

Identification of pulmonary comorbid diseases network based repurposing effective drugs for COVID-19

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Abstract

The number of hospitalization of COVID-19 patients with one or more comorbid diseases is highly alarming. Despite the lack of large clinical data and incomplete understanding of virus pathology, identification of the COVID-19 associated diseases with clinical precision are highly limited. In this regard, our text mining of 6238 PubMed abstracts (as on 23 April 2020) successfully identified broad spectrum of COVID-19 comorbid diseases/disorders (54), and their prevalence on the basis of the number of occurrence of disease terms in the abstracts. The disease ontology based semantic similarity network analysis revealed the six highly comorbid diseases of COVID-19 namely Viral Pneumonia, Pulmonary Fibrosis, Pulmonary Edema, Acute Respiratory Distress Syndrome (ARDS), Chronic Obstructive Pulmonary Disease (COPD) and Asthma. The disease gene bipartite network revealed 15 genes that were strongly associated with several viral pathways including the corona viruses may involve in the manifestation (mild to critical) of COVID-19. Our tripartite network- based repurposing of the approved drugs in the world market revealed six promising drugs namely resveratrol, dexamethasone, acetyl cysteine, Tretinoin, simvastatin and aspirin to treat comorbid symptoms of COVID-19 patients. Our animal studies in rats and literatures strongly supported that resveratrol is the most promising drug to possibly reduce several comorbid symptoms associated with COVID-19 including the severe hypoxemia induced vascular leakage. Overall, the anti-viral properties of resveratrol against corona virus could be readily exploited to effectively control the viral load at early stage of COVID-19 infection through nasal administration.

Introduction

The coronavirus 2019 (COVID-19) positive cases across the world crossed 2544792 and the death toll topped 175694 as on 23rd, April 2020, since its outbreak in early December¹. The number of recovered cases from coronavirus, too, has increased to 700,000. Almost all the countries in the world are still struggling to keep the virus in control and facing huge economic recession due to lockdown². Now the entire world is in desperate need for drugs and vaccines to save our mankind from the pandemic. In this scenario, researchers from all over the world working together to develop drugs to control in its four stages of disease progression.

The early (first) stage of the disease control starts with controlling at the zero-point entry. The virus is primarily spread between people during close contact, often via small droplets sometimes ultrafine mist produced by coughing, sneezing, or talking³. Prevention is always better than cure. As per WHO guidance the most common preventive measures include hand washing, covering mouth while coughing, social distancing and self-isolation for people who are suspect to be infected⁴. But these guidelines are not full proof and does not guarantee the complete protection against the deadly virus. Obviously, debates are already started in the scientific community about the air borne transmission of COVID-19⁵. Once it is spread from the infected persons, major entry points point of the virus are thin epithelial layers of nose and throat, and the viral loads are highest in the nose than the throat^{6,7}. The early symptoms onset starts since the day of infection varied from 7 to 32 days with a maximum viral load⁸. Most of the infected persons were cured with mild or no symptoms of sneezing, vomiting, fever and headache. But keep control of the viral load in these persons are much more crucial than the infected persons because they are more contiguous in spreading the virus⁹. There are numerous viruses follow the upper respiratory path for infection including the common cold influenza virus^{10,11,12,13}. Clinical studies supported that simple hypertonic saline nasal irrigation and gargling an ancient Yogic practice called “Jalaneti” significantly reduced the viral load in the influenza virus patients^{14,15}. Keep in light, identifying an effective antiviral to reduce the viral load in the upper respiratory tract (say a nasal spray) could possibly be one of the best preventive measure to control COVID-19 pandemic.

The remaining three stages (mild, severe and critical) were classified according to the clinical manifestation of the diseases by their severity¹⁶. Specific drugs or vaccines yet to arrive in the market, the most recommended drugs for COVID-19 patients are mainly used to control viral replication such as remdesivir, lopinavir/ritonavir, chloroquine and hydroxychloroquine blocking the

viral proteins but with limited success rates^{17,18,19,20}. The most common mild and severe symptoms are highly related to the symptoms of pneumonia²¹. Many drugs are used to control the mild and severe symptoms of pneumonia of COVID-19 patients²². Only 30% of severe population recovered, but others deteriorate, often quite suddenly, developing a condition called acute respiratory distress syndrome (ARDS)^{23,24}. Importantly, the same diseases (pneumonia and ARDS) actually presents itself with impressive non-uniformity and distinctive features of severe hypoxemia often associated with near normal respiratory system compliance²⁵. Commonly, these patients end up on ventilators and many die. The autopsies of

the lung alveoli of these patients are filled with fluid, white blood cells, mucus, and the detritus of destroyed lung cells²⁶. These distinct etiology of COVID-19 necessitate the need to identify new drugs to treat the different features present in the three stages of severities.

The hospitalization rate for COVID-19 is 4.6 per 100,000 population, and almost 90% of hospitalized patients have one or more comorbidity²⁷. The number of patients admitted in the hospital shown severity in the diseases are having one or more comorbid diseases²⁸. Understanding the various comorbid diseases of COVID-19 could help the doctors in the front line to decide about the mode treatment at the earliest. For instance, hypertension, diabetes, and cardiovascular diseases are seeming to be the most common comorbidities in patients with COVID-19^{28,29}. These diseases generally treated with renin-angiotensin system (RAS), including angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)^{30,31,32}. Use of these ACEIs found to be increased ACE2 levels in human intestine luminal cells and the ACE2 expression highly correlated with COVID-19 virulence³³. Lei Fang et al., questioned the use of ACEIs to treat COVID-19 patient"s severity³⁴. In this context, understanding different comorbidities of COVID-19 is essential for the frontline workers to decide about the mode of treatment strategies in advance.

Keep all the above in view, the current study had the following research objectives: (i) to collect all possible comorbid diseases of COVID-19 from literature mining especially from Pubmed (ii) to construct disease ontology based semantic similarity network to find the most likely comorbid diseases of COVID-19 (iii) to further evaluate the disease comorbidity using gene – disease association network and understand the pathobiology of COVID-19 (iv) exploit the network to repurposing drugs to control the severity of COVID-19 (v) to experimentally verify the efficacy of the proposed drug to control severe hypoxemia (acute hypoxia) induced vascular leakage.

The main outcome of the analysis includes: (i) the disease ontology based semantic network revealed that highly comorbid diseases of COVID-19 were spread across many vital organs especially kidney besides lung and cardiac (ii) the bipartite network (Disease-gene network) revealed many respiratory disorder genes in the host cells were effectively utilized by several

viruses for their entry as well as replication (iii) tripartite network (disease-gene-drug network) revealed a promising drug called „resveratrol“ for COVID-19 treatment (iv) animal experiments of the drug revealed that the drug protect the rat lung from severe hypoxemia (acute hypoxia) induced vascular leakage (v) possible pros and cons of resveratrol to treat COVID-19 patients were discussed in detail.

Results

Text mining based COVID-19 comorbid diseases Network

The total number of unique disease terms associated with COVID-19 was 559. To reduce the influence of the noise on the network, for each disease, we analysed the number of occurrence of disease terms (frequencies) from the 6238 abstracts (Supplementary Table 1). The wordcloud analysis revealed 54 diseases with their term frequencies range from 2 to 552 correspond to font size 1% and 100% (50 out of 54) respectively (Fig. 1, Supplementary Table 2). The strong disease associations were further

ensured by DO score reduced the number of diseases to 54 (Supplementary Table 3). Finally, 44 diseases indicated a dense association among themselves (89 edges) with the DO score threshold at 0.5 (Fig. 2). Like many empirically observed biological networks, the disease-disease network was also a scale-free network whose degree distribution followed a power law (data not shown), that is most nodes connect to only a few other nodes whereas a few nodes act as hubs with a large number of links. The most connected disease hubs were clustered into five categories (cluster 1 to 5) based on their topological properties of the network (Fig. 3 (A, B) Supplementary Table 4). The cluster 1, 2, 3 and 4 constituted most densely connected networks with almost 10 diseases each. The cluster 1 was having the highest number of diseases with the node sizes >10 in 7 out of 44 diseases). In which earlier studies indicated that densely connected diseases in the network should share similar Medical Subject Headings (MeSH) classifications³⁵ (Fig. 3C). The DO terms of the core network were mapped to the MeSH communities and investigated whether they fell under similar disease MeSH classifications. For instance, Cluster 1 shared pulmonary diseases were in the same classes of disease unique code with two sets of diseases closely defined in 3 digits. The set 1 diseases were Pulmonary edema (UID:D011654), Viral pneumonia (UID:D011024) and Pulmonary fibrosis (UID:D011658) whereas the set 2 diseases were Asthma (UID:D001249) and Bronchitis (UID:D001991).

Figure 1: The word cloud represents COVID-19 associated diseases derived through text mining. There are 50 unique major diseases, symptoms and disorders with frequency of appearance ranges from 2 to 552 correspond to font size 1% and 100% respectively. The frequencies are highly correlated with the prevalence of comorbid diseases contribute to the severity in COVID-19 patients²⁹. This consolidated disease network can be readily used by the medical professionals for their regular references.

Figure 2: In the construction of Disease-Disease network, 44 non-isolated diseases (nodes) linked on the basis of disease ontology (DO) based semantic similarity score. The diseases were connected with each other by 89 potential links. The nodes indicate the diseases and node colors on the basis of disease frequency of appearance in the abstracts. The nodes were represented in two shapes circle

(diseases) and square (disorders) as well as in three colors yellow (size > 75), green (sizes 75 to 25) and blue (size < 25). The width of the link between diseases represents the similarity score, the significantly comorbid links with (similarity score > 0.5) shown in gray links. The diseases are grouped based on the human system organs and type of disease/disorder (in different background colors with label).

Figure 3: (A) The DO score based clustering of the 44 comorbid diseases of covid-19 were shown in dendrogram. The dendrogram showing five disease clusters namely clusters 1, 2, 3, 4 and 5. **(B)** In the Heatmap, scaled from 0 to 14, the rows are representing 35 diseases and the column are representing nine topological properties namely Neighborhood, Degree, Eccentricity, Average shortness, topological coefficient, Clustering coefficient, Closeness coefficient, radiality, betweenness of the each disease node. Please note that all the Cluster 1 (pulmonary related diseases) and their symptoms are ranked high in the network in terms of DO association score as well as the network properties (blue backgrounds). **(C)** Highly comorbid pulmonary diseases of COVID-19 represented in the subnetwork. The colors, shapes of the nodes, edges are as in Figure (2). The highly significant (DO score > 0.5) edges are represented red lines.

Assessment of COVID-19 comorbid respiratory diseases by means of associated genes

Using CTD, we associated 203 unique genes with 8 comorbid disorders of Cluster 1. As defined earlier (methods), among 203 genes, 34 genes were involved in interacting with atleast two of the 6 diseases leading to the 79 disease-gene associations. These genes were mainly associated with highly prevalent six diseases of COVID-19 (Fig. 1) excluding the Bronchitis, Pneumothorax and Neonatal asphyxia (Fig. 4). The disease gene relationships were further investigated using disease gene association (DGA) scores derived from various association indices such as Jaccard Index, Simpson Index, Geometric Index and Cosine Index (Supplementary Table 5). The DGA scores revealed that plumonary fibrosis was the most dominant disease in the Cluster 1. In addition, the disease was strongly associated with asthma, Chronic Obstructive Pulmonary Disease (COPD), plumonary edema

and ARDS. In the Figure 4, genes strongly associated with two diseases were referred as „driver genes“. Furthermore, in the network almost 30% of genes (10 genes) were interacting with 3 diseases and revealed the dense disease-gene associations. The functional pathway enrichment of the driver genes revealed the dominant pathway as “oxygen signalling”. In addition, our study identified the clinically relevant disease association especially ARDS (highest prevalent disease of COVID-19) strongly associated with plmonary fibrosis through ACE2, CCL2, EDN1, TIMP1 and viral pneumonia through ACE. These findings highlighted that these 34 genes named “driver genes” could play the major role in the manifestation as well as regulation of the six major diseases/disorders of COVID-19.

Figure 4: The strongly associated pulmonary diseases (D) in red ellipse (second row) and driver genes (G) in green squares of row 3 (G-2D, genes having interaction more than 2 diseases), row 4 (G-3D, genes having interaction more than 3 diseases), row 5 (G-4D, genes having interaction more than 4 diseases), from Cluster 1 is shown as bipartite network. The interaction of each disease with its corresponding genes represented in different color (grey, yellow, violet, pink, blue and black). The number of disease-gene interactions are also mentioned say D-22G, represent the disease asthma interacting with 22 genes and so on. Similarly, the disease- gene-disease association represented in terms of Jaccard score (first row) and the values in square box. Please note the ARDS interacts with viral pneumonia and fibrosis through ACE and ACE2 respectively with the Jaccard score 0.2.

Tripartite network based prepurposing drugs to treat comorbid diseases of COVID-19

A drug to be effective against COVID-19 patients in their severe stage should be within or in the immediate interaction with the “COVID-19-target network”. We used CTD to extract 505 drugs or chemicals associated with the 6 target network diseases. This expanded network contained a total of 662 disease-drug and 2284 drug-gene connections. We applied the filtering strategy described in the Materials and methods section to extract an integrated scale free disease-chemical-gene network. We observed that only few drug nodes with large number of links (Hubs) and the degree distribution followed a power law. The overall network consisted 34 genes, 6 pulmonary diseases and 15 drugs

(Supplimentary Figure 1). We first focused on Food and Drug Administration (FDA) approved drugs namely Dexamethasone, Tretinoin, Acetylcysteine, Oxygen, Simvastatin and Aspirin except the chemical Resveratrol (Fig. 5). Nevertheless, resveratrol is already available as a nutritional supplements in many countries beside its challenges in translation to the clinical drug³⁶. We further investigated whether a network motif analysis could help to prioritize drug targets based on the associations between diseases and their surrounding genes. Based on the “guilt by association” rule - diseases similar to each other are more likely to be affected by the same genes/ pathways, chemicals involved in the same genes are more likely to be highly associated with these diseases. For instance, in the network “Plumony Edema” and “Plumony fibrosis” shared 15 out of 34 genes. Interestingly, these 15 genes also associated with two chemicals “Resveratrol” and “Oxygen” (Fig. 6). Evidently, KEGG pathway enrichment analysis of the 15 genes revealed the key regulation of virus and oncogenic/hypoxic pathways (Fig. 6). This result supported our association rule that similar diseases can be treated by same drugs, allowing us to make hypotheses for drugs repositioning purpose. In this analysis, the most densely connected drug hub was “resveratrol” having its association with 4 diseases (out of 6 diseases) and 28 genes (out of 34 genes) (Fig. 5). In this background “Resveratrol” was repositioned for the treatment highly comorbid respiratory disorders of COVID-19 namely asthma, phenmonia, plumony fibrosis and ARDS.

Figure 5: A tripartite network of pulmonary diseases node (red circles, level 1), drugs node (brown circles, level 2), genes node (green circles, level 3) is shown. The interaction between the different nodes are shown in three color lines. The edges of diseases with drugs and genes are yellow square and green squares respectively. The edges of drugs with diseases and genes are red and blue squares respectively. The numbers inside the squares above and below the circles represent the number of edges of the particular node. Please note that our predicated FDA approved drugs (6) and nutraceutical (1) are strongly interacting with driver genes as well as more than three pulmonary comorbid diseases of COVID-19. Notice the highest number of edges for the drug resveratrol in terms of diseases and genes.

Figure 6: The resveratrol and oxygen chemicals (yellow circle) subgraph of tripartite network is

shown (Figure 6). The 15 genes (out of 34 driver genes) highly perturbed by resveratrol drug are shown in green squares. Please note that the same 15 genes also shared by the chemical oxygen (yellow circle). These genes also perturbed during the disease manifestation of pulmonary fibrosis (red ellipse) and pulmonary edema (red ellipse). Notice that the functional enrichment of these genes strongly associate them with major oxygen signaling pathways (HIF, ERK, MAPK, TLR, .. in cyan circle) and leads to the exacerbation of several virus (pink circles) and cancers (violet circles).

Resveratrol significantly reduced hypoxia induced vascular leakage

The effect of resveratrol on transvascular fluid leakage assessed by quantitation of sodium fluorescein dye leakage (Fig. 7B). After exposure to hypoxia, the mean fluorescein dye leakage (223.33 ± 23.60 rfu/g) of lung tissue was significantly higher ($p < 0.05$) as compared to normoxic condition. The animals pre-treated with resveratrol (15 mg/Kg BW) were exposed to hypoxia showed a significantly lower ($p < 0.05$) mean relative fluorescence values (130.75 ± 5.63 rfu/g) in lungs as compared with hypoxic control (223.34 ± 23.60) animals. Overall, the administration of resveratrol (15 mg/Kg BW) showed a significant decrease in fluorescein dye leakage (lung vascular leakage) in hypoxia exposed animals. However, the rfu values of resveratrol treated hypoxia exposed animals were significantly higher than the normoxic control values.

Figure 7: (A) Rats were injected with drug in their tail vein. **(B)** Rats were exposed to simulated altitude of 25000 feet (7620 m) at 22°C for 8 h to observe the effect of Resveratrol (15 mg/kg BW) on hypobaric hypoxia- induced vascular permeability. Values are mean \pm SD (n=6). Significant test between groups were determined by using one-way ANOVA followed by Tukey test. * versus Control; # versus Hypoxia. The experimental conditions were labelled as normoxia (N), normoxia plus drug (N+D), hypoxia (H) and hypoxia plus drug (H+D)

Discussion

Resveratrol a potential drug to COVID-19 associated comorbid diseases

The number of hospitalization of COVID-19 patients with one or more comorbid diseases is highly alarming²⁹. Despite the lack of large clinical data and incomplete understanding of virus pathology, identification of the COVID-19 associated diseases with clinical precision are highly limited. In this regard, our literature-based approach successfully identified broad spectrum of COVID-19 comorbid diseases (54 diseases) and their prevalence on the basis of node size. The DSN is able to accurately capture all the reported broad spectrum of COVID-19 comorbidities and presented it as a snap shot (Fig. 1). This consolidated disease network can be readily used by the medical professionals for their regular references. The DSN revealed the following important features. (i) Even though severity of the COVID-19 mainly relate to lung dysfunction, the major comorbid diseases are spreading across many vital organs especially heart and kidney. Several clinical reports are coming up in support of our findings also suggesting the same^{23,29,37,38,39,40,41,42,43}. (ii) The diseases densely packed yielding high similarity are likely to be comorbid. In this sense, the sub network clusters of respiratory (Cluster1), nephrology (Cluster 2) and cardio respiratory (Cluster 2 &3) diseases are expected to be comorbid (Fig 3A). As per major clinical studies almost all the disease pairs are proven to be comorbid in COVID-19 patients^{29,40,44}. Evidently, every disease node in the respiratory comorbid network share almost 30% of the entire genes (Fig. 3). Importantly, there are several genes in the host cells utilized by several viruses for their entry as well as replication (Fig. 6). Our study opens up the possibilities that these shared genes also utilized by COVID-19 to establish its virulence against the host cell. In this support, 6 genes associated with COVID-19 from literature are common with these driver genes further explains the common pathobiology (Supplementary Figure 2) For instance, COVID-19 could hijack the host cell oxygen signalling pathway genes (15 shared genes) to activate the oxygen deprivation mechanism in lungs (acute lung hypoxia) possibly leads to multiple disorders related comorbid symptoms of lung fibrosis, asthma, COPD and ARDS. Furthermore, the genes ACE2 (SARS-COV2 binding target) and ACE may switch the severity from severe (viral pneumonia, lung fibrosis) to critical (ARDS) in COVID-19 patient (Fig. 5). (iii) Instead of treating these comorbid diseases with drugs independently, DSN helped us to prioritize the drugs to treat multiple disorders of

COVID-19 (comorbid diseases) simultaneously. Most of our enlisted drugs dexamethasone, acetyl cysteine, and aspirin were showed promising results in their early clinical trials against COVID-19^{45,46,47}. In the rest of drugs resveratrol, Tretinoin and Simvastatin, our study also strongly recommends all of them for the effective treatment of comorbid diseases of COVID-19. For instance, resveratrol is already under clinical trials against the highly comorbid diseases of COVID-19 such as hypertension, diabetics, pneumonia except ARDS and pulmonary edema^{48,49,50,51}.

Resveratrol may use to reduce vascular leakage in lungs during severe hypoxemia (acute hypoxia) in COVID-19 patients

Our study clearly resulted out two highly significant findings (i) the single major symptom dominating the entire disease network is lung inflammation. (ii) Resveratrol caused significant reduction of transvascular fluid leakage in lung alveoli as a result of hypoxia insult. The decrease in lung water content by resveratrol are in agreement with animals treated with Tretinoin⁵², simvastatin⁵³, dexamethasone⁵⁴ and acetyl cysteine⁵⁵. Furthermore, the significant reduction in transvascular leakage in the resveratrol treated animals also confirmed using sodium fluorescein dye as an indicator. Similar study design of rats exposed to hypoxia developed acute pulmonary oedema with highly significant increase in the lung fluids, protein like albumin and other vascular compartments⁵⁶. The acute pulmonary oedema in humans can be encountered in great variety of conditions⁵⁷. Importantly, pulmonary oedema could be predisposing to several of the highly comorbid diseases of COVID-19. From our animal experiments it is completely evident that resveratrol (100 mg/kg bw) considerably reduce the excess accumulation of leverage fluid as the result of acute hypoxic state. In terms of infections, several viral and bacterial infections induced pulmonary inflammation leads excess accumulation of cyokine/chemokines and mucus in the lung alveoli. Several studies it is evident that resveratrol significantly reduce the lung inflammation in infection and thereby suppress the chemokine/cytokine expression in lung alveoli⁵⁸. As mentioned earlier, the autopsies of COVID-19

patient's lung alveoli became stuffed with fluid, white blood cells, mucus and the detritus of destroyed lung cells and completely disrupted the exchange of gases²⁶. The protective effects of resveratrol in respiratory system may help the COVID-19 patients to breathe easier by decreasing the accumulation of pro-inflammatory molecules, water, chemokines, and cytokines in the lung alveoli. The present study suggested that resveratrol is a potentially useful drug for the treatment of COVID-19 patients by considerably reducing the lung inflammation induced mortality.

Resveratrol a potential drug to human coronaviruses (CoVs) with caveat to increase ACE2 level

Most antiviral drugs target specific to viral proteins compromised their efficacy by the rapid evaluation of resistant variants. Consequently, silent information regulator enzymes (SIRT1) of the host cells provide effective therapeutic treatment opportunity to the resistance variants of broad spectrum of viral pathogens⁵⁹. Importantly, sirtuin-activating drug resveratrol inhibit the replication of diverse spectrum of viruses⁶⁰⁻⁶². In addition, resveratrol significantly inhibited MERS-CoV infection and prolonged cellular survival after virus infection⁶³. In this regard, four 2019-nCoV enzymes that could represent antiviral targets are highly conserved, and share a high level of sequence similarity with the corresponding SARS and MERS^{64,65}. It is highly reasonable to consider repurposing resveratrol as a selected therapeutic drug for 2019-nCoV⁶⁶. Instead, the use of resveratrol against severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 (COVID-19) load resistance needs a careful evaluation by the clinicians. It is evident that resveratrol up regulates the ACE2 in host cells involving Sirt1 enzymes and may facilitate infection with SARS-CoV and SARS-CoV-2 (COVID-19)^{67,68}. To the surprise, the SARS-CoV-2 (COVID-19) identified with furin cleavage site at the S1/S2 boundary setting the virus distinct from SARS-CoV and SARS-CoVs⁶⁹. In the contrary, MERS-CoV is also activated by furin, a serine endoprotease that has been implicated in the processing of fusion proteins and cell entry of other RNA viruses, including HIV, avian influenza A/H5N1 virus, Ebola

virus, Zika virus, Marburg virus and flaviviruses⁷⁰. Resveratrol potentially inhibit almost all the above mentioned viral replications in the host cells but not their entry^{63,71,72,73,74,75,76,77,78}. In this regard, we strongly recommend further animal studies are necessary before considering resveratrol for clinical trials.

Nasal administration of resveratrol to control COVID-19 replication in the early stage of infection and to avoid drug metabolism and availability

COVID-19 infected patients expel virus-laden droplets under the right conditions, liquid droplets from sneezes, coughs and just exhaling. The virus-laden droplets deposit to the lining of the nose and throat of the nearby people who inhale them^{79,80}. COVID-19 is turned out to be the most lethal disease in the world with about 68% of the mortality are linked to comorbidity⁸¹. Our study clearly evident that the potential role of resveratrol to control the COVID-19 epidemic. Unfortunately, the therapeutic effect of resveratrol is highly limited due to its poor water solubility, instability, short plasma half-life, and extensive metabolism in the intestine and liver^{82,83,84,85}. Therefore, non-invasive parenteral routes must be considered to bring resveratrol to the lungs. Especially for the intranasal deposition of COVID-19 especially in nose and throat during the early stage of infection could be exploited effectively to administrate a sufficient amount of resveratrol. In support of this intranasal administration of resveratrol three times a week for 25 weeks resulting in 45% decrease in tumour volume/mouse⁸⁶. In this study, 200 mM hydroxypropyl- β -cyclodextrin (HPCD) saline solution is used to solubilize 24 mg/ml (105 mM) of resveratrol, allowing the administration of a high amount of RES (1.2 mg/mouse) in a limited volume (50 μ l) through intranasal instillation⁸⁶. Another advantage for resveratrol is used as a food supplement in many countries establish the low toxicity⁸⁷. Furthermore, the clinical trial of resveratrol carboxymethyl- β -glucan solution thrice daily during two months in children with allergic rhinitis is capable of significantly improving nasal symptoms in children without

any adverse events⁸⁸.

Materials And Methods

Data mining and extraction of bio-entity

In this study, our goal was to find out the unique relationship between major diseases associated with COVID-19. Pubtator an online text mining tool was used to rank each abstract based on the keyword appearance and annotate the diseases⁸⁹. Our version of the PubTator annotations was downloaded on April 23, 2020. Approximately 16.5 million Medline abstracts were searched for the disease keyword “COVID-19”, using the Pubtator and the virus keyword severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was omitted. The total number of Pubmed Identification numbers (PMIDs) retrieved from the COVID-19 was 6238 as on 23rd April 2020. These PMIDs were submitted to the pubtator to extract high-quality named entity annotations of (1) drugs and other chemicals, (2) genes and (3) diseases related to human from each abstract. The R Package “PubMedWordcloud” was used to construct word cloud based on the disease term frequencies⁹⁰. Disease Ontology (DO) score was used to rank the associations among the COVID-19 associated diseases. The R package “DOSE” was used to calculate the DO scores among the diseases obtained from COVID-19 text mining⁹¹. Diseases that missed their links with DO score cut-off >0.5 were left out from their disease correlation matrix. The network was constructed in cytoscape 3.6⁹². The term frequency of each diseases and DO scores between them were added to the COVID-19 comorbid network. The analysis of the generated network was carried out by Cytoscape network analyser to obtain the topological values. The topological values were clustered to narrow down the significant cluster of diseases/disorders using “*pvclust*” and “*pheatmap*” package in R^{93,94}.

COVID-19 Comorbid pulmonary Disease-Gene Bipartite Network

The extraction of genes relationship from Comparative Toxicogenomics Database (CTD) was introduced in the COVID-19 associated pulmonary diseases network as an additional layer of

complexity⁹⁵. Then, the strength of the relationship of the disease-gene pairs were calculated and represented as a disease-gene association score. The standard association indices include the Jaccard Index, Simpson Index, Geometric index and Cosine index were used for measuring profile similarity in our network with Guide for Association Index for Networks webtool (GAIN)⁹⁶. The similarity between interacting diseases is determined based on the number of shared gene nodes and the total number of diseases connected to these genes. For example, if we define Dg_1 as the set of diseases associated with gene g_1 and Dg_2 as the set of diseases associated with gene g_2 . $|Dg_1|$ and $|Dg_2|$ are the number of diseases associated with g_1 and g_2 , respectively. $|Dg_1 \cap Dg_2|$ indicates the number of shared partners of Dg_1 and Dg_2 . The calculations of these indices are summarized in Table (Supplementary Table 5).

Construction of tripartite Network

To identify potential drug candidates relevant to the bipartite network, we constructed a tripartite network having three communities ($k=3$) i.e. diseases, genes (excluding miRNA) and chemicals. In this tripartite network, all the three communities were closely interconnected to each other such as gene dysfunction may cause one or more core associated diseases that further can be cured by some drugs correcting these gene functions. CTD database was used to get the information regarding associated curated drugs/chemicals with core disease network⁹⁵. The Disease-Gene core bipartite network was enriched with the chemicals to construct the tripartite disease-gene-drug/chemical network. The biological networks of disease, genes, and chemicals were visualized with Cytoscape 3.6⁹². We hypothesize that the potential network motifs in the tripartite network can represent basic interrelationships among diseases, drugs, and genes. We filtered out the drugs with minimum 50% vertices associated to genes and interaction with 3 diseases as well. Specifically, we focus on the three-vertex nodes because they reflect the framework involving all the three communities to achieve particular functions. Out of all possible combinations, we build the tripartite network with potentially relevant interactions comprised of 458 vertices of three different types: 6 diseases, 34 genes and 15

chemicals. Moreover, the tripartite included three different types of interaction edges: about 79 disease-to-gene, over 51 disease-to-chemicals and over 328 genes-to-chemicals links (Supplementary Figure 1). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway based gene set enrichment analysis was carried out for the 34 genes of interest⁹⁷.

Ethical approval

Animal Ethical Committee of the Institute in accordance with Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), of the Government of India has approved the study (IAEC No. DIPAS/ IAEC/ 2017/ 18). The ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines for reporting animal research was followed⁹⁸.

Animal Experiments

In all our study, male Sprague-Dawley (SD) rats (200–220 g) were used. The animals were maintained in the Institute animal house (Animal facility, DIPAS) at 23 °C±2 °C with a 12– 12 h day-night cycle with suitable accessibility of nourishment. The experiments were carried out following the approval and guidelines of the ethics committee of the institute. The rats were randomly subdivided into 4 batches containing four experimental groups with replicates (n) of 6 in each group (Supplementary Figure 3). Animals from hypoxic groups were exposed to a simulated altitude of 25000 feet (7620 m) in animal decompression chamber at 22 °C (Decibel Instruments, India) coupled to a mercury barometer for 8 h⁹⁹. The airflow in the chamber was 2 L/min with relative humidity maintained at 50–55%. After exposure to hypoxia, the animals were anesthetized using ketamine (80 mg/kg) and xylazine (20 mg/kg), lungs were dissected out enbloc after perfusion with ice-cold phosphate buffer saline (PBS) to remove the blood and snap frozen at –80°C for further analysis.

Determination of vascular permeability

The permeability assays were performed by the method of Purushothaman et al, using sodium

fluorescein dye (Sigma, USA) extravasation as an indicator of vascular leakage⁵⁶ after exposing the rats for 8 h of hypoxia. Rat tail vein were injected with sodium fluorescein dye (15mg/kg/BW) in PBS (Fig. 7A). The injected rats were anesthetized after half an hour of dye injection. The rats were perfused through the left ventricle with 30 mL of phosphate- buffered saline to remove the fluorescein from the vascular bed. The lung was harvested from the rats for further studies. The fluorescein dye permeability in lung was measured at an excitation wavelength of 485 nm and an emission wavelength of 531nm using a Spectro fluorimeter (FLUO star Omega). The lung weight was measured and incubated in formamide for 16 hours to extract sodium fluorescein¹⁰⁰. The absorption values were obtained as relative fluorescence units (rfu) per gram dry weight of the tissue. The relative percentage change in fluorescein absorbance for the treatment groups 2, 3 and 4 were calculated in comparison with control group 1 (normoxic state).

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Contributions

RS and JCP conceptualized, data collected/analysed, result visualized and drafted the manuscript for this study. PK, YKS, LG and BK analysis and drafting the manuscript. All authors have read and approved the final manuscript.

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The authors declare that they have no competing interests.

Consent for publication

Not Applicable.

Figures



Figure 1

The word cloud represents COVID-19 associated diseases derived through text mining. There are 50 unique major diseases, symptoms and disorders with frequency of appearance ranges from 2 to 552 correspond to font size 1% and 100% respectively. The frequencies are highly correlated with the prevalence of comorbid diseases contribute to the severity in COVID-19 patients²⁹. This consolidated disease network can be readily used by the medical professionals for their regular references.

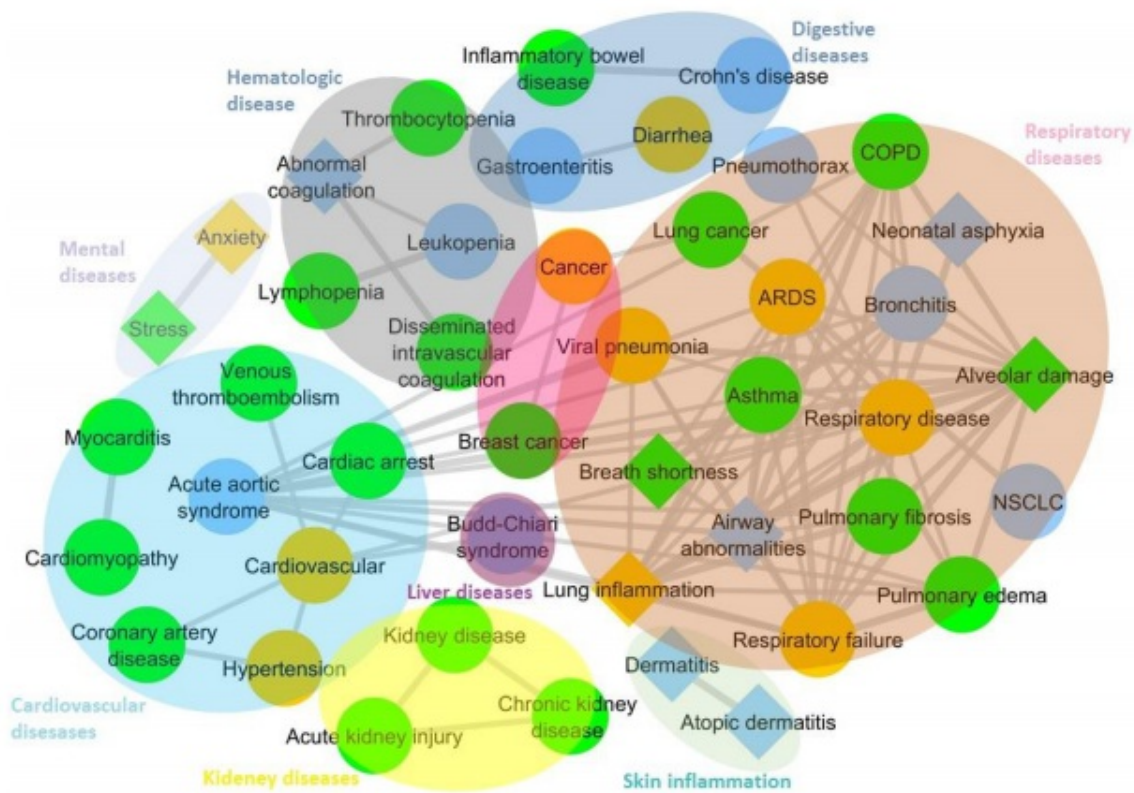
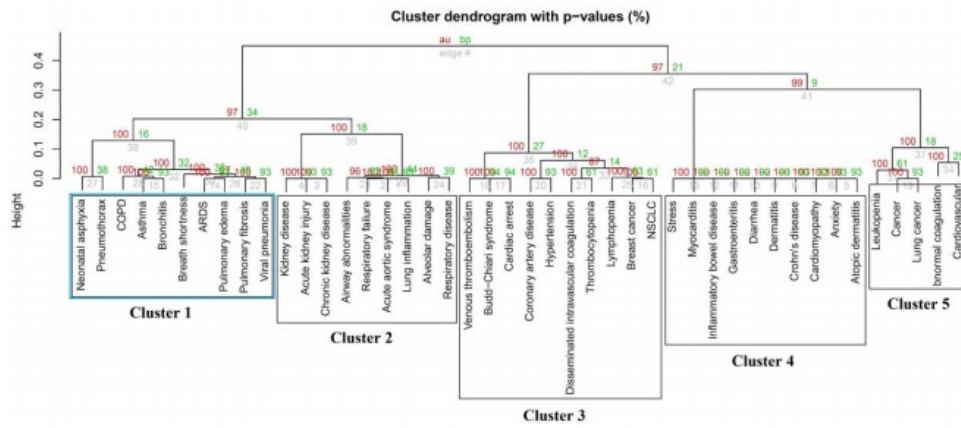


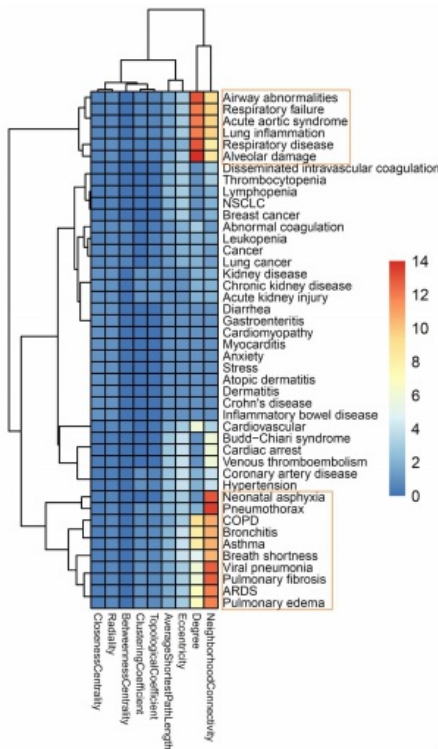
Figure 2

In the construction of Disease-Disease network, 44 non-isolated diseases (nodes) linked on the basis of disease ontology (DO) based semantic similarity score. The diseases were connected with each other by 89 potential links. The nodes indicate the diseases and node colors on the basis in disease frequency of appearance in the abstracts. The nodes were represented in two shapes circle (diseases) and square (disorders) as well as in three colors yellow (size > 75), green (sizes 75 to 25) and blue (size < 25). The width of the link between diseases represents the similarity score, the significantly comorbid links with (similarity score > 0.5) shown in gray links. The diseases are grouped based on the human system organs and type of disease/disorder (in different background colors with label).

A



B



C

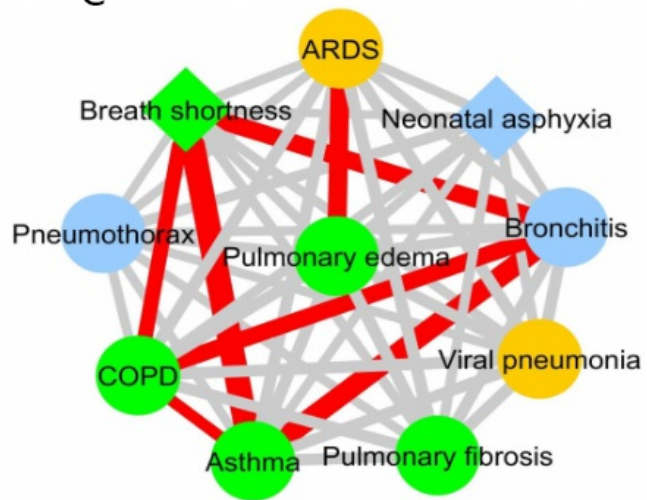


Figure 3

(A) The DO score based clustering of the 44 comorbid diseases of covid-19 were shown in dendrogram. The dendrogram showing five disease clusters namely clusters 1, 2, 3, 4 and 5. (B) In the Heatmap, scaled from 0 to 14, the rows are representing 35 diseases and the column are representing nine topological properties namely Neighborhood, Degree, Eccentricity, Average shortness, topological coefficient, Clustering coefficient, Closeness coefficient, radiality, betweenness of the each disease node. Please note that all the Cluster

1 (pulmonary related diseases) and their symptoms are ranked high in the network in terms of DO association score as well as the network properties (blue backgrounds). (C) Highly comorbid pulmonary diseases of COVID-19 represented in the subnetwork. The colors, shapes of the nodes, edges are as in Figure (2). The highly significant (DO score > 0.5) edges are represented red lines

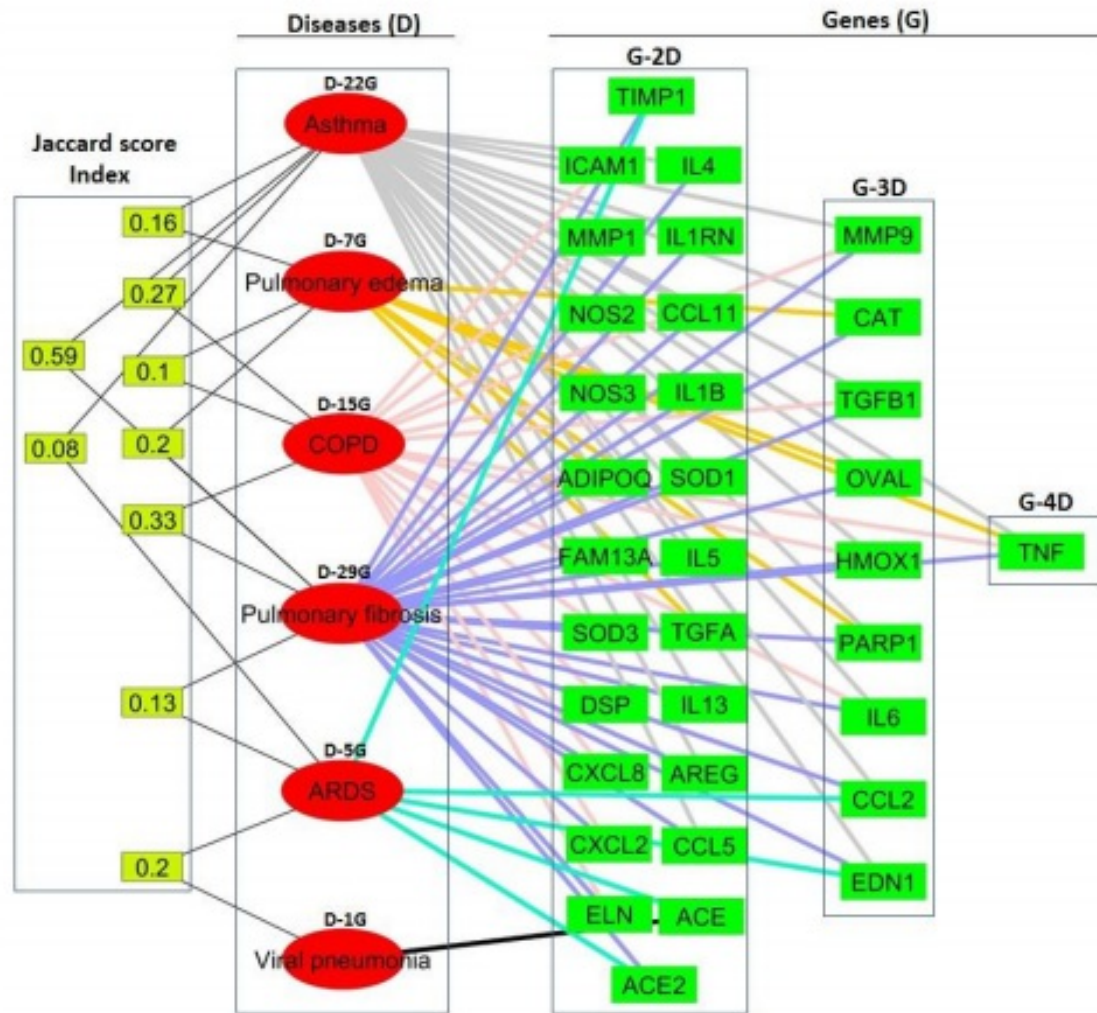


Figure 4

The strongly associated pulmonary diseases (D) in red ellipse (second row) and driver genes (G) in green squares of row 3 (G-2D, genes having interaction more than 2 diseases), row 4 (G-3D, genes having interaction more than 3 diseases), row 5 (G-4D, genes having interaction more than 4 diseases), from Cluster 1 is shown as bipartite network. The interaction of each disease with its corresponding genes is represented in different colors (grey, yellow, violet, pink, blue and black). The number of disease-gene interactions are also mentioned, say D-22G, represent the disease asthma interacting with 22 genes and so on. Similarly, the disease-gene-disease association is represented in terms of Jaccard score (first row) and the values in square boxes. Please note that ARDS interacts with viral pneumonia and fibrosis through ACE and ACE2 respectively with the Jaccard score of 0.2.

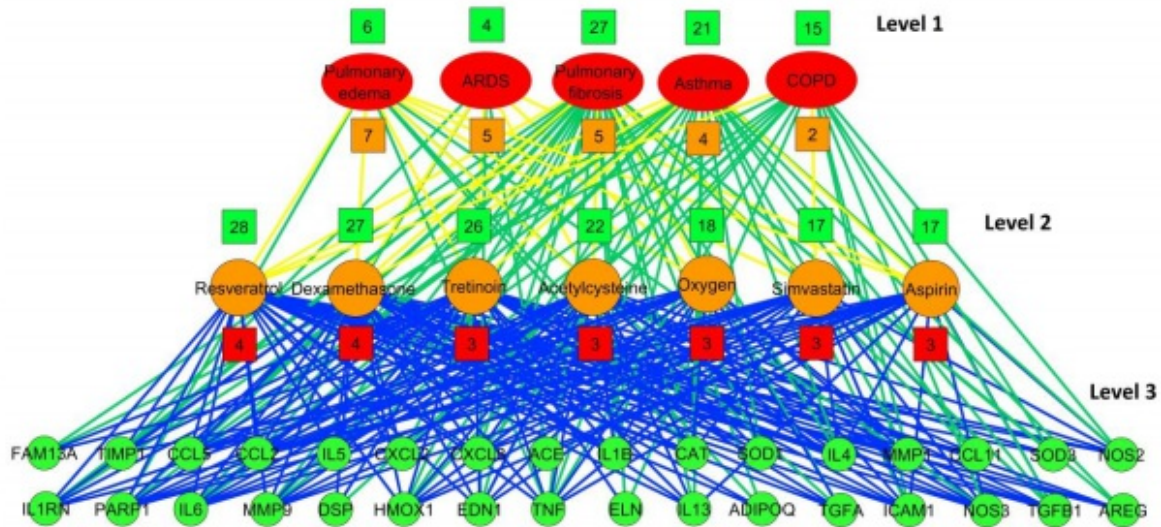


Figure 5

A tripartite network of pulmonary diseases node (red circles, level 1), drugs node (brown circles, level 2), genes node (green circles, level 3) is shown. The interaction between the different nodes are shown in three color lines. The edges of diseases with drugs and genes are yellow square and green squares respectively. The edges of drugs with diseases and genes are red and blue squares respectively. The numbers inside the squares above and below the circles represent the number of edges of the particular node. Please note that our predicated FDA approved drugs (6) and nutraceutical (1) are strongly interacting with driver genes as well as more than three pulmonary comorbid diseases of COVID-19. Notice the highest number of edges for the drug resveratrol in terms of diseases and genes.

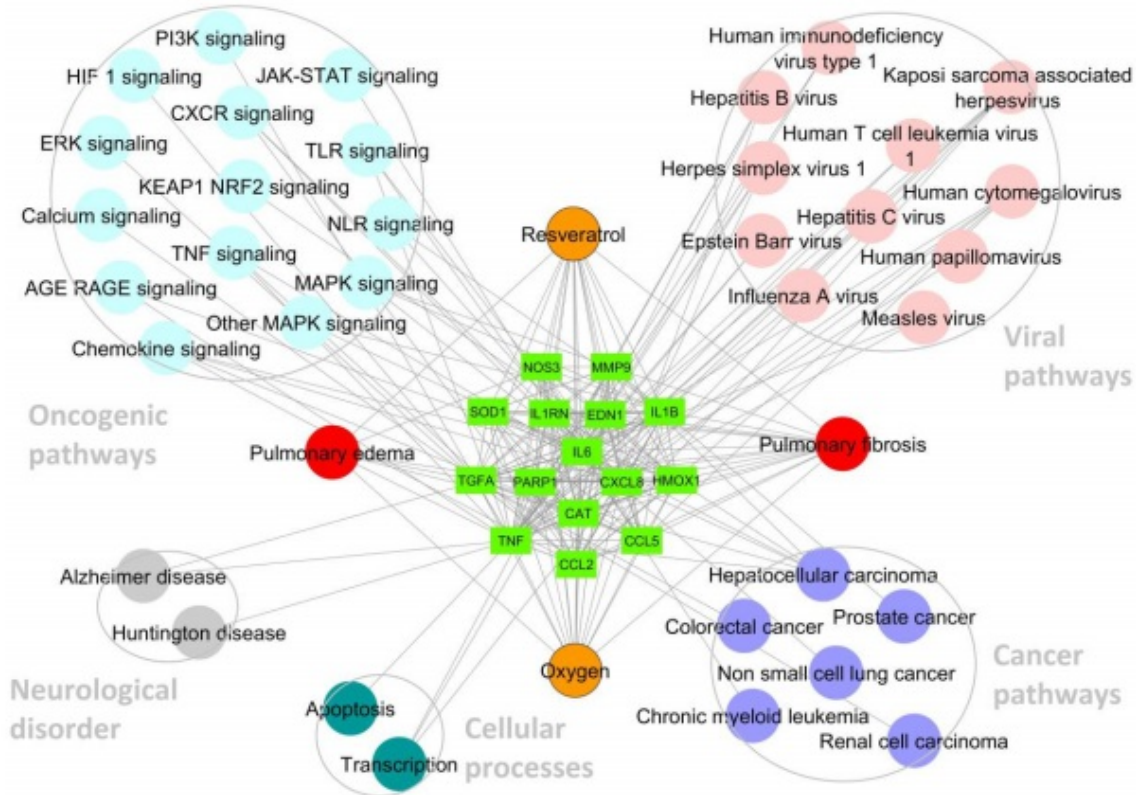


Figure 6

The resveratrol and oxygen chemicals (yellow circle) subgraph of tripartite network is shown (Figure 6). The 15 genes (out of 34 driver genes) highly perturbed by resveratrol drug are shown in green squares. Please note that the same 15 genes also shared by the chemical oxygen (yellow circle). These genes also perturbed during the disease manifestation of pulmonary fibrosis (red ellipse) and pulmonary edema (red ellipse). Notice that the functional enrichment of these genes strongly associate them with major oxygen signaling pathways (HIF, ERK, MAPK, TLR, .. in cyan circle) and leads to the exacerbation of several virus (pink circles) and cancers (violet circles).



Figure 7A

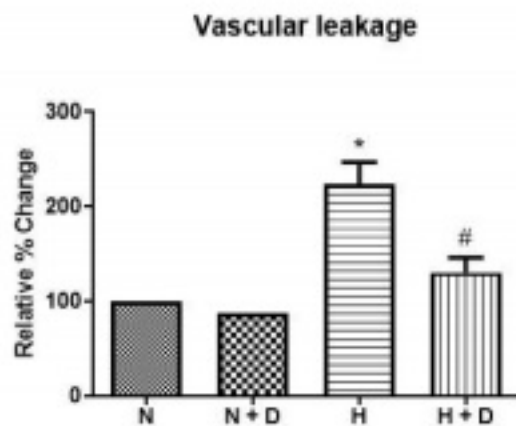


Figure 7B

Figure 7

(A) Rats were injected with drug in their tail vein. (B) Rats were exposed to simulated altitude of 25000 feet (7620 m) at 22°C for 8 h to observe the effect of Resveratrol (15 mg/kg BW) on hypobaric hypoxia-induced vascular permeability. Values are mean \pm SD (n=6). Significant test between groups were determined by using one-way ANOVA followed by Tukey test. * versus Control; # versus Hypoxia. The experimental conditions were

labelled as normoxia (N), normoxia plus drug (N+D), hypoxia (H) and hypoxia plus drug
(H+D)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

[Identificationofpulmonarycomorbid diseasesnetworkbasedrepurposingeffectivedrugsforCOVID19.xlsx](#)