for repurposing against mild, moderate, and severe COVID-19. The incorporation of disease-state specific omics data significantly influenced the predicted drug candidates. Both immune-suppressive and pathway-targeting mechanisms emerged as potential approaches for COVID-19 treatment. To facilitate replication of our approach, we provide a containerized workflow with an expanded readme file at https://github.com/francis-agamah/Network-based-multi-omics-disease-drug-associations_drugs-for-COVID-19-disease-phases. All other data and its supplementary information files generated during this study are included in the github repository.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

The authors have consented for the work to be published.

Availability of data and materials

Data and code

To facilitate replication of our approach, we provide a containerized workflow with an expanded readme file at https://github.com/francis-agamah/Network-based-multi-omics-disease-drug-associations_drugs-for-COVID-19-disease-phases. All other data and its supplementary files generated during this study are included in the github repository.

Funding

This work was partially funded by an LSH HealthHolland grant to the TWOC consortium, a large-scale infrastructure grant from the Dutch Organization of Scientific Research (NWO) to the Netherlands X-omics initiative (184.034.019), and a Horizon2020 research grant from the European Union to the EATRIS-Plus infrastructure project (grant agreement: No 871096).

Authors' contributions

FEA, EC, and PH conceived the study. FEA conducted the data analysis and prepared the first draft. PH, TE, MS, DM, and, EC supervised the work. TE, MS, EC, DM, and PH contributed to the revision of the article. All authors contributed to the article and approved the submitted version.

Acknowledgments

Computations were performed using cloud computing facilities provided by ilifu (https://www.ilifu.ac.za/, South Africa) and High-Performance Computing from CHPC (https://www.chpc.ac.za/).

Supplementary Files

Supplementary data

Supplementary file 1

Supplementary file 2

Supplementary file 3

Supplementary file 4

Supplementary file 5

Figure legends

Figure 1. Diagram illustrating the workflow implemented in this study. The workflow begins with curating multi-omics data and drug data followed by a random walk with restart network analysis using both data-driven and hypothesis-driven approaches. Next, we prioritized and characterized candidate drugs followed by drug prediction robustness analysis. Finally, we concluded the analysis by validating the predicted drug candidates.

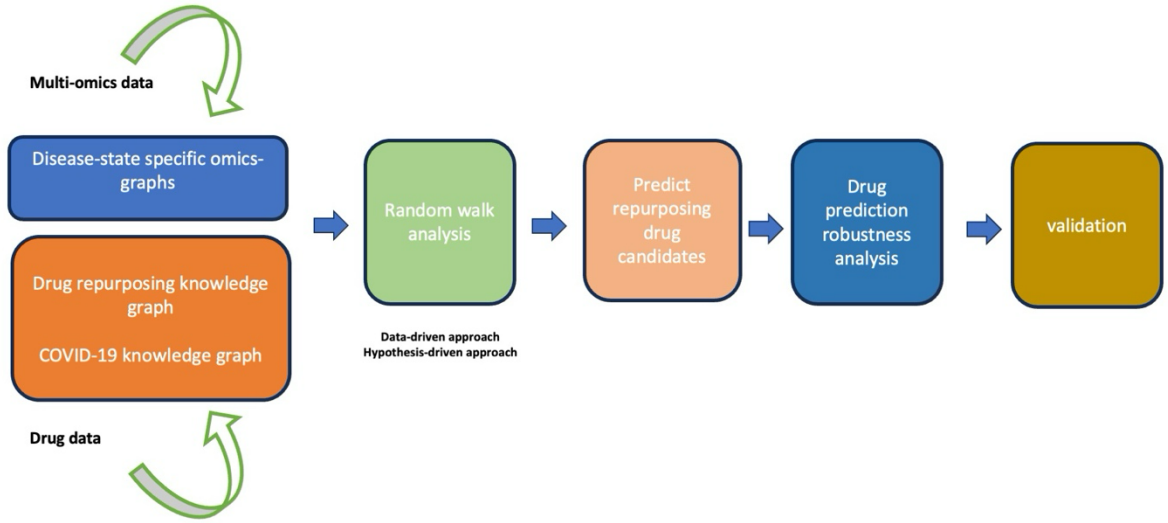

Figure 2. Graph representation of interactions between drugs and other features as observed from predicting candidate drugs using existing knowledge graphs and hypothesis-driven seeds. Blue edges represent interactions between drugs (green nodes). Cyan edges represent interactions between biological processes (pink nodes) and drugs. Red edges represent biological process-proteins (grey nodes) interactions and biological process-transcript (yellow nodes). Black edges represent drug-protein, drug-transcript, protein-transcript, and transcript-transcript interactions. The graphs were generated by defining filtering criteria based on node degree between 4 and 1633 in cytoscape.

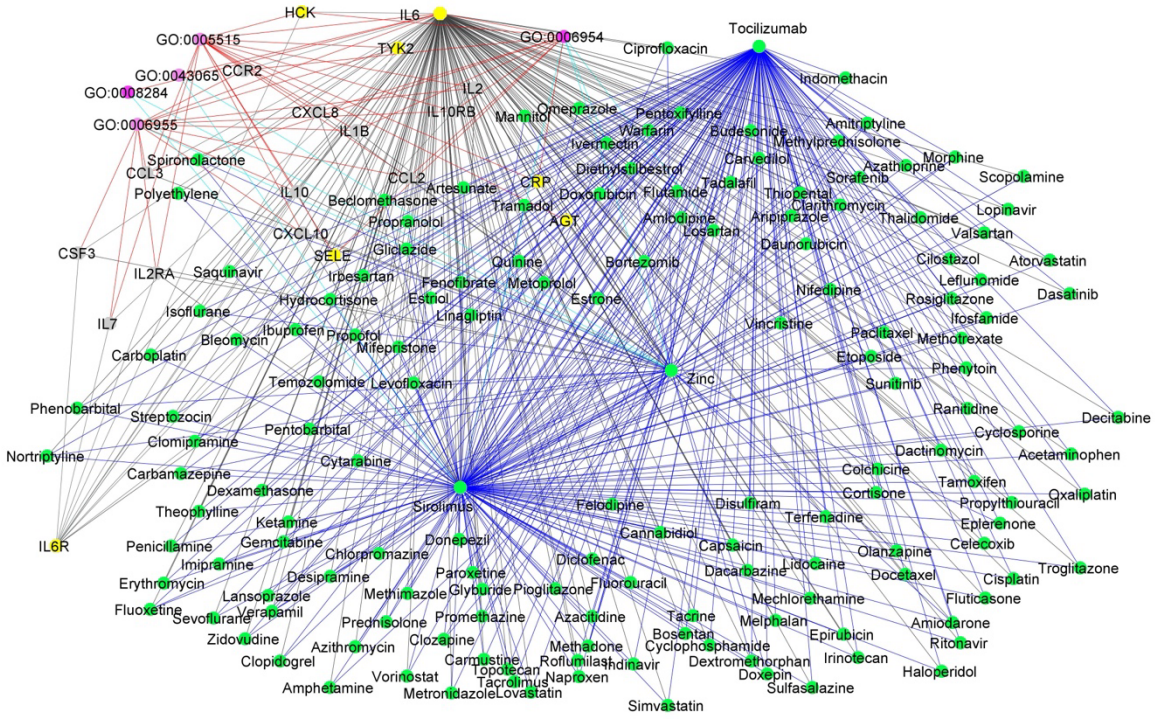

Figure 3. (A) Graph representation of the interaction between drugs (green nodes), proteins (yellow nodes), transcripts (grey nodes), metabolites (red nodes), and biological process (pink nodes) as observed from predicting candidate drugs using existing knowledge graphs, mild disease-state specific omics-graphs, and hypothesis-driven seeds. The graph reveals distinct subnetworks formed by hubs CCL2, CCL4, and NELFCD demonstrating extensive interactions with drug candidates, seed nodes (IL-6 and IL-6R), and other molecular features (B) Graph representation of the interaction between drugs (green nodes), proteins (yellow nodes), transcripts (grey

nodes), metabolites (red nodes), and biological process (pink nodes) as observed from predicting candidate drugs using existing knowledge graphs, moderate disease-state specific omics-graphs, and hypothesis-driven seeds. The graph reveals distinct subnetworks formed by hubs NFKB1, IL-10, and NELFCD demonstrating extensive interactions with drug candidates, seed nodes (IL-6 and IL-6R), and other molecular features (C) Graph representation of the interaction between drugs (green nodes), proteins (yellow nodes), transcripts (grey nodes), metabolites (red nodes), and biological process (pink nodes) as observed from predicting candidate drugs using existing knowledge graphs, severe disease-state specific omics-graphs, and hypothesis-driven seeds. The graph reveals distinct subnetworks formed by hubs CXCL1, CCL4, and JAK2 demonstrating extensive interactions with drug candidates, seed nodes (IL-6 and IL-6R), and other molecular features. Yellow edges represent drug-protein and drug-transcript pairwise interactions. Red edges represent biological process-protein interactions and biological process-transcripts interactions. Green edges represent protein-protein interactions. Black edges represent transcript-transcript interactions and protein-transcript interactions. Blue edges represent drug-drug interactions. Light blue edges represent biological processes-biological process interactions and biological process-pathway interactions. The graphs were generated by defining filtering criteria based on node degree between 4 and 1633 in cytoscape.

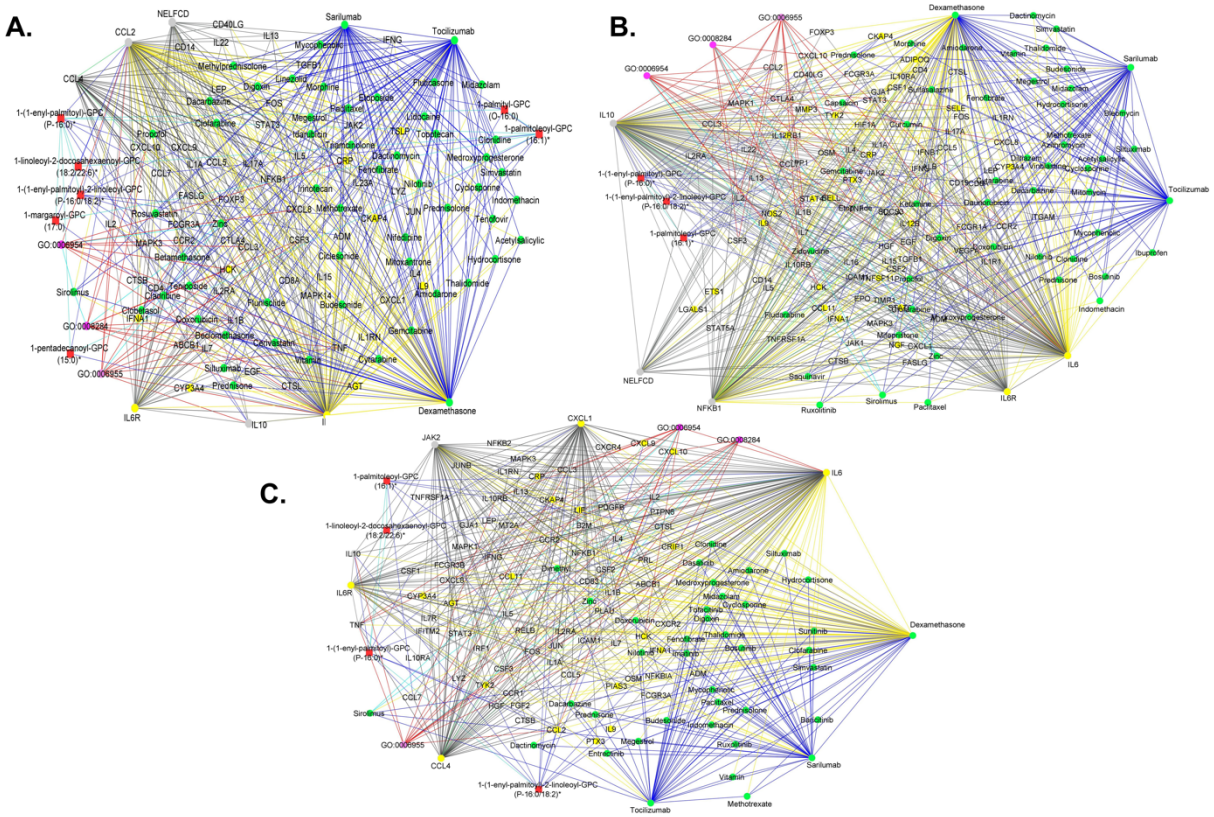

Figure 4. (A) Graph representation of the interaction between drugs (green nodes), proteins (yellow nodes), transcripts (grey nodes), metabolites (red nodes), lipids (blue nodes), and biological processes and pathways (pink nodes) as observed from predicting candidate drugs using existing knowledge graphs, mild disease-state specific omics-graphs, and data-driven seeds. The graph reveals distinct subnetworks formed by hub CCL4, demonstrating extensive interactions with drug candidates and other molecular features including seed nodes (STAT1 and SOD2) (B) Graph representation of the interaction between drugs (green nodes), proteins (yellow nodes), transcripts (grey nodes), metabolites (red nodes), lipids (blue nodes), and biological processes and pathways (pink nodes) as observed from predicting candidate drugs using existing knowledge graphs, moderate disease-state specific omics-graphs, and data-driven seeds. The graph reveals distinct subnetworks formed by hub HGF, demonstrating extensive interactions with drug candidates and other molecular features including seed nodes (STAT1 and SOD2), as well as a subnetwork formed among lipids. (C) Graph representation of the interaction between drugs (green nodes), proteins (yellow nodes), transcripts (grey nodes), metabolites (red nodes), lipids (blue nodes), and biological processes and pathways (pink nodes) as observed from predicting candidate drugs using existing knowledge graphs, severe disease-

state specific omics-graphs, and data-driven seeds. The graph reveals distinct subnetworks formed by hub HGF, demonstrating extensive interactions with drug candidates and other molecular features including seed nodes (STAT1 and SOD2), as well as a subnetwork formed among lipids. Yellow edges represent drug-protein and drug-transcript pairwise interactions. Red edges represent biological process-protein interactions and biological process-transcripts interactions. Pink edges represent pairwise interactions between lipids. Green edges represent protein-protein interactions. Black edges represent transcript-transcript interactions and protein-transcript interactions. Dark blue edges represent drug-drug interactions. Light blue edges represent biological processes-biological process interactions and biological process-pathway interactions. The graphs were generated by defining filtering criteria based on node degree between 4 and 1633 in cytoscape.

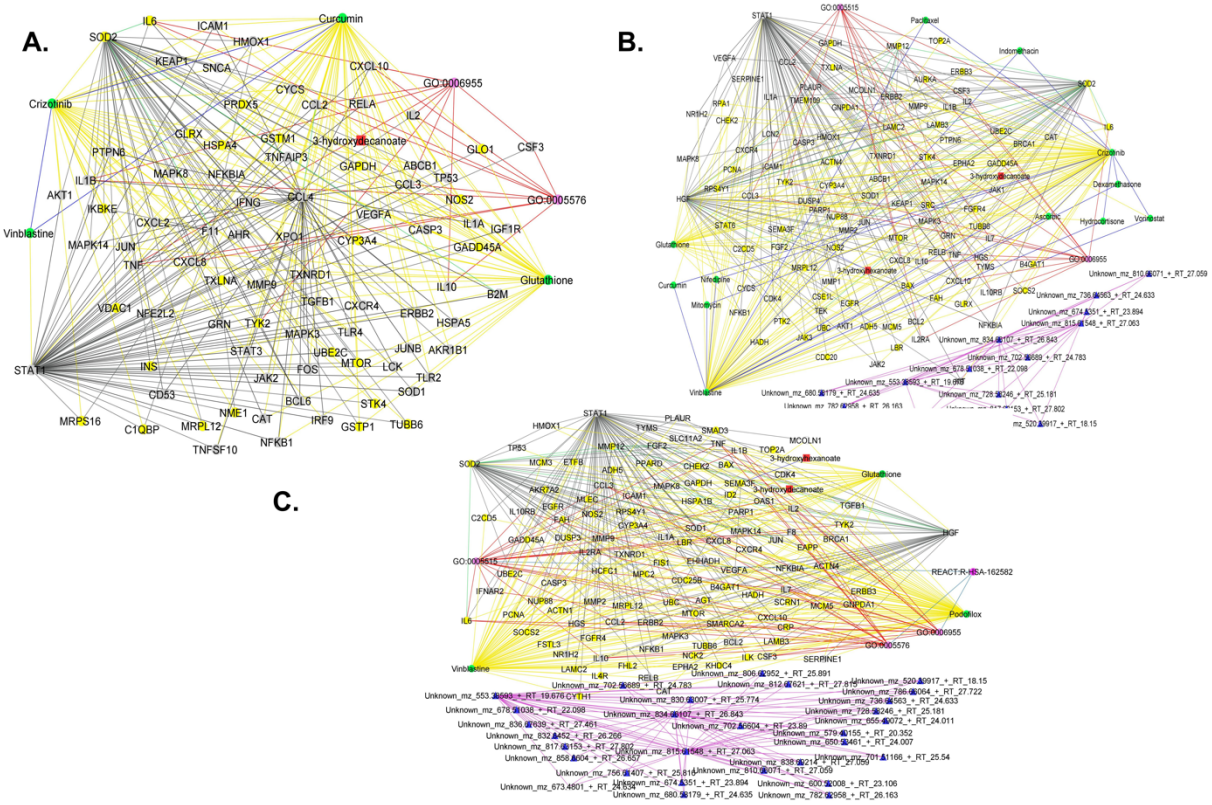

Table legends

Table 1. Description of the node-types in drug repurposing knowledge graph

Node-type	Number of features
Anatomy	400
Anatomical Therapeutic Chemical (Atc)	4048
Biological Process	11381
Cellular Component	1391
Compound	24313
Disease	5103
Gene	39220
Molecular Function	2884
Pathway	1822
Pharmacologic Class	345
Side Effect	5701
Symptom	415
Taxonomy (Tax)	215

Table 2. Description of the node-types in COVID-19 Knowledge Graph

Node-type	Number of features
SARS-CoV-2 baits	23
Host genes and drug targets	10959
Pathways	274
Drugs (chemical/compound)	4266
Biological process (Phenotypes)	1893

Table 3. Top 20 potential COVID-19 drugs, ranked according to their measure of proximity to IL-6 and IL-6R seed nodes as determined through RWR analysis of DRKG and COVID-19 KG. The references point to publications that have reported the drugs' mechanism of action potentially linked with COVID-19.

Drug name	Drug Category	Mechanism of action potentially linked with COVID-19	Measure of proximity	Reference*
Tocilizumab	Interleukin-6 (IL-6) receptor antagonist	Suppresses immune response by blocking IL-6 signalling	0.0353861	[121]
Zinc	Essential mineral / Nutrient	Interferes with viral RNA synthesis to inhibit replication	0.0007941	[122]
Sirolimus	Immunosuppressive drug	Expresses immunomodulatory and anti-inflammatory properties and inhibits the expression of proinflammatory cytokines.	0.0003784	[123, 124]
Choline	Essential nutrient	Supports cell membrane integrity and neurotransmitter function	0.0003440	[125]
Ivermectin	Antiparasitic drug	Inhibits viral replication and modulate the host immune response	0.0003056	[126]
Dactinomycin	Anticancer	Expresses immune modulatory properties and inhibits viral cellular transcription	0.0002734	[80, 81]
Losartan	Angiotensin receptor blocker	Reduce the activity of the renin-angiotensin system	0.0002327	[127]
Ribavirin	Antiviral	Interferes with viral RNA synthesis and replication	0.0002168	[128, 129]
Azithromycin	Antibiotic	Expresses anti-viral and anti-inflammatory properties	0.0002000	[130]
Tenofovir	Antiviral	Interferes with viral RNA synthesis to inhibit replication	0.0001930	[131]
Acetaminophen	Analgesic	Expresses antipyretic and analgesic effects and inhibit the cyclooxygenase (COX) pathways.	0.0001665	[132, 133]
Dexamethasone	Corticosteroid	Suppresses immune response	0.0001633	[99]
Methotrexate	Immunosuppressive drug	Suppresses immune response	0.0001624	
Cyclosporine	Immunosuppressive drug	Express anti-inflammatory and anti-viral properties	0.0001614	[134, 135]
Cisplatin	Anticancer		0.0001555	
Tacrolimus	Immunosuppressive drug	Mitigate the hyperinflammatory response	0.0001532	[136]
Indomethacin	Non-steroidal anti-inflammatory drug	Expresses anti-inflammatory properties and reduces pain and fever	0.0001505	[64, 137]
Cannabidiol	Cannabinoid	Inhibits viral replication by up-regulating the host inositol-requiring enzyme-1α ribonuclease endoplasmic reticulum stress response and interferon signalling pathways	0.0001488	[61]
Doxorubicin	Anticancer	Expresses antiviral and immunomodulatory properties.	0.0001486	[62]
Diclofenac	Non-steroidal anti-inflammatory drug	Expresses anti-inflammatory properties and reduces pain and fever	0.0001481	[137]

Table 4. Top 20 potential drugs for mild, moderate, and severe COVID-19, ranked according to their measure of proximity to IL-6 and IL-6R seed nodes as determined through RWR analysis of COVID-KG, DRKG, and DSOG. The references point to publications that have reported the drugs' mechanism of action potentially linked with COVID-19.

Drug	Drug category	Mechanism of action potentially linked with COVID-19	Measure of proximity in mild	Measure of proximity in moderate	Measure of proximity in severe	Reference*
Dexamethasone	Corticosteroid	Suppresses immune response	0.0033655	0.0033691	0.0033697	[99]
Sarilumab	Anti-interleukin 6 (IL-6) receptor monoclonal antibody	Suppresses immune response by blocking IL-6 signalling	0.0031924	0.0031908	0.0031911	[138]
Tocilizumab	Anti-interleukin 6 (IL-6) receptor monoclonal antibody	Suppresses immune response by blocking IL-6 signalling	0.0031908	0.0031894	0.0031897	[121]
Zinc	Essential mineral / Nutrient	Expresses antiviral properties and interferes with viral RNA synthesis to inhibit replication	0.0002730	0.0002681	0.0002692	[122, 139]
Sirolimus	Immunosuppressive drug	Expresses immunomodulatory and anti-inflammatory properties and inhibits the expression of proinflammatory cytokines.	0.0001524	0.0001526	0.0001530	[123, 124]
Histamine	Depressor amine	Expresses immunomodulatory and anti-inflammatory properties	0.0001420	0.0001413	0.0001416	[140, 141]
Curcumin	Natural compound	Expresses immune modulatory and anti-inflammatory properties that inhibit severe inflammation and cytokine storm.	0.0001366	0.0001358	0.0001363	[142, 143]
Cyclosporine	Immunosuppressive drug	Express anti-inflammatory and anti-viral properties	0.0001352	0.0001370	0.0001369	[134, 135]
Doxorubicin	Anticancer	inhibit the protease-mediated viral entry to the host cell	0.0001314	0.0001316	0.0001318	[62]
Morphine	Opioid pain medication	Contribute to improving respiratory failure	0.0001301	0.0001281	0.0001284	[144]
Dactinomycin	Anticancer	Expresses immune modulatory properties and inhibits viral cellular transcription	0.0001292	0.0001290	0.0001288	[80, 81]
Simvastatin	lipid-lowering drug	Expresses anti-inflammatory, immunomodulatory properties and reduce viral replication	0.0001290	0.0001289	0.0001287	[145, 146]

Hydrocortisone	Corticosteroid	Expresses anti-inflammatory and immunomodulatory properties	0.0001274	0.0001279	0.0001276	[99]
Vitamin C	Essential mineral / Nutrient	Express antioxidant properties and improves immune function	0.0001268	0.0001269	0.0001276	[106]
Mycophenolic acid	Immunosuppressive drug	Expresses immunomodulatory properties	0.0001236	0.0001236	0.0001239	[100]
Methotrexate	Immunosuppressive drug	Expresses immunomodulatory properties	0.0001182	0.0001195	0.0001194	
Dopamine	Catecholamine neurotransmitter	Influences the expression of *ACE2*	0.0001178	0.0001187	0.0001197	[147]
Indomethacin	Non-steroidal anti-inflammatory drug	Expresses anti-inflammatory properties and reduces pain and fever	0.0001170	0.0001165	0.0001162	[64]
Paclitaxel	Anticancer	Express anti-inflammatory and anti-viral properties	0.0001159	0.0001159	0.0001161	
Metformin	Biguanide antihyperglycemic	Inhibits viral replication	0.0001158	0.0001158	0.0001164	[148]

Table 5. Node degree, betweenness, and closeness centrality measures for the drug repurposing candidates predicted using the hypothesis-driven approach.

Drug name	Degree mild	Degree moderate	Degree severe	Betweenness mild	Betweenness moderate	Betweenness severe	Closeness mild	Closeness moderate	Closeness severe
Dexamethasone	1633	1632	1633	0.6282	0.5881	0.6293	0.6355	0.6233	0.6228
Tocilizumab	830	829	830	0.11436	0.1008	0.1103	0.4643	0.4482	0.4571
Sarilumab	469	469	469	0.0286	0.0246	0.0283	0.4432	0.4289	0.4373
Sirolimus	7	8	6	0.0063	0.0068	0.0054	0.4831	0.4889	0.4512
Vitamin C	6	6	4	0.0047	0.0034	0.0004	0.4860	0.4525	0.4460
Cyclosporine	5	6	4	0.0007	0.0014	0.0004	0.4769	0.4832	0.4460
Dactinomycin	5	4	4	0.0007	0.0003	0.0004	0.4769	0.4367	0.4460
Paclitaxel	5	5	4	0.0007	0.0009	0.0004	0.4769	0.4739	0.4460
Simvastatin	5	5	4	0.0007	0.0009	0.0004	0.4769	0.4739	0.4460
Hydrocortisone	4	5	4	0.0004	0.0007	0.0004.	0.4528	0.4454	0.4460
Zinc	4	5	4	0.0005	0.0011	0.0005.	0.3652	0.3903	0.3637
Indomethacin	4	5	4	0.0004	0.0009	0.0004	0.4528	0.4739	0.4460
Mycophenolic acid	4	5	4	0.0004	0.0009	0.0004	0.4528	0.4739	0.4460
Doxorubicin	4	5	4	0.0004	0.0009	0.0004	0.4528	0.4739	0.4460
Methotrexate	4	5	4	0.0004	0.0007	0.0004	0.4528	0.4454	0.4460
Morphine	4	4	3	0.0005	0.0007	0.0003	0.4768	0.4738	0.4459
Curcumin	3	4	3	0.0	0.0001	0.0004	0.4644	0.4716	0.4483
Metformin	3	3	2	0.0	0.0	0.0	0.4644	0.4355	0.4354
Histamine	3	3	1	0.0002	0.0	0.0	0.3866	0.3705	0.3601
Dopamine	1	1	1	0.0	0.0	0.0	0.3615	0.3584	0.3601

Table 6. Top 20 potential drugs for mild, moderate, and severe COVID-19, ranked according to their measure of proximity to STAT1, SOD2, 3-hydroxyoctanoate, and unknown_mz_815.61548_+_RT_27.063 seed nodes as determined through RWR analysis of COVID-KG, DRKG, and DSOG. The references point to publications that have reported the drugs' mechanism of action potentially linked with COVID-19.

Drug	Drug category	Mechanism of action potentially linked with COVID-19	Measure of proximity in mild	Measure of proximity in moderate	Measure of proximity in severe	Reference*
Glutathione	Antioxidant	Protect cells from damage caused by oxidative stress	0.0007061	0.0007044	0.0007044	[105, 106]
Crizotinib	Tyrosine kinase inhibitor	Express immune modulatory properties and could inhibit receptor tyrosine kinases and affect cellular processes relevant to viral replication	0.0007022	0.0007005	0.0007002	[112]
Curcumin	Natural compound	Expresses antiviral properties, immune modulatory and antioxidant properties that may contribute to inhibit inflammation, oxidative stress, and reduce lung injury	0.0006966	0.0006948	0.0006951	[142]
Vorinostat	Histone deacetylase inhibitor	Express anti-inflammatory and antiviral properties	0.0006943	0.0006952	0.0006954	[113]
Vinblastine	Anticancer	Disrupt microtubule dynamics, leading to mitotic spindle dysfunction and cell cycle arrest.	0.0006920	0.0007029	0.0007022	[149]
Iron	Essential mineral / Nutrient	Expresses anti-inflammatory and immunomodulatory properties	0.0006917	0.0006899	0.0006944	[150]
Mebendazole	Antihelminthic	Express antiviral and immune modulatory properties and may interfere viral replication	0.0006913	0.0006913	0.0006910	[102]
Podofilox	Topical agent	Stimulate the production of interferon-γ, a cytokine that plays a role in the immune response.	0.0006900	0.0007003	0.0007002	[151]
Valine	Essential amino acid	Protein synthesis	0.0006893	0.0006891	0.0006891	[152, 153]
Acetylcysteine	Antioxidant and glutathione inducer	Express antioxidant, immunomodulatory, and mucolytic properties	0.0006878	0.0006877	0.0006878	[154]
Thimerosal	Methyltransferase inhibitor	Induces Th2-type cytokines via influencing cytokine secretion by human dendritic cells	0.0006826	0.0006824	0.0006824	

Fludarabine	Chemotherapy drug	Inhibits type I interferon-induced expression of *ACE2*	0.0006813	0.0006811	0.0006812	[93]
Calcipotriol	Anti-psoriatic	Enhance cell differentiation	0.0006800	0.0006800	0.0006800	
Teniposide	Cytotoxic drug	Inhibits SARS-CoV-2 3-chymotrypsin-like cysteine protease	0.0001087	0.0001091	0.0001096	[155]
Omacetaxine	Cephalotaxine ester and protein synthesis inhibitor	Inhibits protein translation and interfere with viral replication	0.0001015	0.0000955	0.0001009	[156]
Etoposide	topoisomerase II inhibitor	Express anti-inflammatory properties and suppresses cytokine production	0.0001010	0.0000973	0.0001022	[157, 158]
L-Glutamine	Amino acid	Expresses immune modulatory, anti-inflammatory and antioxidant properties	0.0000945	0.0000943	0.0000942	[159, 160]
Carglumic acid	Analog of N-acetylglutamate (NAG)	Express enzyme properties for processing excess nitrogen produced when the body metablizes proteins	0.0000942	0.0000939	0.0000939	
Pregabalin	Anticonvulsant drug	Reduces COVID-19-related pain and cough	0.0000591	0.0000591	0.0000591	[161]
Threonine	Essential amino acid	Expresses immune modulatory, anti-inflammatory and antioxidant properties	0.0000579	0.0000578	0.0000579	[153]

Table 7. Node degree, betweenness, and closeness centrality measures for the drug repurposing candidates predicted using the data-driven approach.

Drug name	Degree mild	Degree moderate	Degree severe	Betweenness mild	Betweenness moderate	Betweenness severe	Closeness mild	Closeness moderate	Closeness severe
Crizotinib	1919	1947	2	0.5147	0.4171	0.0025	0.5478	0.5297	0.3987
Curcumin	1076	4	2	0.3281	0.0005	0.0	0.5389	0.4317	0.3983
Glutathione	212	234	118	0.0397	0.0350	0.0439	0.3532	0.3611	0.3657
Vinblastine	4	1905	1378	0.0009	0.4787	0.6440	0.4364	0.5639	0.5556
Acetylcysteine	2	2	1	0.0	0.0	0.0	0.3106	0.3028	0.2743
Calcipotriol	2	2	1	0.0	0.0	0.0	0.3178	0.3186	0.3370
Etoposide	2	2	2	0.0	0.0	0.0001	0.3987	0.3993	0.3715
Fludarabine	2	3	2	0.0	0.0	0.0	0.3178	0.3902	0.3983
Iron	2	2	1	0.0	0.0	0.0	0.3106	0.3028	0.2743
Mebendazole	2	2	1	0.0	0.0	0.0	0.3178	0.3186	0.3370
Omacetaxine	2	2	1	0.0	0.0	0.0	0.2438	0.2466	0.2460
Podofilox	2	2	478	0.0	0.0	0.1438	0.3178	0.31863	0.4092
Teniposide	2	2	2	0.0	0.0	0.0001	0.3987	0.3993	0.3715
Thimerosal	2	2	1	0.0	0.0	0.0	0.3106	0.3028	0.2743
Valine	2	2	1	0.0	0.0	0.0	0.3106	0.3028	0.2743
Vorinostat	2	4	2	0.0009	0.0005	0.0	0.4199	0.4317	0.3983
Carglumic acid	1	1	1	0.0	0.0	0.0	0.2610	0.2653	0.2678
L-Glutamine	1	1	1	0.0	0.0	0.0	0.2610	0.2653	0.2678
Threonine	1	2	1	0.0	0.0	0.0	0.3106	0.3028	0.2743
Pregabalin	1	1	1	0.0	0.0	0.0	0.3539	0.3463	0.3463

Supplementary Table 1. Description of the edge-types in Drug Repurposing Knowledge Graph

Source	Predicate	Subject	Object	Number of edges
bioarx	DrugHumGen	Compound	Gene	24501
bioarx	DrugVirGen	Compound	Gene	1165
bioarx	Coronavirus_ass_host_gene	Disease	Gene	129
bioarx	Covid2_acc_host_gene	Disease	Gene	332
bioarx	HumGenHumGen	Gene	Gene	58094
bioarx	VirGenHumGen	Gene	Gene	535
DGIDB	ACTIVATOR	Gene	Compound	316
DGIDB	AGONIST	Gene	Compound	3012
DGIDB	ALLOSTERIC MODULATOR	Gene	Compound	317
DGIDB	ANTAGONIST	Gene	Compound	3006
DGIDB	ANTIBODY	Gene	Compound	188
DGIDB	BINDER	Gene	Compound	143
DGIDB	BLOCKER	Gene	Compound	979
DGIDB	CHANNEL BLOCKER	Gene	Compound	352
DGIDB	INHIBITOR	Gene	Compound	5971
DGIDB	MODULATOR	Gene	Compound	243
DGIDB	OTHER	Gene	Compound	11070
DGIDB	PARTIAL AGONIST	Gene	Compound	75
DGIDB	POSITIVE ALLOSTERIC MODULATOR	Gene	Compound	618
DRUGBANK	carrier	Compound	Gene	720
DRUGBANK	ddi-interactor-in	Compound	Compound	1379271
DRUGBANK	enzyme	Compound	Gene	4923
DRUGBANK	target	Compound	Gene	19158
DRUGBANK	treats	Compound	Disease	4968
DRUGBANK	x-atc	Compound	Atc	15750
GNBR	A+	Compound	Gene	1568
GNBR	A-	Compound	Gene	1108
GNBR	B	Compound	Gene	7170
GNBR	C	Compound	Disease	1739
GNBR	E+	Compound	Gene	1970
GNBR	E-	Compound	Gene	2918
GNBR	E	Compound	Gene	32743
GNBR	J	Compound	Disease	1020
GNBR	K	Compound	Gene	12411
GNBR	Mp	Compound	Disease	495
GNBR	N	Compound	Gene	12521
GNBR	O	Compound	Gene	5573
GNBR	Pa	Compound	Disease	2619
GNBR	Pr	Compound	Disease	966

GNBR	Sa	Compound	Disease	16923
GNBR	T	Compound	Disease	54020
GNBR	Z	Compound	Gene	2821
GNBR	B	Gene	Gene	8164
GNBR	D	Gene	Disease	500
GNBR	E+	Gene	Gene	10838
GNBR	E	Gene	Gene	418
GNBR	G	Gene	Disease	2055
GNBR	H	Gene	Gene	2509
GNBR	I	Gene	Gene	5434
GNBR	J	Gene	Disease	30234
GNBR	L	Gene	Disease	48384
GNBR	Md	Gene	Disease	1279
GNBR	Q	Gene	Gene	19372
GNBR	Rg	Gene	Gene	11018
GNBR	Te	Gene	Disease	2836
GNBR	U	Gene	Disease	6432
GNBR	Ud	Gene	Disease	407
GNBR	V+	Gene	Gene	8689
GNBR	W	Gene	Gene	280
GNBR	X	Gene	Disease	1324
GNBR	Y	Gene	Disease	1948
GNBR	in_tax	Gene	Tax	14663
Hetionet	AdG	Anatomy	Gene	102240
Hetionet	AeG	Anatomy	Gene	526407
Hetionet	AuG	Anatomy	Gene	97848
Hetionet	CbG	Compound	Gene	11571
Hetionet	CcSE	Compound	Side Effect	138944
Hetionet	CdG	Compound	Gene	21102
Hetionet	CpD	Compound	Disease	390
Hetionet	CrC	Compound	Compound	6486
Hetionet	CtD	Compound	Disease	755
Hetionet	CuG	Compound	Gene	18756
Hetionet	DaG	Disease	Gene	12623
Hetionet	DdG	Disease	Gene	7623
Hetionet	DlA	Disease	Anatomy	3602
Hetionet	DpS	Disease	Symptom	3357
Hetionet	DrD	Disease	Disease	543
Hetionet	DuG	Disease	Gene	7731
Hetionet	GcG	Gene	Gene	61690
Hetionet	GiG	Gene	Gene	147164
Hetionet	GpBP	Gene	Biological Process	559504

Hetionet	GpCC	Gene	Cellular Component	73566
Hetionet	GpMF	Gene	Molecular Function	97222
Hetionet	GpPW	Gene	Pathway	84372
Hetionet	Gr>G	Gene	Gene	265672
Hetionet	PCiC	Pharmacologic Class	Compound	1029
INTACT	ASSOCIATION	Compound	Gene	1447
INTACT	DIRECT INTERACTION	Compound	Gene	155
INTACT	PHYSICAL ASSOCIATION	Compound	Gene	203
INTACT	ADP RIBOSYLATION REACTION	Gene	Gene	58
INTACT	ASSOCIATION	Gene	Gene	112390
INTACT	CLEAVAGE REACTION	Gene	Gene	93
INTACT	COLOCALIZATION	Gene	Gene	3468
INTACT	DEPHOSPHORYLATION REACTION	Gene	Gene	303
INTACT	DIRECT INTERACTION	Gene	Gene	6950
INTACT	PHOSPHORYLATION REACTION	Gene	Gene	1328
INTACT	PHYSICAL ASSOCIATION	Gene	Gene	129318
INTACT	PROTEIN CLEAVAGE	Gene	Gene	67
INTACT	UBIQUITINATION REACTION	Gene	Gene	371
STRING	ACTIVATION	Gene	Gene	81355
STRING	BINDING	Gene	Gene	315875
STRING	CATALYSIS	Gene	Gene	343533
STRING	EXPRESSION	Gene	Gene	757
STRING	INHIBITION	Gene	Gene	28959
STRING	OTHER	Gene	Gene	310690
STRING	PTMOD	Gene	Gene	15113
STRING	REACTION	Gene	Gene	400426

Supplementary Table 2. Description of the edge-types in COVID-19 Knowledge Graph

Edge-type	**Number of interactions**
COVID-19 genes interaction with chemicals	28634
Phenotypes (disease gene-associated biological processes) interactions with COVID-19 drugs (chemical/compound)	1571
Phenotypes (disease gene-associated biological processes) interactions with COVID-19 genes	1610
SARS-CoV-2 baits interaction with host genes	1114
Pathways interaction with COVID-19 genes	692

Supplementary Table 3. Selected data-driven seeds for random walk network exploration

Approach	Seed node	Integrated centrality score	Feature type
Data-driven	STAT1	53529.0403	Transcript
	SOD2	2215.5746	Protein
	3-hydroxyoctanoate	1506.9998	Metabolite
	Unknown_mz_815.61548_+_RT_27.063	9936.9781	Lipid

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