



# Host Factor Interaction Networks Identified by Integrative Bioinformatics Analysis Reveals Therapeutic Implications in COPD Patients With COVID-19

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### Specialty section:

This article was submitted to  
Respiratory Pharmacology,  
a section of the journal  
Frontiers in Pharmacology

**Received:** 01 June 2021

**Accepted:** 11 November 2021

**Published:** 23 December 2021

### Citation:

Zheng W, Wang T, Wu P, Yan Q, Liu C,  
Wu H, Zhan S, Liu X, Jiang Y and  
Zhuang H (2021) Host Factor  
Interaction Networks Identified by  
Integrative Bioinformatics Analysis  
Reveals Therapeutic Implications in  
COPD Patients With COVID-19.  
*Front. Pharmacol.* 12:718874.  
doi: 10.3389/fphar.2021.718874

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**Background:** The COVID-19 pandemic poses an imminent threat to humanity, especially for those who have comorbidities. Evidence of COVID-19 and COPD comorbidities is accumulating. However, data revealing the molecular mechanism of COVID-19 and COPD comorbid diseases is limited.

**Methods:** We got COVID-19/COPD -related genes from different databases by restricted screening conditions (top500), respectively, and then supplemented with COVID-19/COPD-associated genes (FDR<0.05, |LogFC|≥1) from clinical sample data sets. By taking the intersection, 42 co-morbid host factors for COVID-19 and COPD were finally obtained. On the basis of shared host factors, we conducted a series of bioinformatics analysis, including protein-protein interaction analysis, gene ontology and pathway enrichment analysis, transcription factor-gene interaction network analysis, gene-microRNA co-regulatory network analysis, tissue-specific enrichment analysis and candidate drug prediction.

**Results:** We revealed the comorbidity mechanism of COVID-19 and COPD from the perspective of host factor interaction, obtained the top ten gene and 3 modules with different biological functions. Furthermore, we have obtained the signaling pathways and concluded that dexamethasone, estradiol, progesterone, and nitric oxide shows effective interventions.

**Conclusion:** This study revealed host factor interaction networks for COVID-19 and COPD, which could confirm the potential drugs for treating the comorbidity, ultimately, enhancing the management of the respiratory disease.

**Keywords:** COPD, COVID-19, comorbidity, bioinformatics analyses, host factor interaction networks

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic resulting from the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a dramatic increase in hospitalizations for pneumonia with multiple organ dysfunction. It's reported that approximately 60–90% of hospitalized infected patients have comorbidities, most of which include hypertension, diabetes, cardiovascular disease, chronic pulmonary disease and so forth (Garg et al., 2020; Richardson et al., 2020). Given that Chronic Obstructive Pulmonary Disease (COPD) patients are prone to viral exacerbations (Bafadhel et al., 2011; George et al., 2014; Wilkinson et al., 2006) and the devastating impact the COVID-19 may have on the lungs, it is natural for them to fear in the context of the COVID-19 pandemic. The prevalence of COPD amongst hospitalized COVID-19 patients have been reported in many countries or regions, with estimates ranging from 0 to 10% in China (Guan et al., 2020a; Cai et al., 2020; Lian et al., 2020; Liu et al., 2020; Yan et al., 2020), 2.4–14% in New York City (Goyal et al., 2020; Kuno et al., 2020; Palaiodimos et al., 2020; Richardson et al., 2020), and 5.6–9.2% in Italy (Cecconi et al., 2020; Inciardi et al., 2020; Lagi et al., 2020). What's more, several studies have found that pre-existing COPD greatly increases the risk of severe disease and death in COVID-19 patients. A Chinese multicenter study involving 1590 COVID-19 patients showed that COPD carried an odds ratio of 2.681 (95% CI 1.424–5.048;  $p = 0.002$ ) for ICU admission, mechanical ventilation, or death; 62.5% of severe cases had a history of COPD and 25% of those who died were COPD patients (Guan et al., 2020b). Feng et al. (2020) has also found significant differences ( $p < 0.001$ ) between critically ill (15.7%) and moderate (2.3%) patients in the subgroup of COPD.

Currently, the interaction mechanism between COPD and COVID-19 remains unclear and there is little direct evidence about the management of COPD in people with COVID-19 (Halpin et al., 2021). It seems that the highly expressed angiotensin converting enzyme 2 (ACE2) receptors in the COPD airway, the SARS-CoV-2 receptor, were to blame, but evidence has not been shown yet to confer increased susceptibility or increased severity of disease (Leung et al., 2020; Yao et al., 2020). Moreover, COPD patients also feature endothelial cell dysfunction and increased coagulopathy, which may provide explanations for the increased risk of worse outcomes from COVID-19 (Kasahara et al., 2001; Minakata et al., 2005; Husebø et al., 2021).

Host factor networks, based on the integration of systems biology and bioinformatics, serves as a critical strategy for exploring viral diseases as well as non-viral diseases. On one hand, since viruses are obligate intracellular parasites and depend on the host to complete their life cycle, the goal of regulating virus replication can be achieved by changing the expression level of host factors closely related to virus survival. Thus, the identification of host factors involved in regulating the virus life cycle can help reveal the virus-host interaction mechanism. On the other hand, host factor networks can also further enhance our understanding of COPD, the complex and heterogeneous disease both in the clinical and biological aspects. For example, a

series of studies on genome-scale identification of SARS-CoV-2 host factor networks reveals new insights into SARS-CoV-2 biology and inform ongoing drug development efforts (Daniloski et al., 2021; Hoffmann et al., 2021; Wei et al., 2021); Morrow and others (Morrow et al., 2015) used integrative genomics to identify host factors associated with specific COPD phenotypes and described a network-co-expression module that was related to the frequency of COPD exacerbations. Obeidat and others reported three co-expression modules (including interleukin 8 and 10 related pathways) associated with the severity of airflow limitation, which reveals novel gene signatures in peripheral blood for COPD patients (Obeidat et al., 2017). In short, host interaction networks allow the identification of subnetworks corresponding to the functional units of a living system, which can help us explore the pathophysiology of the disease from multiple levels, and provide insights for clarifying the virus-host immune interaction mechanism, identifying the host's gene function, predicting underlying drugs and patient classification (Tan et al., 2007).

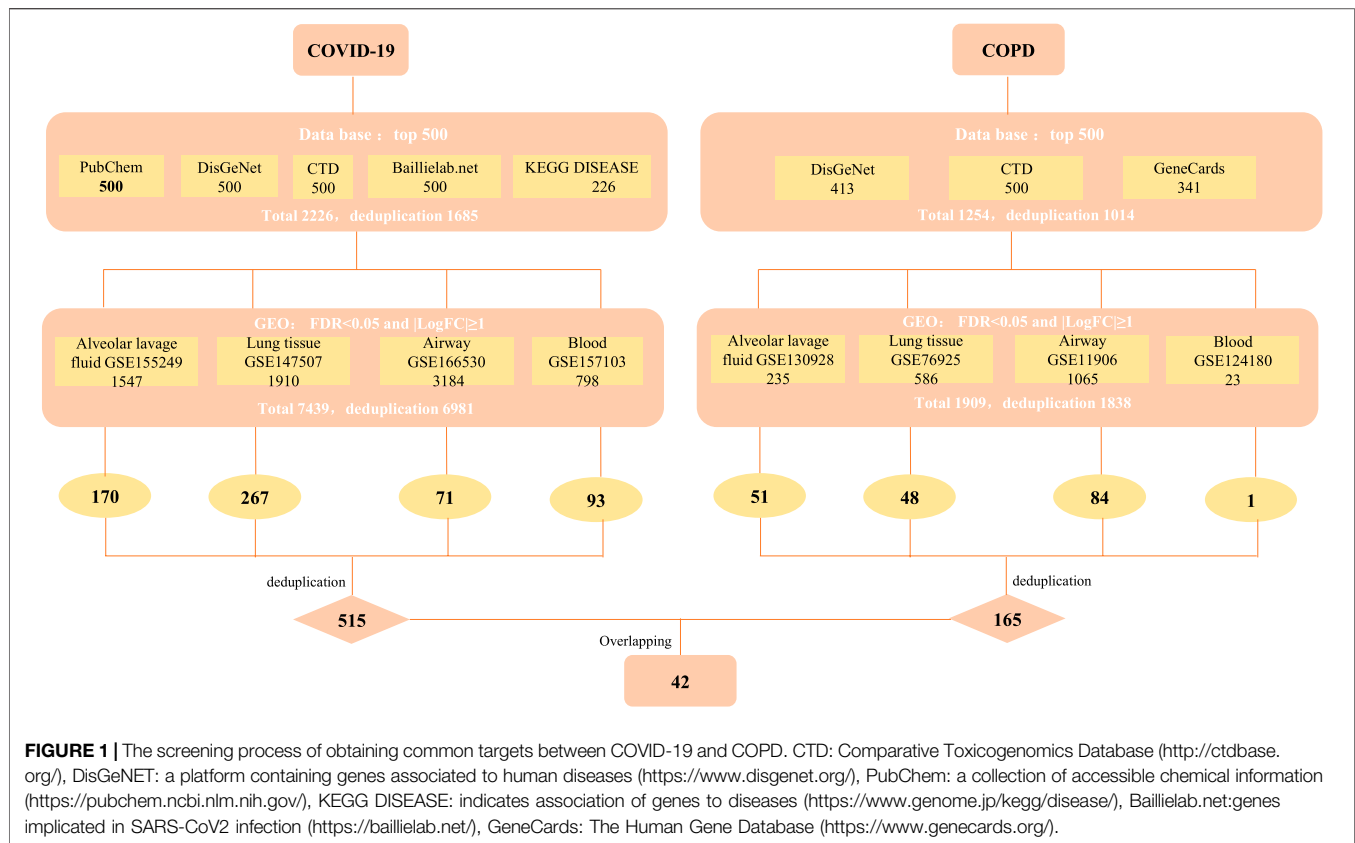
Therefore, we have adopted a strategy of integrative bioinformatics analysis to explore the host factor networks of COVID-19 and COPD comorbid diseases. Here, several online databases and bio-datasets were employed to identify the co-factors of COPD and COVID-19. On this basis, a series of biological information analyses were performed in an attempt to clarify the shared pathogenic molecular mechanism of comorbidities and to predict potential therapeutic drugs. Our results provide a new perspective of comorbidity interaction and identify host-derived therapeutic targets for COVID-19 and COPD.

## MATERIALS AND METHODS

### Collection of COVID-19 and COPD-Related Genes

The data source for COVID-19/COPD consists of two parts, namely, databases and data sets. For COVID-19-associated genes, we referred the PubChem (<https://pubchem.ncbi.nlm.nih.gov/#query=covid-19>), CTD (<http://ctdbase.org/>), DisGeNET (<https://www.disgenet.org/covid/diseases/summary/>), baillielab net (<https://baillielab.net/maic/covid19>) and KEGG DISEASE (<https://www.genome.jp/kegg/disease/>) databases and data sets of (Grant et al., 2021; Blanco-Melo et al., 2020; Mahmud et al., 2021; Singh et al., 2021; Overmyer et al., 2021; Mo et al., 2021). Regarding COPD-related genes, we considered DisGeNET (<https://www.disgenet.org/>), CTD (<http://ctdbase.org/>) and GeneCards (<https://www.genecards.org/>) databases and data sets of (O'Beirne et al., 2020; Han et al., 2021; Morrow et al., 2017; Hu et al., 2018; Raman et al., 2009; Huang et al., 2019; Morrow et al., 2019; Shen et al., 2021). These selected data sets above represent different clinical samples of COVID-19/COPD, specifically including alveolar lavage fluid, lung tissue, airway and peripheral blood.

The top 500 genes of each database were gathered according to their ranking rules. The data sets were analyzed using GEO2R, R and limma package (Ritchie et al., 2015). Genes from data sets that meet the Benjamini–Hochberg adjusted  $p$ -values (False discovery rate, FDR)  $< 0.05$  and  $|\log_2FC| \geq 1$  were selected as



differentially expressed genes (DEGs). Subsequently, intersection genes of the two parts were selected as candidate targets for further analysis. The date of access to these websites was October 6, 2021.

## Analysis of TF-Gene Interactions and Gene-miRNA Coregulatory Network

The NetworkAnalyst tool (version 3.0, <https://www.networkanalyst.ca/>) (Zhou et al., 2019a) was used to evaluate the interaction of TF genes with common genes associated with COVID-19 and COPD comorbidities, as well as gene-miRNA interactions. The basic data of the TF-gene interaction network comes from the ENCODE ChIP-seq database (<https://www.encodeproject.org/>), using only peak intensity signals <500 and predicted regulatory potential score <1 (using the BETA Minus algorithm). The basic data of gene-miRNA interaction comes from miRNA-gene interaction data collected by miRTarbase comprehensively verified by experiments. Relevant results were visualized by Cytoscape (version 3.8.1, <https://cytoscape.org/>) (Shannon et al., 2003).

## Protein-Protein Interaction Analysis and Network Construction

Common host factors were uploaded to STRING (version 11.0, <https://string-db.org/>) (Szklarczyk et al., 2019) for generating PPIs network. Here, we set the minimum

interaction score required by the PPI network to a medium confidence level: 0.4, and the *p*-value for PPI enrichment: 1.0e-16. The PPI results were analyzed and visualized through Cytoscape. And MCODE analysis of PPI network was subsequently performed and visualized through Metascape (<https://metascape.org/>) (Zhou et al., 2019b).

## Gene Ontology and Pathway Enrichment Analysis

We conducted gene ontology (GO) analysis and pathway enrichment analysis to characterize the biological mechanisms and signaling pathways of common host factor networks. GO biological processes and GO molecular functions are drawn by the WEB-based genome analysis toolkit webgestalt (Hu et al., 2021) (<http://www.webgestalt.org/>), and the KEGG pathway analysis results are generated by R and clusterprofiler (Yu et al., 2012) package. A cutoff of Benjamini-Hochberg adjusted *p*-values < 0.05 was adopted in this apart.

## Tissue Specific Enrichment Analysis of Top Genes

In this study, we used the multigene query function available on GTEx (Sun et al., 2021) (<https://www.gtexportal.org/home/multiGeneQueryPage>, accessed October 16, 2021) to perform tissue-specific enrichment analysis of 42 COVID-19 genes that overlap with COPD.

**TABLE 1** | Sources of genetic selection.

Disease	Database or GEO	Data sources	Amount of raw data	Filter condition	Amount of data after filtering and deduplication	Merge	Overlapping genes	
COVID	Data base	PubChem	629	If the raw data is greater than 500, then take 500; if the raw data is less than 500, then all are included	500	1,685	515	
		DisGeNet	1843		500			
		CTD	500		500			
		Baillielab.net	2000		500			
		KEGG DISEASE	231		226			
	GEO	Alveolar lavage fluid GSE155249	57,928	FDR <0.05 and  LogFC ≥1	1,547	6,981	—	—
		Lung tissue GSE147507	23,710		1910			
COPD	Data base	Airway GSE166530	3,188	If the raw data is greater than 500, then take 500; if the raw data is less than 500, then all are included	3,184	1,014	165	
		Blood GSE157103	1,054		798			
		DisGeNET	448		413			
		CTD	53,814		500			
		GeneCards	341		341			
	GEO	Alveolar lavage fluid GSE130928	54,675	FDR <0.05 and  LogFC ≥1	235	1838	—	—
		Lung tissue GSE76925	32,831		586			
		Airway GSE11906	54,675		1,065			
		Blood GSE124180	31,786		23			

## Candidate Drugs Analysis

Overlapping genes were uploaded to ShinyGO (Ge et al., 2020) v0.741 (<http://bioinformatics.sdstate.edu/go/>) for further candidate drug prediction. Preset all available gene sets, *p*-value cutoff (FDR, adjusted in the hypergeometric test) < 0.05 and show the top 30 pathways. Finally, the candidate drugs from the STITCH database are screened out from the enrichment results. STITCH (Li et al., 2021) (<http://stitch.embl.de/>) is a powerful search tool for predicting drug-target relationships. In this analysis, we used 42 genes shared by COVID-19 and COPD to predict drug candidates for COVID-19 and COPD comorbidities.

## RESULTS

### Identification of Common Host Factors Between COVID-19 and COPD

We strictly screened the host factors of COVID-19. First, we searched COVID-19-related host factors from PubChem, DisGeNET, CTD, baillielab net and KEGG DISEASE, respectively. In order to improve the credibility of the data, we choose to filter the first 500 entries in each database. If it is less than 500 entries, all retrieved data will be included. Based on this, we obtained 500 host factors (after deduplication) in PubChem, CTD, DisGeNET, and baillielab net, respectively, and 226 host factors (after deduplication) in KEGG DISEASE. The host factors of the five databases are combined to a total of 1,685 after deduplication. At the same time, we also searched for COVID-19 factors in data sets that contain clinical samples. According to the screening thresholds of FDR<0.05 and |LogFC|≥1, 1,547, 1910, 3,184, and 798 differentially expressed genes (DEGs) were

obtained in GSE155249, GSE147507, GSE166530 and GSE157103 after deduplication. The host factors of the four data sets are combined and deduplicated into a total of 6,981. In the end, there were 515 overlapping genes in the COVID-19 databases and data sets (Figure 1 and Table 1).

Similarly, to determine the host factors of COPD, we searched DisGeNET, CTD, and GeneCards to get the top 500 genes of these databases. After combining the database genes and deduplication, a total of 1014 COPD host factors were gained. In addition, we also supplemented the COPD host factors in the data sets and got 235, 586, 1,065 and 23 DEGs in GSE130928, GSE76925, GSE11906 and GSE124180 respectively. A total of 1838 host factors were obtained after merging and removing duplicates. Finally, we combined the host factors obtained by the two methods, and selected overlapping genes as the disease host factors for COPD, a total of 165. Additionally, after collecting data from the COVID-19 and COPD datasets, we sorted out the overlapping genes between different tissues, as shown in Table 2. At the same time, in order to understand more intuitively which genes are included in each database or data set, we have also traced the source distribution of 42 genes (see Supplementary Table S1).

Finally, we cross-processed the overlapping factors that were strictly screened for the two diseases and finally got 42 common host factors.

### TF-Gene Interaction and Gene-miRNA Interaction

The TF-gene interaction network consists of 285 nodes and 717 edges (Figure 2 and Supplementary Table S2). Among them, CFB is regulated by 58 TF-genes, FOS is regulated by 51 genes,

**TABLE 2 |** Overlapping genes in different tissues.

Gene source	Overlapping genes
Alveolar lavage fluid	MMP2, MMP7, RTN1, S100P, SLC22A4, RNASE6, EPS8, PRKCB, TIMP3, HS3ST1, GCLM, RASSF5, AFAP1L1, MERTK, MCOLN2, SPRY2, PLXNC1, CHST13, IFITM2, BNIP3, AOC3, CDK6, ANKRD22, SCD, SPP1, SECTM1, OSM, SPRED1, IGFBP2, GALM, GCH1, TNS1, SNCA, SLC26A11, TRERF1, SOCS3, ZC3H12C, CCL2, DFNA5, MMP12, FLT1, IFITM3, MARCKS, FAM198B, CYTL1, ADAM28, VNN1, MCOLN3, RASSF2, SLC20A1, ISG20, TRPC6, CADM1, TMEM163, SERPINE1, VCAN, SLC39A8, RASAL2, HS3ST2, CD84, SH3RF1, LINC01010, MLLT11, CYBRD1, GATM, FAM101B, AKT3, CYP1B1, XYLT1, ACKR3
Lung tissue	NOL8, TLR1, SMC3, TRAF5, SELL, CCL19, CCAR1, ARL13B, SAMSN1, PIK3AP1, DNAJB4, APOBEC3A, HPGDS, FCGR3A, ANP32A, CHIT1, CARD16, P2RY14, CTR9, DYRK3, MPHOSPH10, SH3PX2D2B, GLT8D1, FAHD2A, GBP1P1, EVI2B, CWC22, MPLKIP, PI4K2B, DCAF13, IRF2, LUC7L3, TMEM133, SYAP1, ACAD8, PLOG1, ZC3H7A, POU2AF1, RTN3, HMG3, PPIG, PLAGL1, ILK, SMAD7, FAM26F, HNRNPC, MCTS1, CAPZA1, POLR2K, GIMAP7, C1D, CYP51A1, ITM2A, GBP3, CBY1, DENND4C, SREK1, FCRLA, KCN3, LOC101927769, CPNE4, VGLL3, AQP2, NMNAT2, IFITM10, AHRR, JPH2, PSD2, CDH11, DCTN1AS1, FGF22, SMIM1, SYNPO2L, LOC101927914, ELFN2, TAL1, FRMD8P1, TSPAN18, CLEC5A, GRP, JAKMIP3, LOC102546299, SLC30A3, PLK5, LCN8, GBX1, LINC00269, ITLN1, KCNIP3, EWSAT1, PITX2, TPH1, CDH6, PRICKLE2AS3, SULT4A1, SOX9AS1, C1QTNF4, SEMA5B, FRMD1, KCN4, CLEC14A, NAT16, KCNQ2, LINC00942, CBLN4, LOC101927870, GLB1L3, PITX3, PSMA8, NR1I2, ARHGEF10, ELAVL3, LOC400622, KCNA1, NKD1, SCUBE3, LOC101929552, MAPK12, OBP2A, RPL13AP17, OR5K1, NHLH2, PAX1, TCF4AS1, SGK2, PTGIR, GFRA2, COL8A1, GREM2, LINC00652, UNC5C, GPBAR1, LOC254028, VWC2, HHLA1, MYOZ3, KIZAS1, ABCB6, DKKL1, ATP8B5P, ADAM11, FAM167AAS1, HAP1, SYT16, PIK3CDAS1, PHACTR3, LOC158434, HIF3A, OR5H1, BDNF, CALCA, APLP1, ZIC1, LRRN4, FBXO17, BMP4, KLC3, MEIS3, NTRK3, SYT1, MIR924HG, DDN, AVPR1A, C10orf126, BRSK2, LOC101927636, LHX6, CYP1B1AS1, INMT, CTD2350J17.1, ART3, LINC01056, C1orf127, RAMP2, ATOH7, LHX9, CNPY1, DHR52
Airway	CCL3L1, FCER1A, TRIM6
Blood	

and FKBP5 is regulated by 43 TF-genes. See **Supplementary Table S2** for details. In addition, the gene-miRNA interaction network has a subnet with at least 3 nodes as shown below. Subnet 1 (**Figure 3** and **Supplementary Table S3**) is composed of 638 nodes and 879 edges, and subnet 2 (**Figure 4** and **Supplementary Table S3**) is composed of 6 nodes and 5 edges.

## Protein-Protein Interaction Network and MCODE Analysis

The PPI network in this study was generated by string based on 42 common host genes and then introduced into Cytoscape for visual representation and network topology analysis. In the end, we get 42 nodes, 199 edges, and the average node degree is 9.48. In this study, we rank the nodes in the PPI network according to their degree values. The top ten targets are CCL2, MMP9, IL1A, LEP, SERPINE1, CXCL10, EGF, CCL4, STAT1, and HIF1A (**Figure 5**). In addition, set the cluster finding parameters

(node score cutoff: 0.2, k-core: 2, max depth: 100), through MCODE analysis (**Figure 6**), we classify 42 host factors, and finally get three different biological functions subnet. Module A mainly reflects the interleukin-1 receptor binding function. In its visualization diagram, we can clearly see that MMP9, IL1A, FOS, LEP, EGF, HIF1A and other nodes occupy important positions. Module B mainly functions as the Chemokine activity. Among them, the degree of CXCL10, CXCL5, and CCL4 is higher. In module C, the active function of estrogen 16-alpha-hydroxylase is more prominent. The analysis of its function shows that the signal receptor binding function mediated by CCL2 and MMP9 is the potential mechanism of the host factor interaction network between COVID-19 and COPD.

## GO, KEGG Enrichment Analysis

The directed acyclic graph (DAG) analysis of GO's biological process shows that the biological processes (**Figure 7** and **Table 3**) in COVID-19 and COPD comorbidities mainly have 5 branches, of which angiogenesis, cytokine-mediated signaling pathway, and cell migration are separate Branch. The defense response is immediately followed by the inflammatory response. At the same time, immune response and response to biotic stimulus are carried out in parallel, and response to biotic stimulus links response to external biotic stimulus and response to oxygen-containing compound processes, and finally ends with response to other organism. The molecular functions in COVID-19 and COPD comorbidities (**Figure 8** and **Table 4**) mainly have two major branches, among which the enrichment ratio of chemokine activity is the highest. Receptor regulator activity, receptor ligand activity, cytokine activity and chemokine activity belong to the same branch; signaling receptor binding, cytokine receptor binding, chemokine receptor binding and chemokine activity belong to the same branch; serine hydrolase activity, serine-type peptidase activity and serine-type endopeptidase activity both belong to another branch.

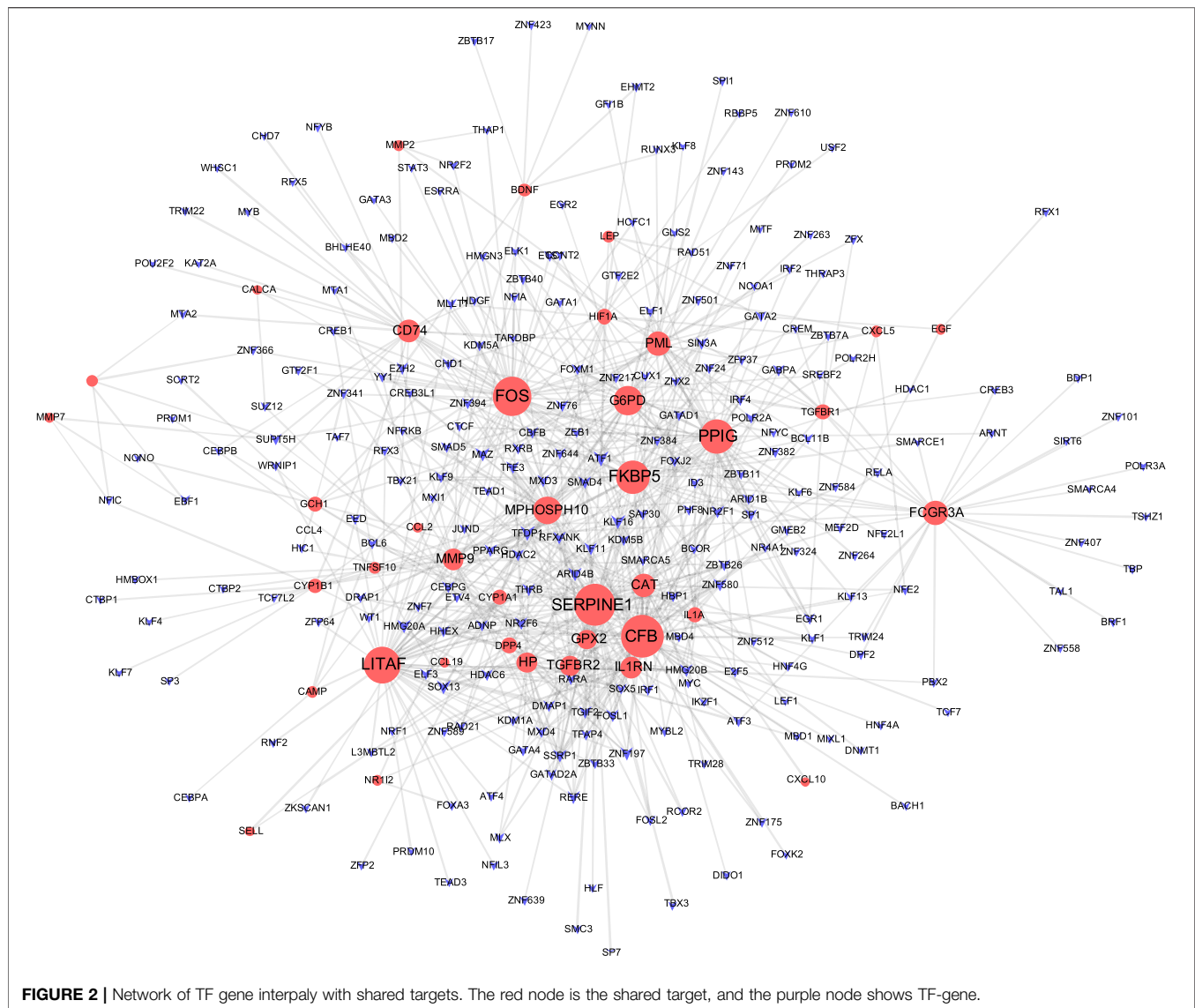
At the same time, pathway enrichment analysis showed (**Table 5**) that cytokine-cytokine receptor interaction, AGE-RAGE signaling pathway in diabetic complications, viral protein interaction with cytokine and cytokine receptor, osteoclast differentiation and IL-17 signaling pathway play an important role between COVID and COPD.

## Tissue Specific Enrichment Analysis of Host Factor Interaction Network

Tissue specific enrichment analysis showed that the co-host factors of COVID-19 and COPD comorbidities were most densely distributed in the lungs, spleen, liver, blood, small salivary glands, breast-breast tissue, prostate and vagina (**Figure 9**).

## Drug Prediction Through Common Host Factors

Based on a series of bioinformatics explorations on the interaction network between COVID-19 and COPD host factors, we finally made predictions about possible effective intervention drugs. Our research found that dexamethasone,



estradiol, progesterone, and nitric oxide have certain intervention effects, as shown in Table 6.

## DISCUSSION

All the work done in this research is to explore possible interaction pathways between COVID-19 and COPD from the perspective of host factors. On the basis of the front, we tried to find supporting evidence for the increased risk of pneumonia and poor prognosis when COPD patients were simultaneously infected with the SARS-COV-2 virus, and finally made reasonable predictions about the drug components that may be effective for intervention. The first step of our work was to screen out appropriate disease datasets/databases, find out the potential host factor of COVID-19/COPD, and then count the overlapping genes to obtain 42 common host factors. Based on the common host factors, a series of bioinformatics analyses were carried out.

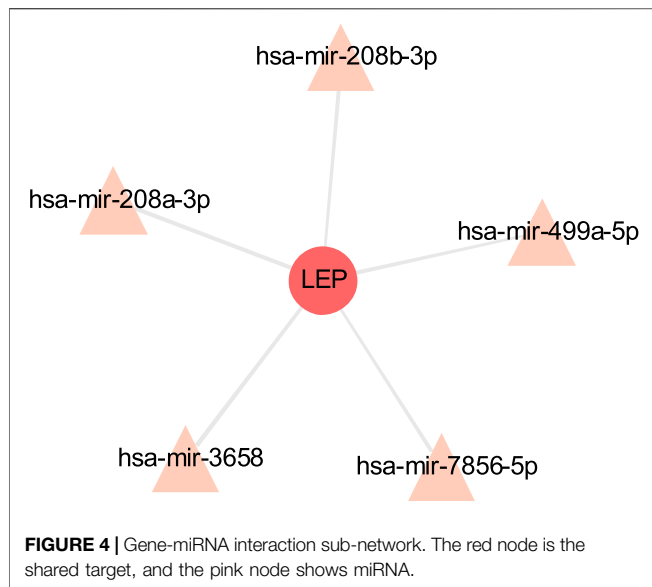
## Intersection Genes of COVID-19 and COPD Show the Key Host Factors of Comorbidity

After rigorously screening and processing genes, we have identified multiple shared genes exposed in the immune response of COVID-19 with COPD conditions (including CCL2, MMP9, IL1A, LEP, SERPINE1, CXCL10, EGF, CCL4, STAT1, and HIF1A). Most of these common genes have been shown to be related to the strong biological relevance of pathogenesis and pathology of COVID-19 and COPD.

## TF-Gene Interaction and Gene-miRNA Interaction Analysis

Transcriptome analysis of host cells after virus infection is helpful to identify the dynamics of host immune response, so it is necessary to understand the expression of host factors after co-infection of COVID-19 and COPD. The TF gene acts as a regulator based on

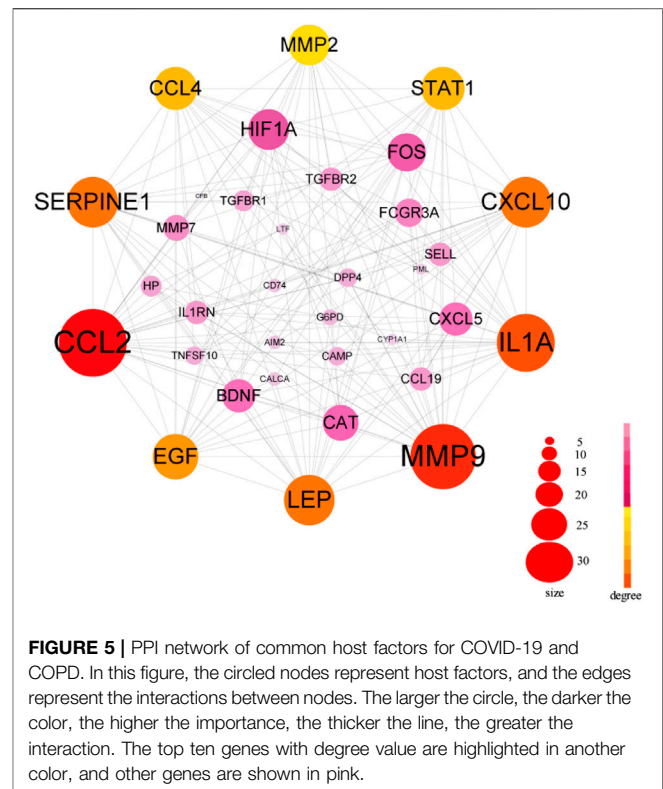




lie in the over-induction of the cytokine storm. In addition, the interaction between SARS-CoV spiking protein and ACE2 receptor mediated the phosphorylation of ERK1/2, which also led to the upregulation of CCL2 expression (Chen et al., 2010). In the early stages of SARS-CoV-2 infection, chemokine (CCL2) is broadly up-regulated by pro-inflammatory cytokine stimulation as a chemoattractant for effector cells such as monocytes, neutrophils, and leukocytes from the blood to the site of tissue injury. In addition, CCL2 can act as an autocrine factor that promotes viral replication in infected macrophages (Sabbatucci et al., 2015). In a high-density antibody microarray study of serum proteins from COVID-19 patients, a significant correlation between CCL2 and CXCL10-mediated cytokine signaling pathways has been demonstrated (Hou et al., 2020). This study suggests that CCL2 and CXCL10 have the potential to be used as anti-inflammatory targets for COVID-19 therapy (Zhang et al., 2020).

Matrix metalloproteinase 9 (MMP9) is particularly associated with COPD pathophysiology characterized by tissue remodeling. MMP9 mediates pulmonary inflammation through neutrophil chemotaxis, extracellular matrix degradation and enhanced inflammation, which is a key feature of the acute exacerbation phase of COPD (Mercer et al., 2005; Wells et al., 2015). Earlier reports suggested that human coronavirus infection increases MMP9 secretion (Desforges et al., 2007). Similarly, recent studies suggest that MMP9 stimulates the migration of inflammatory cells and further exacerbates lung tissue destruction by promoting inflammation and degradation of the pulmonary capillary barrier (Davey et al., 2011), which may serve as one of the early indicators of respiratory failure in patients with COVID-19 (Ueland et al., 2020).

The MCODE analysis unearthed modules with potentially different biological functions in the network nodes, providing a clearer direction for bioinformatics analysis. In this study, 3 subnetworks were obtained after dividing the 42 obtained host

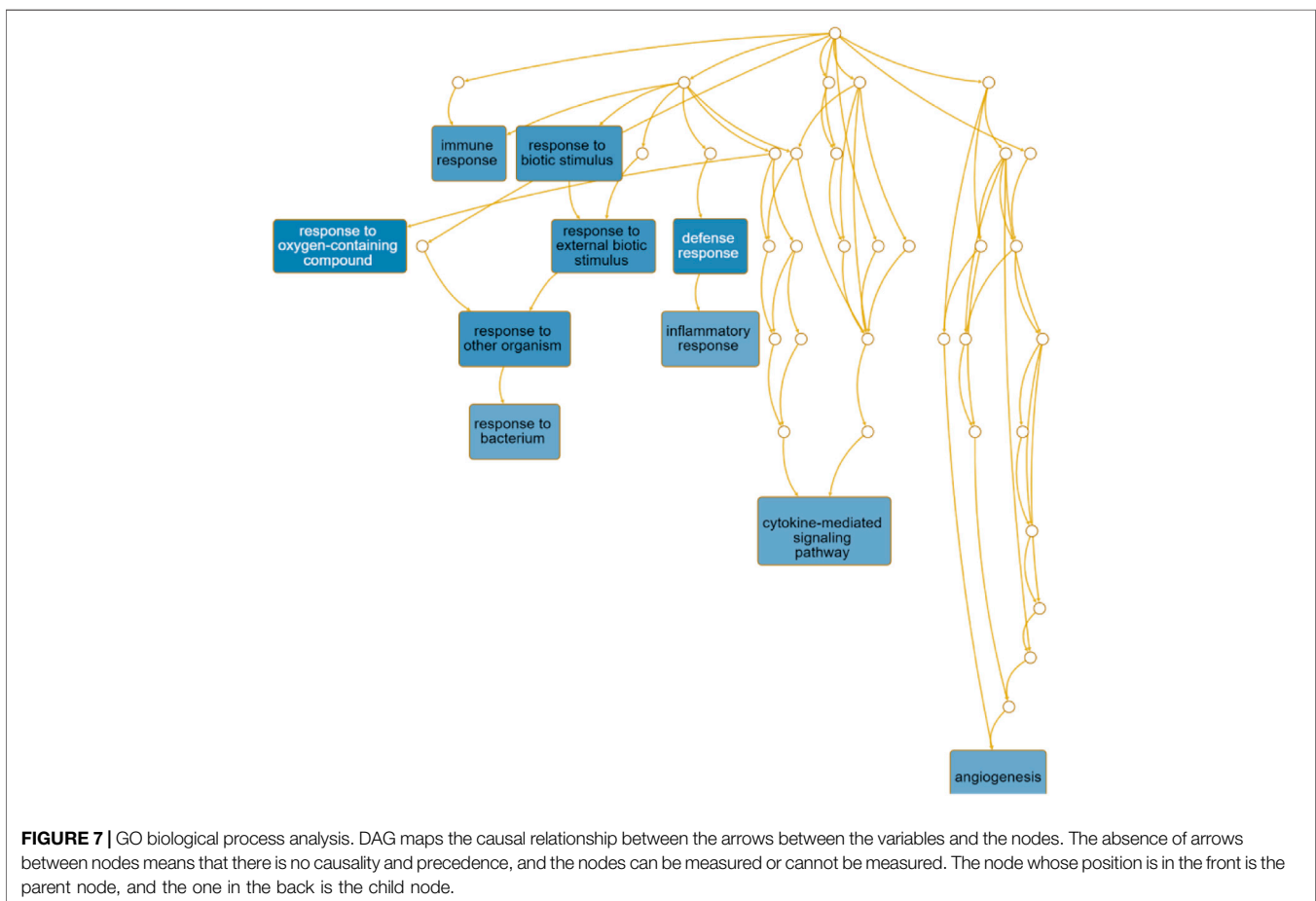
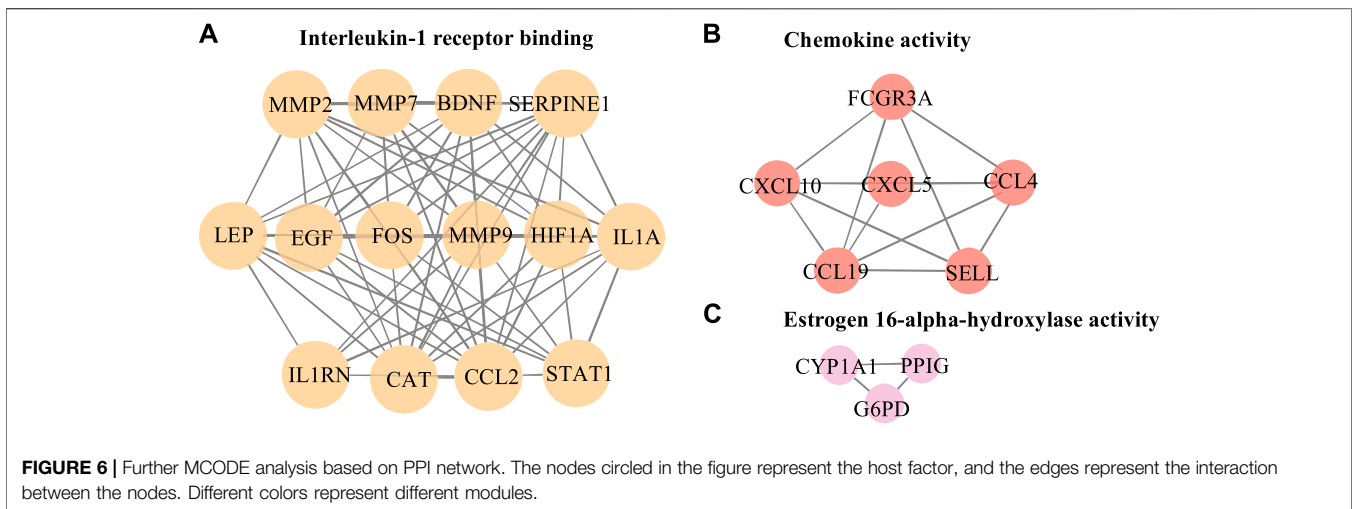


factors for COVID-19 and COPD comorbidity. Among them, module A focused on receptor binding, including interleukin-1 receptor binding, the RNA polymerase II core promoter sequence-specific DNA binding, the histone acetyltransferase binding, metalloendopeptidase activity, growth factor receptor binding, cytokine receptor binding, receptor ligand activity, receptor regulator activity and signaling receptor binding, etc. CCL2, MMP9, IL1A, HIF1A, and LEP occupy a prominent position in the whole module. Accumulating evidence suggests that infection with viruses activates extracellular signaling and induces IL-1 production (Liu et al., 2013). IL1A is upregulated in patients with mild COVID-19 and also enriched in alveolar lavage fluid of severe patients, playing an important role in innate immune virus infection (Shaath et al., 2020) and IL1A, as a pro-inflammatory cytokine, plays an important role in smoke-induced neutrophilic inflammation, dendritic cell recruitment and activation in COPD patients also plays a central role (Botelho et al., 2011).

## GO, KEGG Highlights the Immune Mechanisms of Host Factors and Significant Shared Signaling Pathways

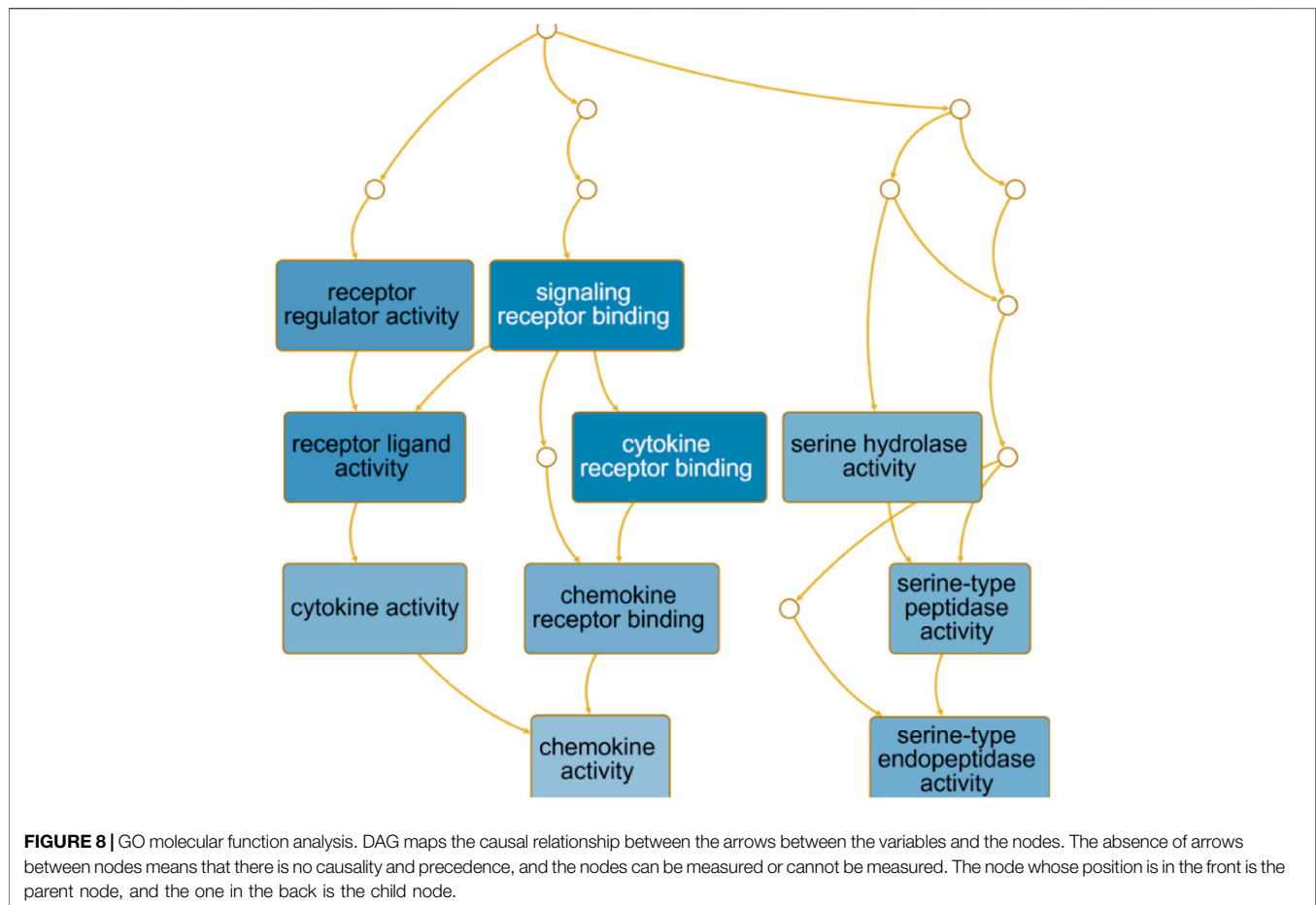
The directed acyclic graph (DAG), as a visual representation of the causal hypothesis (Suttorp et al., 2015), has clear advantages in estimating the effect of one variable on another and is a common tool for determining appropriate adjustment





strategies for epidemiological analyses (Ferguson et al., 2020). This structured approach facilitates visual clarification of the underlying relationships and serves as a visual aid in scientific discussions. Therefore, the GO analysis in this study abandoned the traditional network diagram format and adopted a DAG visualization approach to elucidate the mechanisms of comorbidity between COVID-19 and COPD.

The importance of angiogenesis is underscored by its separate branch in the biological processes of comorbidity, which is also the highest enrichment ratio of all genes. A 7-person clinical trial (Ackermann et al., 2020) had reported severe SARS-CoV-2 virus-associated endothelial damage and extensive vascular thrombosis in the lung cells of Covid-19 patients due to excessive cytokine storm, and significant neointimal growth in the lungs of Covid-19



patients through an infected angiogenic mechanism (Magro et al., 2020). In contrast, COPD, a pulmonary and systemic inflammatory process with progressive obstruction of pulmonary airflow, epithelial-mesenchymal transition and extracellular matrix remodeling similarly affects pulmonary and airway angiogenesis (Eapen et al., 2018). Our findings suggest that chemokine activity also plays an important role in the biological function of comorbidities. Chemokines recruit innate and adaptive immune cells to sites of inflammation, enhance their cytotoxic function and inhibit viral host responses, limiting viral infection (Melchjorsen et al., 2003). At the same time, viruses link innate and adaptive immune responses by inducing the production of inflammatory chemokines and promoting Th1-polarized immune responses. For COVID-19, CCL2 recruits neutrophils, monocytes, and macrophages, and CXCL9 and CXCL16 recruit T cells and NK cells to the site of viral infection (Proudfoot, 2002; Xu et al., 2020). Interestingly, CXCL10 increases with disease severity and is a key marker for detection in asymptomatic infected individuals (Chi et al., 2020). And chemoreceptors have long been a fertile area for research as anti-inflammatory therapeutic targets in COPD (Donnelly and Barnes, 2006).

In addition, KEGG enrichment analysis revealed important shared signaling pathways, cytokine-cytokine receptor interactions, viral protein interactions with cytokines and cytokine receptors, and IL-17 signaling pathways in diabetic complications. The No. 1 cytokine-cytokine receptor interaction

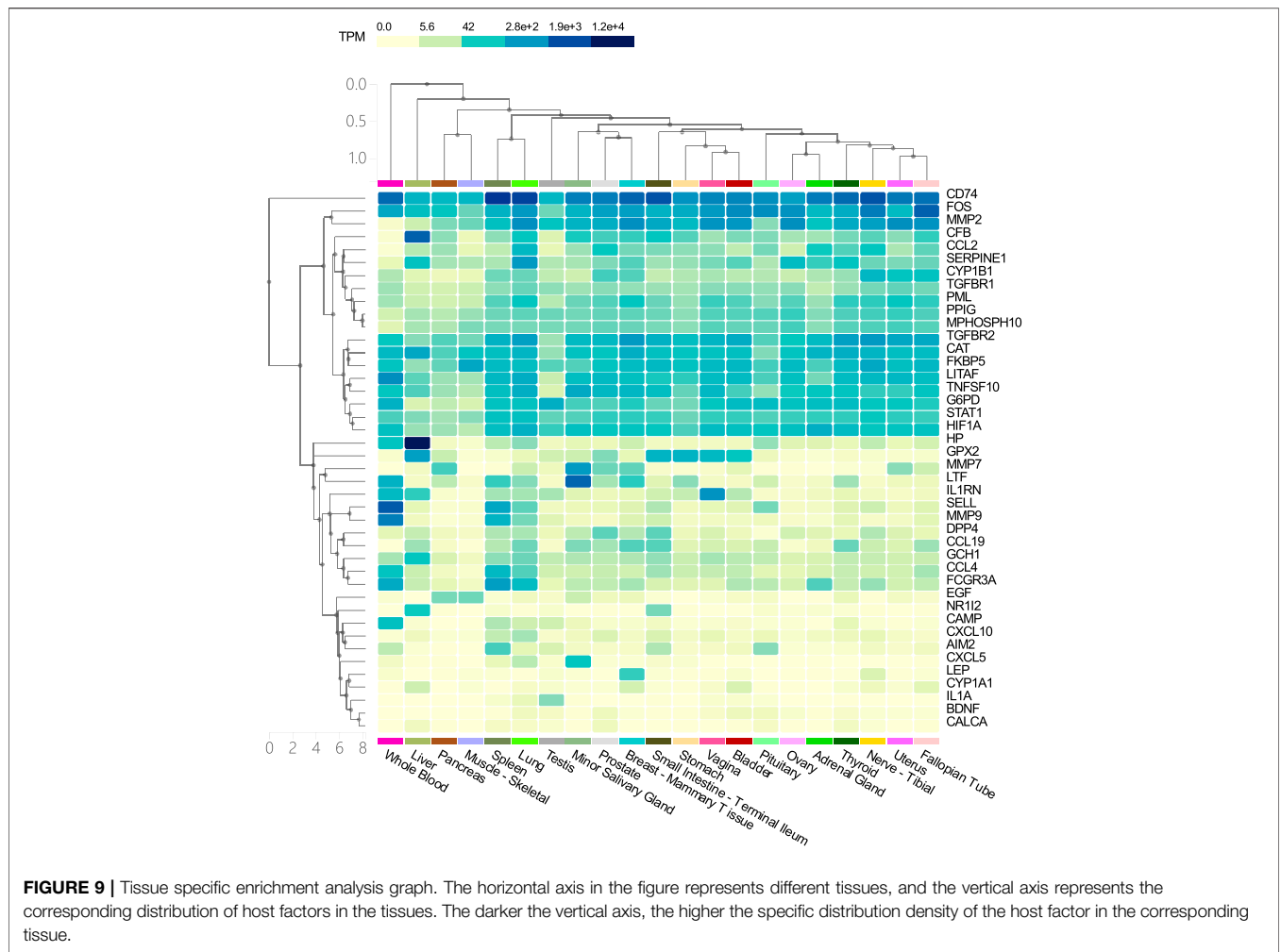
pathway is enriched with 11 host factors, mainly chemokine ligands and transforming growth factor  $\beta$  receptors. Viral infection and inflammation will cause changes in TGF- $\beta$  activity (Xia et al., 2017).

### Tissue Specific Enrichment Analysis Indicates the Expression of Certain Specific Host Factors

Our results suggest that the common host factors for COVID-19 and COPD comorbidity are most densely distributed in the lung, spleen, liver, blood, minor salivary glands, breast tissue, prostate, and vagina. As to why genes selected from alveolar lavage fluid, lung tissue, airway and blood samples are enriched in other organs and tissues, we think it may be due to the flow of blood that leads to the linkage between different tissues, or the intersection genes may also be derived from other tissues at the same time, because the genes from the database are not limited to samples of blood, lung tissue, alveolar lavage fluid and airway.

### The Intervention Drug Reveals Therapeutic Implications for COPD Patients With COVID-19

As shown in the potential intervention drugs or ingredients for COVID-19 and COPD comorbidities (Table 6), our study found



**FIGURE 9 |** Tissue specific enrichment analysis graph. The horizontal axis in the figure represents different tissues, and the vertical axis represents the corresponding distribution of host factors in the tissues. The darker the vertical axis, the higher the specific distribution density of the host factor in the corresponding tissue.

**TABLE 3 |** GO-BP enrichment analysis.

GeneSet	Description	Size	Overlap	Expect	Enrichment Ratio	p Value	FDR
GO:1901700	response to oxygen-containing compound	1,556	24	3.82837254	6.268982	5.11E-15	4.64E-11
GO:0006952	defense response	1,518	23	3.73487758	6.158167	4.02E-14	1.83E-10
GO:0051707	response to other organism	897	18	2.206973116	8.155967	7.61E-13	1.80E-09
GO:0043207	response to external biotic stimulus	899	18	2.211893903	8.137823	7.90E-13	1.80E-09
GO:0009607	response to biotic stimulus	926	18	2.278324532	7.900543	1.30E-12	2.37E-09
GO:0006955	immune response	1919	23	4.721495439	4.871338	5.78E-12	8.76E-09
GO:0019221	cytokine-mediated signaling pathway	705	15	1.734577532	8.647639	4.89E-11	6.35E-08
GO:0006954	inflammatory response	717	15	1.764102256	8.502908	6.20E-11	6.88E-08
GO:0009617	response to bacterium	595	14	1.463934229	9.563271	6.81E-11	6.88E-08
GO:0001525	angiogenesis	487	13	1.198211714	10.8495	8.08E-11	7.30E-08

that dexamethasone, estradiol, progesterone, and nitric oxide, etc. all demonstrated effective intervention. In a randomized controlled trial, the RECOVERY Collaborative Group (Horby et al., 2021) found that using dexamethasone at a daily dose of 6 mg for 10 consecutive days reduced mortality for 28 days in patients receiving respiratory support for COVID-19. Glucocorticoids are also recommended in the updated guidelines of the United Kingdom chief medical officers and

the National Institutes of Health in the United States for inpatient use of COVID-19. There is no definitive clinical data on the clinical outcomes of the use of glucocorticoids in COPD patients who are infected with COVID-19 at the same time (Halpin et al., 2020; Halpin et al., 2021), but our results suggest that there is bioinformatics evidence for the use of dexamethasone for treatment. Nevertheless, more laboratory and clinical trials are needed before dexamethasone becomes a potential therapeutic

**TABLE 4** | GO-MF enrichment analysis.

GeneSet	Description	Size	Overlap	Expect	Enrichment Ratio	p Value	FDR
GO:0005102	signaling receptor binding	1,538	19	3.783177	5.022233	6.55E-10	8.21E-07
GO:0005126	cytokine receptor binding	274	10	0.673986	14.8371	8.75E-10	8.21E-07
GO:0048018	receptor ligand activity	468	11	1.151188	9.555347	1.12E-08	7.03E-06
GO:0030545	receptor regulator activity	514	11	1.264339	8.700199	2.95E-08	1.38E-05
GO:0004252	serine-type endopeptidase activity	182	7	0.447684	15.63602	2.71E-07	1.02E-04
GO:0042379	chemokine receptor binding	61	5	0.150048	33.32267	3.76E-07	1.18E-04
GO:0008236	serine-type peptidase activity	204	7	0.5018	13.94978	5.86E-07	1.57E-04
GO:0017171	serine hydrolase activity	208	7	0.511639	13.68152	6.68E-07	1.57E-04
GO:0005125	cytokine activity	217	7	0.533777	13.11408	8.88E-07	1.85E-04
GO:0008009	chemokine activity	47	4	0.115611	34.59886	5.21E-06	9.70E-04

**TABLE 5** | KEGG enrichment analysis.

ID	Description	GeneRatio	p value	p.adjust	Qvalue	Count
hsa04060	Cytokine-cytokine receptor interaction	11	6.17E-08	9.44E-06	6.37E-06	11
hsa04933	AGE-RAGE signaling pathway in diabetic complications	7	3.25E-07	2.49E-05	1.68E-05	7
hsa04061	Viral protein interaction with cytokine and cytokine receptor	6	6.08E-06	0.00031	0.000209	6
hsa04380	Osteoclast differentiation	6	2.52E-05	0.000963	0.000649	6
hsa04657	IL-17 signaling pathway	5	6.99E-05	0.00214	0.001443	5
hsa05142	Chagas disease	5	0.000103	0.002589	0.001746	5
hsa05164	Influenza A	6	0.000132	0.002589	0.001746	6
hsa04659	Th17 cell differentiation	5	0.000135	0.002589	0.001746	5
hsa04668	TNF signaling pathway	5	0.000161	0.002733	0.001842	5
hsa04062	Chemokine signaling pathway	6	0.00024	0.00367	0.002474	6
hsa04926	Relaxin signaling pathway	5	0.000311	0.004262	0.002874	5
hsa04068	FoxO signaling pathway	5	0.000334	0.004262	0.002874	5
hsa05212	Pancreatic cancer	4	0.000414	0.004483	0.003022	4
hsa05140	Leishmaniasis	4	0.000435	0.004483	0.003022	4
hsa05418	Fluid shear stress and atherosclerosis	5	0.000439	0.004483	0.003022	5
hsa05208	Chemical carcinogenesis - reactive oxygen species	6	0.000536	0.005122	0.003453	6
hsa05210	Colorectal cancer	4	0.000662	0.005962	0.00402	4
hsa05235	PD-L1 expression and PD-1 checkpoint pathway in cancer	4	0.000754	0.00641	0.004322	4
hsa05161	Hepatitis B	5	0.000883	0.006531	0.004403	5
hsa05323	Rheumatoid arthritis	4	0.00089	0.006531	0.004403	4
hsa05219	Bladder cancer	3	0.000896	0.006531	0.004403	3
hsa00380	Tryptophan metabolism	3	0.000962	0.006692	0.004512	3
hsa04620	Toll-like receptor signaling pathway	4	0.00135	0.008984	0.006057	4
hsa05152	Tuberculosis	5	0.001416	0.009024	0.006084	5
hsa04010	MAPK signaling pathway	6	0.002243	0.01373	0.009257	6

drug in the future. In addition, studies have found that 17 $\beta$ -estradiol administration can effectively reduce the up-regulation of ACE2-dependent NOX2, MCP-1 and ROS, and alleviate endothelial dysfunction and multiple organ failure mediated by COVID-19 inflammation during the pathogenesis (Youn et al., 2021). Experiments have pointed out that the combination of progesterone and glucocorticoids can synergistically reduce lung inflammation in mice caused by chronic ozone exposure (Fei et al., 2017). And, progesterone has a certain role in COPD airway remodeling (Zhang et al., 2018). In addition, estrogen can also promote the separation of endothelial nitric oxide synthase (eNOS) from plasma membrane acupoints, thereby activating NO pathways and vascular adsorption, and playing a role in regulating blood vessels (Hisamoto and Bender, 2005). These data provide support for our research results, but there are no relevant clinical and experimental studies on the use of this ingredient in COVID-

19 and COPD comorbidities. This will be one of the contents of our future work research.

## CONCLUSION

In order to explore the mechanism of co-morbidity between COVID-19 and COPD, after carefully screening the COVID-19 and COPD data sets and strictly processing co-host genes, we conducted a series of bioinformatics analyses from the perspective of host factor interactions, and initially discovered drugs or active ingredients for potential interventions. We found that the main biological process of COPD patients infected with COVID-19 is angiogenesis, and the main molecular function is chemokine activity. In addition, we also found that the cytokine-cytokine receptor interactions signaling pathway is a common pathway for the progression of the two diseases. Finally, we

**TABLE 6** | Drug stitch enrichment analysis.

Enrichment FDR	Genes in list	Total genes	Functional category
1.02E-25	23	409	STITCH dexamethasone (CID000005743)
1.02E-25	22	340	STITCH dexamethasone (CID100003003)
2.36E-18	18	367	STITCH estradiol (CID100000450)
4.94E-18	17	310	STITCH progesterone (CID000005994)
3.30E-16	14	194	STITCH nitric oxide (CID100000945)

concluded that dexamethasone, estradiol, progesterone, and nitric oxide are potentially effective therapeutic drugs, providing a clearer direction for future clinical research.

## LIMITATION

First of all, our research is based on co-expressed genes, involving non-coding RNA, but we have not conducted studies on post-translational modification and interference with other metabolites. This is related to the content of our research, but they are not the subject of this research. Therefore, we will supplement the research in future work. Secondly, although the study selected sample data from airway, lung, and peripheral blood for tissue-specific enrichment analysis, the results showed that the co-host factors of COVID-19 and COPD comorbidities were also enriched in spleen, liver, blood, minor salivary glands, breast tissue, prostate, and vagina. We speculate that the peripheral blood may mediate this process, or it may be because we also selected genes from the database. The genes in the database are not distinguished according to the source of the tissue, so there is a certain amount of confounding. Finally, given the limitations of bioinformatics predictions, candidate drugs may also affect counter-regulatory genes not identified in this study. We must admit that this is the limitation of our research. Therefore, we are trying to find positive intermediary evidence to support the prediction results, and we also look forward to future *in vivo* and *in vitro* experiments to prove this.

## DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

## AUTHOR CONTRIBUTIONS

WZ conceived and designed the study, plotted the figures based on network pharmacology, using online databases. TW conducted data analysis and wrote discussions and abstracts. PW conducted a literature search on the background of this disease and wrote part

of the article. QY is responsible for most of the image processing. CL organized the data and standardized the image format. HW annotated the picture and wrote the conclusion. SZ reviewed the manuscript. HZ, YJ and XL reviewed and revised the manuscript. All authors read and approved the final version of the manuscript.

## FUNDING

This research was funded by grants from the “Double First-Class” and High-level University Discipline Collaborative Innovation Team Project of Guangzhou University of Chinese Medicine (Grant No.2021XK16), the Guangdong Provincial Department of Education Innovation Team Project (Grant No .2018KCXTD007), the Scientific Research Project of Guangdong Provincial Bureau of Traditional Chinese Medicine (Grant No.20212056), the Key-Area Research and Development Program of Guangdong Province (Grant No. 2020B1111100002), the National Natural Science Foundation of China (Grant Nos. 81973814 and 81904132), the Natural Science Foundation of Guangdong Province (Grant No. 2017A030310129), the Natural Science Foundation of Guangdong Province (Grant No. 2020A1515010589), the XL Famous Traditional Chinese Medicine Inheritance Studio from the Traditional Chinese Medicine Bureau of Guangdong Province (Grant No. 201805), the Construction Project of Respiratory Department National Clinical Medical Research Center (Grant No. 2110200309), 2018 Guangzhou University of Chinese Medicine National University Student Innovation and Entrepreneurship Training Project (Grant No. 201810572038), 2020 National College Student Innovation and Entrepreneurship Training Project of Guangzhou University of Chinese Medicine (Grant No. 202010572001), the Student Learning Team Incubation Project of Innovation Academy from The First Affiliated Hospital of Guangzhou University of Chinese Medicine (Grant No. 2018XXTD003), and the Technology Research of COVID-19 Treatment and Prevention and Special Project of Traditional Chinese Medicine Application-Research on the platform construction for the prevention and treatment of viral infectious diseases with traditional Chinese medicine (Grant No. 2020KJCX-KTYJ-130).

## ACKNOWLEDGMENTS

We thank the SCI Writing Program at GZUCM 2020 for its valuable assistance. We thank the English courses for Ph. D. candidates of SCI paper writing of Guangzhou University of Chinese Medicine in 2020 (We thank the English teachers Shuaishuai Liu and Guoqi Shi). We thank our team leader XL.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2021.718874/full#supplementary-material>

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