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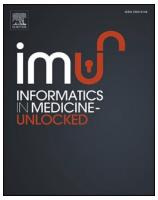

Identification of differentially expressed genes and their major pathways among the patient with COVID-19, cystic fibrosis, and chronic kidney disease

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ABSTRACT

The SARS-CoV-2 virus causes Coronavirus disease, an infectious disease. The majority of people who are infected with this virus will have mild to moderate respiratory symptoms. Multiple studies have proved that there is a substantial pathophysiological link between COVID-19 disease and patients having comorbidities such as cystic fibrosis and chronic kidney disease. In this study, we attempted to identify differentially expressed genes as well as genes that intersected among them in order to comprehend their compatibility. Gene expression profiling indicated that 849 genes were mutually exclusive and functional analysis was done within the context of gene ontology and key pathways involvement. Three genes (PRPF31, FOXN2, and RIOK3) were commonly upregulated in the analysed datasets of three disease categories. These genes could be potential biomarkers for patients with COVID-19 and cystic fibrosis, and COVID-19 and chronic kidney disease. Further extensive analyses have been performed to describe how these genes are regulated by various transcription factors and microRNAs. Then, our analyses revealed six hub genes (PRPF31, FOXN2, RIOK3, UBC, HNF4A, and ELAVL). As they were involved in the interaction between COVID-19 and the patient with CF and CKD, they could help researchers identify potential therapeutic molecules. Some drugs have been predicted based on the upregulated genes, which may have a significant impact on reducing the burden of these diseases in the future.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense single-stranded RNA virus that causes severe respiratory syndrome in humans [1], reported for the first time in Wuhan, China. As of July 22, 2022, there had been 565,207,160 confirmed cases of COVID-19 reported to the World Health Organization (WHO), with 6,373,739 deaths, and a total of 12,219,375,500 vaccination doses had been delivered as of July 18, 2022 (https://covid19.who.int/). SARS-CoV-2 targets the angiotensin-converting enzyme 2 (ACE2), which is a cell surface receptor present in the heart, kidney, blood vessels, and lungs [2]. All coronaviruses have spike proteins containing N-terminal and C-terminal domains, and two major subunits (S1 and S2), which are responsible for the viral entry [3].

Cystic fibrosis (CF) is a lung disease characterized by mucus blockage and chronic airway inflammation. Mutations in the CF transmembrane conductance regulator (CFTR) gene, which codes a protein that controls sodium and water resorption as well as chloride and bicarbonate transport through mucosal surfaces, are responsible for this disease. Poor mucociliary clearance and viscous secretions have been documented as a result of several CFTR mutations. Therefore, a systemic disease develops that affects the lower airways and digestive system. Chronic pulmonary infections induce respiratory symptoms that subsequently lead to impaired lung function and respiratory failure, which is the major cause of mortality in people with CF [4]. In addition to thick mucus, CFTR failure in bronchial epithelia causes an enhanced inflammatory response and a reduced immune response, rendering it vulnerable to acute infections and long-term bacterial colonization of the lungs [5].

Chronic kidney disease (CKD) is a chronic disorder marked by structural and functional abnormalities in the kidney as a result of some factors. The global burden of CKD is burgeoning. Chronic renal disease is

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expected to become the fifth highest cause of death worldwide by 2040, with one of the most significant anticipated rises of any major cause of death [6]. The causes of CKD are complex and heterogeneous. Environmental as well as genomic factors can play a role in the development of the disease. Infections are associated with CKD, which is very common in many lower middle income countries due to inadequate access to clean water, poor sanitary settings, and excessive proportions of disease transmitting vectors [7].There are several clinical biomarkers that can be used to identify chronic kidney disease, including serum creatinine levels, cystatin C levels, estimated glomerular filtration rates, and urinary albumin-creatinine ratios or urinary protein-creatinine ratios [8].

It has been proven that respiratory viruses are linked to long-term respiratory infections in people with CF and they can lead to pulmonary exacerbation, deteriorating lung function, and increased mortality in this population [9,10]. Several theories have been proposed to explain the considerable clinical impact of the SARS-CoV-2 virus in CF patients.

When entering a host cell, SARS-CoV-2 employs the ACE-2 receptor. Usually, infection causes a massive drop in ACE-2 expression on cell surfaces. However, the degree of this down-regulation appears to be lower in CF patients than in non-CF individuals [11]. Down-regulation of ACE-2 is linked to an increase in the inflammatory response to the virus, suggesting that this event might contribute to the severity of COVID-19 in CF patients [11]. The impact of COVID-19 is linked to the CF patient's baseline lung function. As a result, it is probable that patients with severe lung disease are more likely to experience an exacerbation and, as a consequence, they are more likely to develop severe COVID-19 manifestations [12]. According to one report, clinical features associated with a severe type of CF have been linked to an increased likelihood of COVID-19 hospitalization [13]. People with CF are considered extremely vulnerable due to the significant likelihood of serious viral respiratory infections [14].

Other organ abnormalities, such as kidney dysfunction leading to acute renal injury, have been recorded in patients with SARS-CoV-2 infection in addition to lung involvement [15], raising concern about the clinical outcomes and prognosis of individuals with comorbidities, including chronic renal disease (CKD). According to a meta-analysis of 73 studies examining the link between multi-organ dysfunction and COVID-19 development, patients with CKD were more likely to develop severe SARS-CoV-2 infection [16]. People with CKD and COVID-19 may die at a higher rate than those with CKD but no COVID-19 [17]. The ACE-2 receptor, which functions as an entry portal into the cells, is also expressed in the proximal tubular cells of the nephron, and viral nucleocapsid protein has been detected in PCT and urine, which could explain the apparent 'Nephrotropism' in COVID-19 [18–20].

Based on the previous observations, COVID-19, CF, and CKD may share some pathological similarities. We have identified DEGs for three datasets, indicating an interpretation of gene transcript abundance changes within a transcriptome [21]. To better understand this compatibility, we looked into gene ontology (GO) and some cell informative pathways are shared by these three diseases. To demonstrate their strong relationship, we have attempted to build protein-protein interactions (PPIs) networks and identified hub genes. Moreover, TF-miRNA and gene-chemical interactions have been observed to show the gene regulatory network (GRN). Finally, some suitable drug molecules were suggested by targeting the upregulated significant genes in the whole dataset. The entire investigation was carried out using transcriptome datasets.

2. Materials and method

2.1. Data set retrieval and identification of DEGs

The NCBI GEO database was selected to analyze three datasets, GSE147507, GSE38267, and GSE66494, for patients with SARS-CoV-2, CF, and CKD, respectively. (https://www.ncbi.nlm.nih.gov/). We used the limma package of R to find out the genes that were expressed differentially between 23 SARS-CoV-2 infected patients and 22 healthy controls (among the total 110 samples). This package is widely renowned for assessing differentially expressed genes (DEGs) [22]. In addition, GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r/) statistical tool was employed for the identification of DEGs of both CF and CKD. This package uses GEO query and limma R packages from the Bioconductor (an open-source software project based on the R program) [23] to determine DEGs by comparing infected patients and healthy controls. Then, from the GSE38267 dataset, 23 CF patients and 28 healthy controls were analysed to find out genes that were expressed differentially. A microarray profile of 53 CKD patients and 8 controls were reported in the GSE66494 dataset. The cut-off was set at 0.05 for the adjusted *P*-value to identify the relevant genes. The outline of the workflow is illustrated in Fig. 1.

2.2. GO and pathway analysis

GO and pathway-based analyses are required to comprehend the biological implications of DEGs. Functional knowledge is arranged and recorded in GO in a way that can be computationally analysed, which is crucial for advanced biomedical research. GO is a computational and statistical method for investigating a group of genes and their biological, molecular, and cellular features, as well as their cell informative pathways [24,25]. Enrichment analysis can be performed on a group of genes identified in genome-wide studies to investigate if they are enriched with genes from a specific pathway or functional category [26]. ShinyGOv0.741 online tool was employed for the enrichment and GO analysis, which is based on 315 organisms' annotation databases, including 184 at Ensembl (vertebrates, release 96) [27]. We depicted the Kyoto Encyclopedia of Genes and Genomes (KEGG), WikiPathways, and Reactome. KEGG is a computer-based demonstration of the biological system, which is classified into chemical genomics, and system information [28,29]. Wiki Pathways [30] is a collective approach for creating and maintaining information about biological pathways, whereas the Reactome database offers curated annotations on a wide range of molecular and cellular biology areas [31]. The adjusted *P*-value <0.05 was set as a standard value for quantifying the most significant listed GO and pathways for common DEGs.

2.3. Analysis of the PPIs network

The inspection and characterization of the PPIs network with its behaviours are the primary goals in cellular as well as systems biology for understanding and learning about cellular machinery activities [32–34]. PPIs have been employed in a variety of biological studies, including pathway discovery [35], functional module partitioning [36], and annotation of novel protein functions [36,37]. To represent functional and physical interaction, we built a PPIs network of proteins based on upregulated DEGs among the three disease categories using the Network Analyst (https://www.networkanalyst.ca/) online tools and string interactome database [38]. The assessment of protein-protein interactions provides significant information about the activities of proteins, which is considered a vital step in drug discovery and systems biology. After network generation, we visualized the PPIs network with the Cytoscape software version v3.8.2 (https://cytoscape.org/). It is free-source software in which multiple datasets are aggregated to enhance the performance of various interactions like PPIs, genetic interactions, and protein-DNA interactions [39].

2.4. Establishment of a network of hub genes and submodules

Hub nodes are widely considered as tightly connected nodes through the edges of PPI's sophisticated networking structure. Hub genes and organizing network nodes were detected by applying the Cytoscape plugin cytoHubba (http://apps.cytoscape.org/apps/cytohubba) [40].

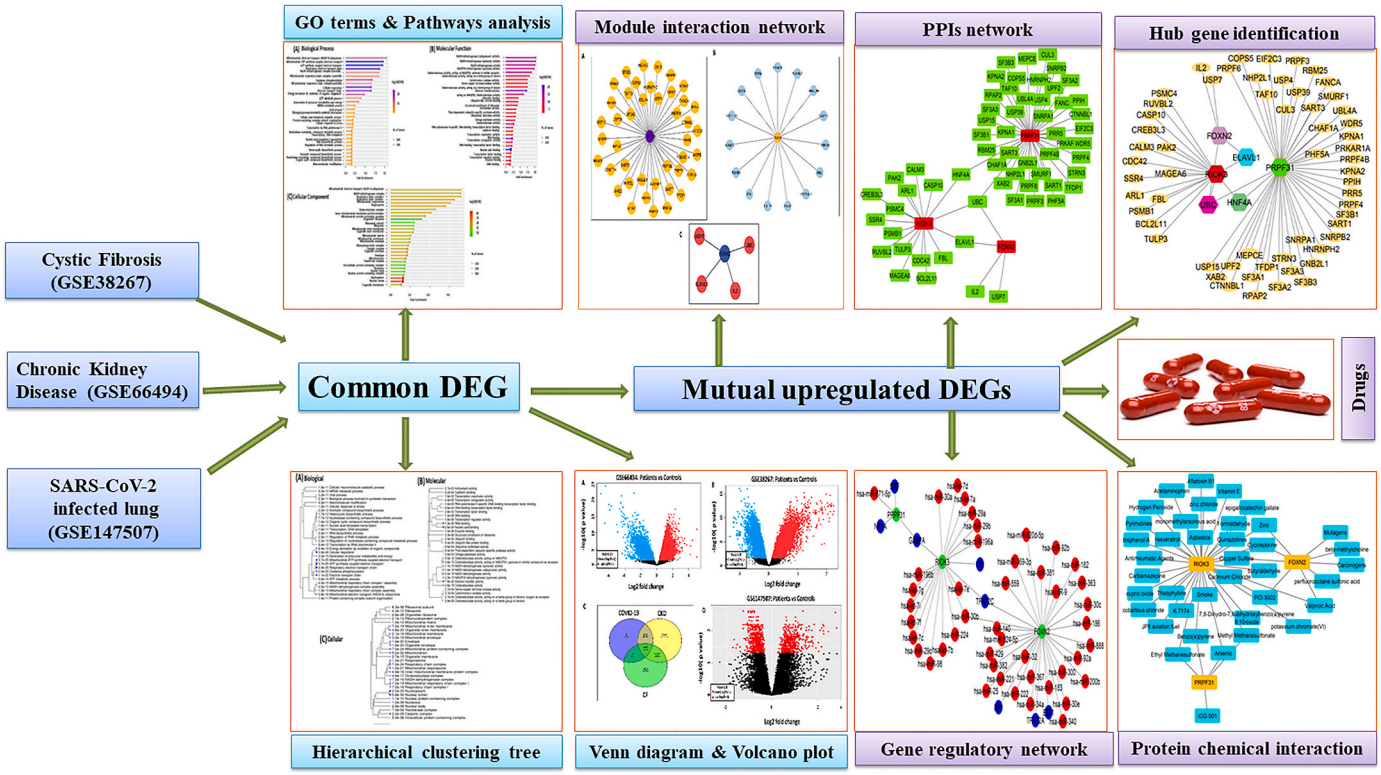

Fig. 1. Workflow of the current analysis. The study consisted of several major steps. The primary step involves gathering gene expression datasets from NCBI GEO. Three datasets GSE147507, GSE38267, and GSE66494 are analysed for the patients of SARS-CoV-2, CF, and CKD, respectively. DEGs were identified using R and GEO2R. Similar DEGs were identified from total DEGs of three datasets using Venn diagram, and volcano plot employed to show significant genes. Corresponding similar DEGs were used to perform GO and pathway analysis. Then, attempted to construct the protein-protein interaction network (PPI), identify hub genes, module analysis, gene regulatory networks, and protein chemical interaction. In the final stage we have suggested some suitable drugs.

Modules are the sites where the hub nodes are tightly integrated into the PPIs network. ClusterViz (http://apps.cytoscape.org/apps/clusterviz) is another Cytoscape plugin that was used to analyze modules in the existing network.

2.5. Recognition of the TF–miRNA co-regulatory network

The RegNetwork repository database of the Network Analyst platform (https://www.networkanalyst.ca/) has been selected for the identification of the TF-miRNA networks [41]. These TF-miRNAs influenced DEGs in the transcriptional and post- transcriptional stages. The Cytoscape software was used to visualize this network.

2.6. Therapeutic drugs prediction

Suitable drug selection is essential for limiting the severity of SARS-CoV-2 infection in patients with comorbidities such as CF and CKD. The Enrichr platform's Drug Signatures Database (DSigDB) was employed to predict some prophylaxis. This database contains 22,527 gene sets, 19,531 genes, and 17,389 distinct chemicals [42]. Drugs with an adjusted *P* value <0.05 were thought to be promising therapies for the ailment.

3. Results

3.1. Data collection and DEGs determination from three datasets

The studied datasets were selected from NCBI GEO. The various experiments' data are stored in this database that allows researchers to obtain the gene expression profiles [43]. Regarding the COVID-19 (GSE147507) dataset, we have found 1039 DEGs as compared to controls (adjusted *P* value <0.05). GSE38267 dataset revealed 17227 differentially expressed genes. Finally, 19554 genes were found to be differentially expressed from GSE66494 dataset. We removed duplicated genes and the values lacked specific gene symbols from whole datasets. The identified DEGs between patients and healthy controls were based on log2 fold change, in which absolute value >1.0 and an adjusted *P*-value <0.05 were considered as a cutoff to determine significant DEGs from the studied database. We found 849 similar DEGs among three disease groups after subjecting them to a Venn diagram. The volcano plots showed the pattern of upregulated and downregulated genes among the studied subjects, and the intersection of the three datasets was represented in the Venn diagram (Fig. 2).

3.2. GO and pathway analysis

We constructed a summary of the graphical representation of GO terms (Fig. 3) and its hierarchical tree (Fig. 4). In addition to GO, three pathways (Fig. 5) such as KEGG, Wiki pathways, Reactome, and their summarised hierarchical trees (Fig. 6) were depicted based on mutual DEGs from the three datasets. For all the pathways and hierarchical trees, the top 20 highly enriched significant terms have been demonstrated.

3.3. PPIs integration for the commonly upregulated DEGs

We scrutinized the up-regulated DEGs based on the logFC (logFC >1, which was considered the upregulated DEGs) value of the three datasets. For COVID-19, CF, and CKD, three genes (PRPF31, FOXN2, and RIOK3) have been found to be up-regulated. To view the interaction profile among the other genes, these DEGs were submitted to a web based platform called Network Analyst. The network was then visualized in

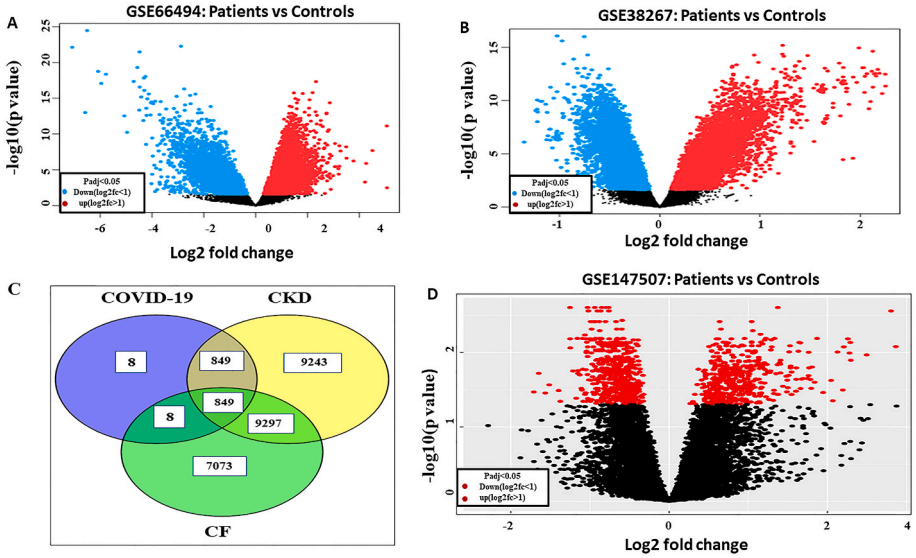

Fig. 2. Profiling of common DEGs and their expression regulation. The volcano plots (A), (B), and (D) show the DEGs that were up or down regulated in the GSE66494, GSE38267, and GSE147507 datasets. The Venn diagram (C) demonstrates the shared DEG of three datasets.

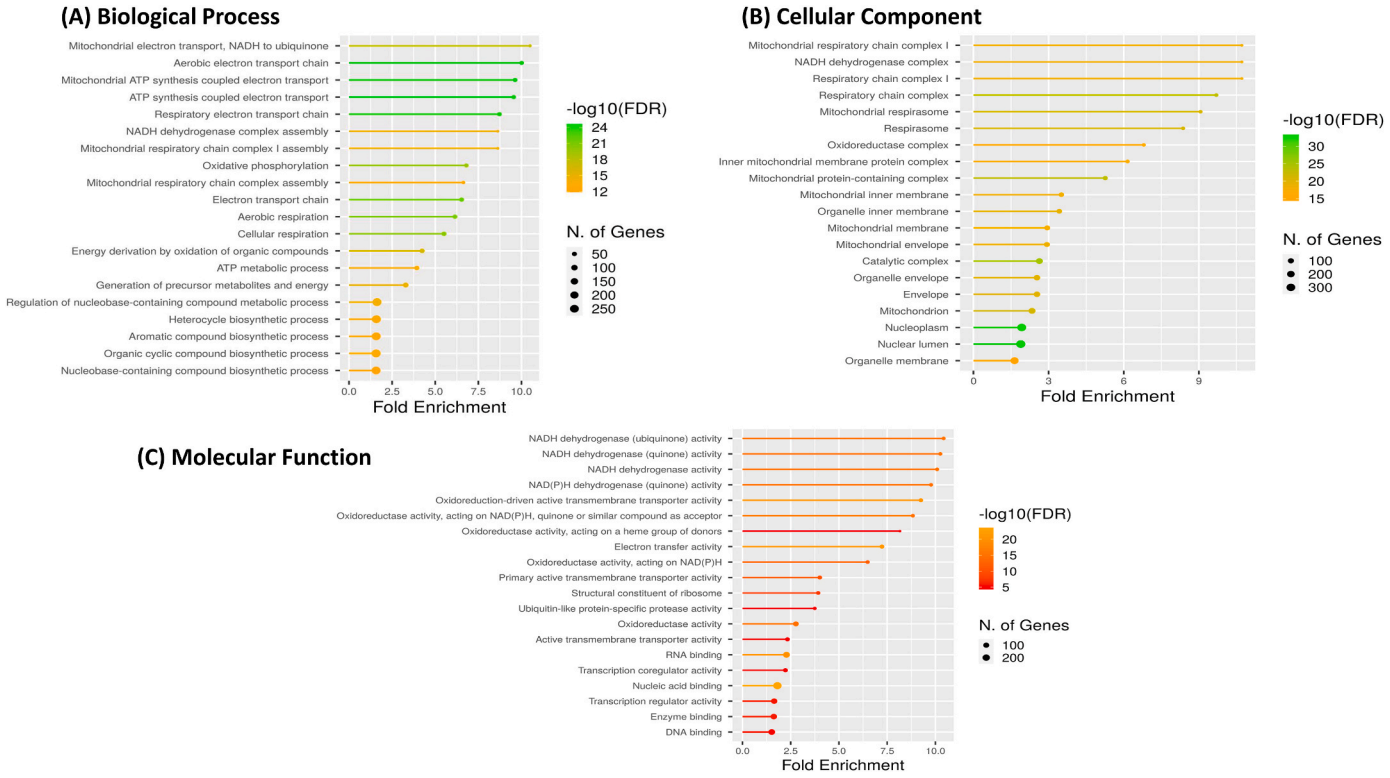

Fig. 3. Gene ontology of COVID-19 and the diseases of CF and CKD based on common DEGs.No. Of genes indicate the genes involved in each GO function. (A) Shows the Biological Process. (B) Displays Cellular Component. (C) Molecular Function.

Cytoscape, which consists of 64 nodes, 65 edges, and 3 seeds that had strong interactions (Fig. 7).

3.4. Detection of hub genes based on topological analysis and module identification from the PPIs network

The degree of protein nodes was calculated by using the CytoHubba application in Cytoscape software to determine hub genes [39]. The degree of the topological algorithm was utilized to detect the central gene. Six genes (PRPF31, FOXN2, RIOK3, UBC, HNF4A, and ELAVL1) have been reported as the hub genes and their topological characteristics have been described (Table 1). These six genes are intricately linked to one another. (Fig. 8). It is very important to identify the hub genes because they could be potential biomarkers for future therapy in many diseases. As it is related to therapy, we tried to identify the module network to observe the close connectivity among genes (Fig. 9). Three sub-module networks have been uncovered that were primarily interconnected and classified them based on modularity (Table 2). EAGLE algorithm of Cytoscape was used to obtain this result.

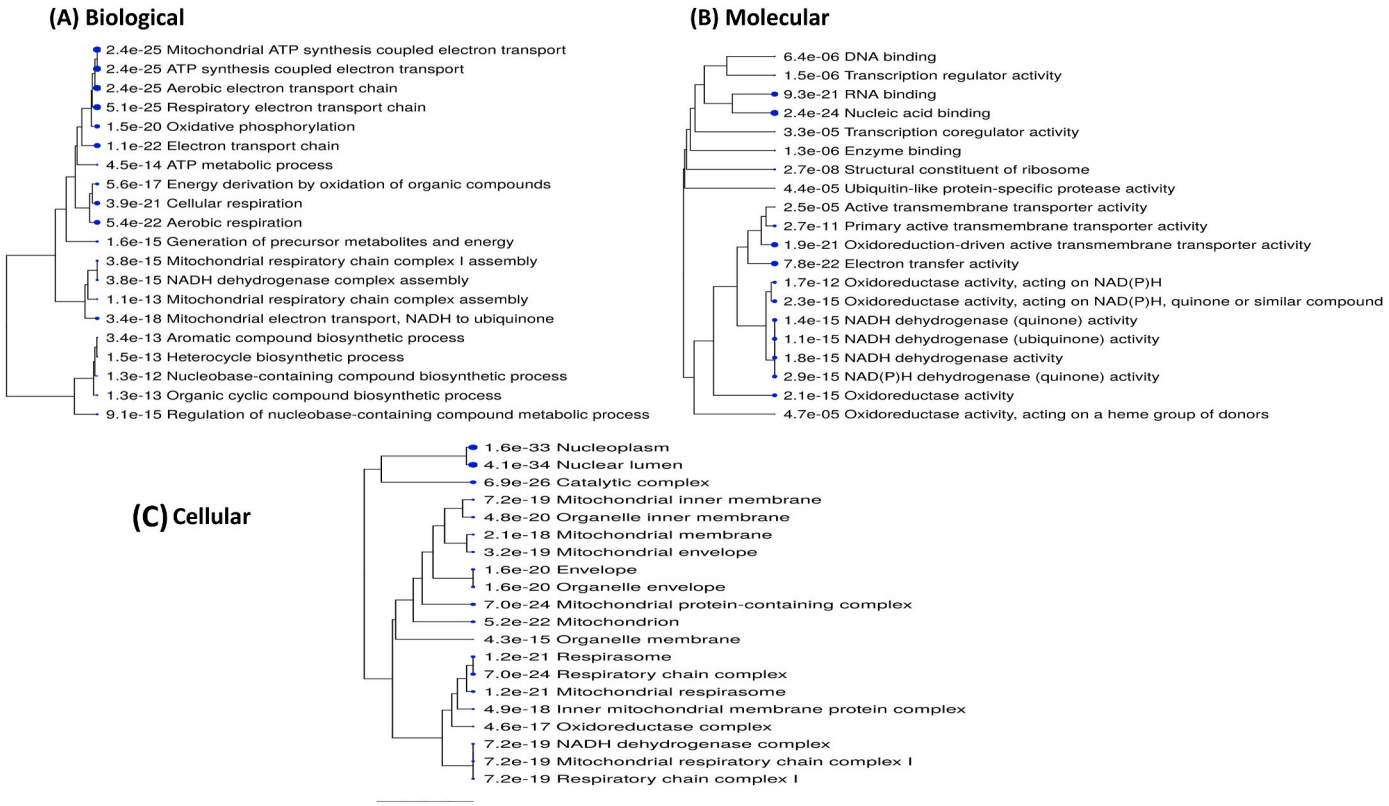

Fig. 4. Hierarchical clustering tree describes the relatedness of each GO function into each other. Bigger dots indicate more significant *P*-values.

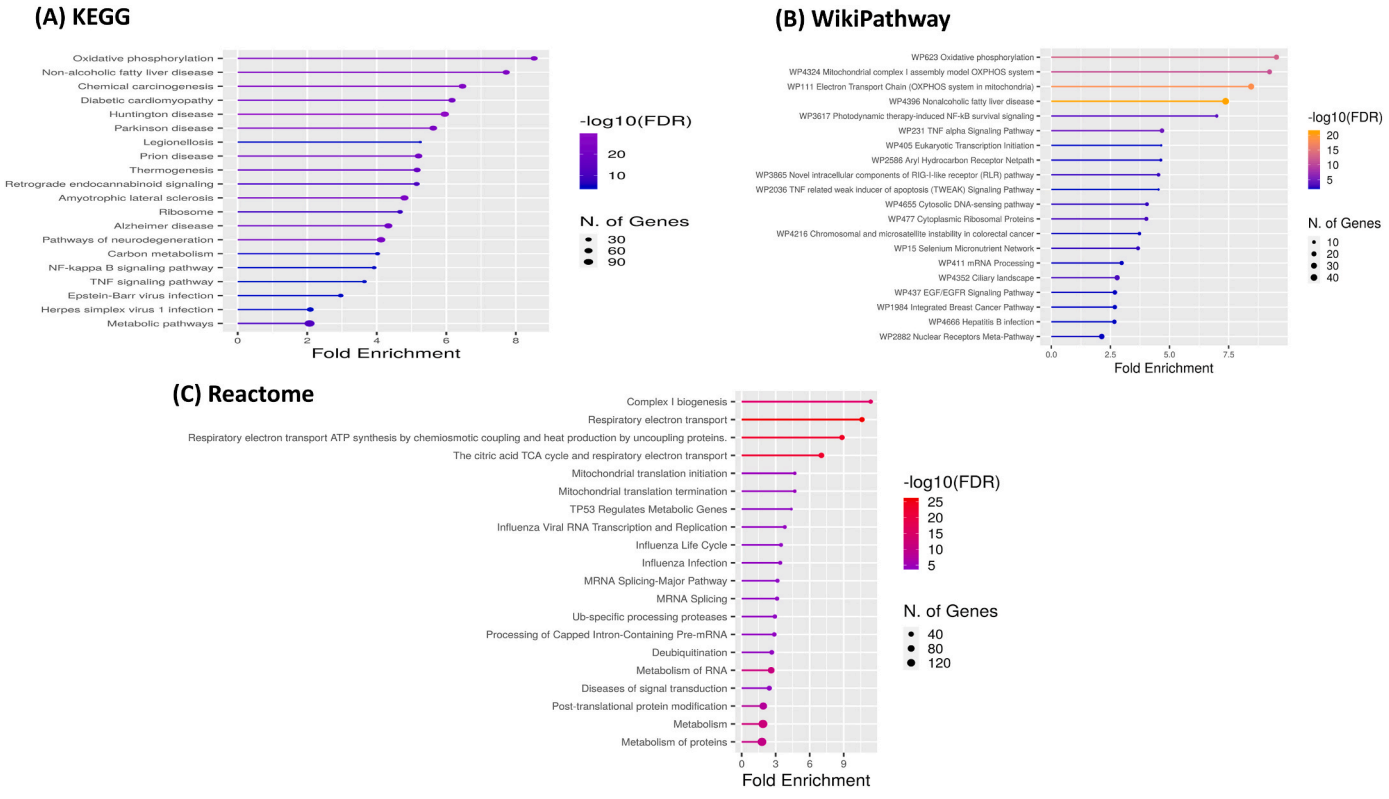

Fig. 5. Informative pathway identification of common DEGs. No of genes indicates the genes involved in each pathway. Top 20 processes are considered based on the most significant *P*- value.

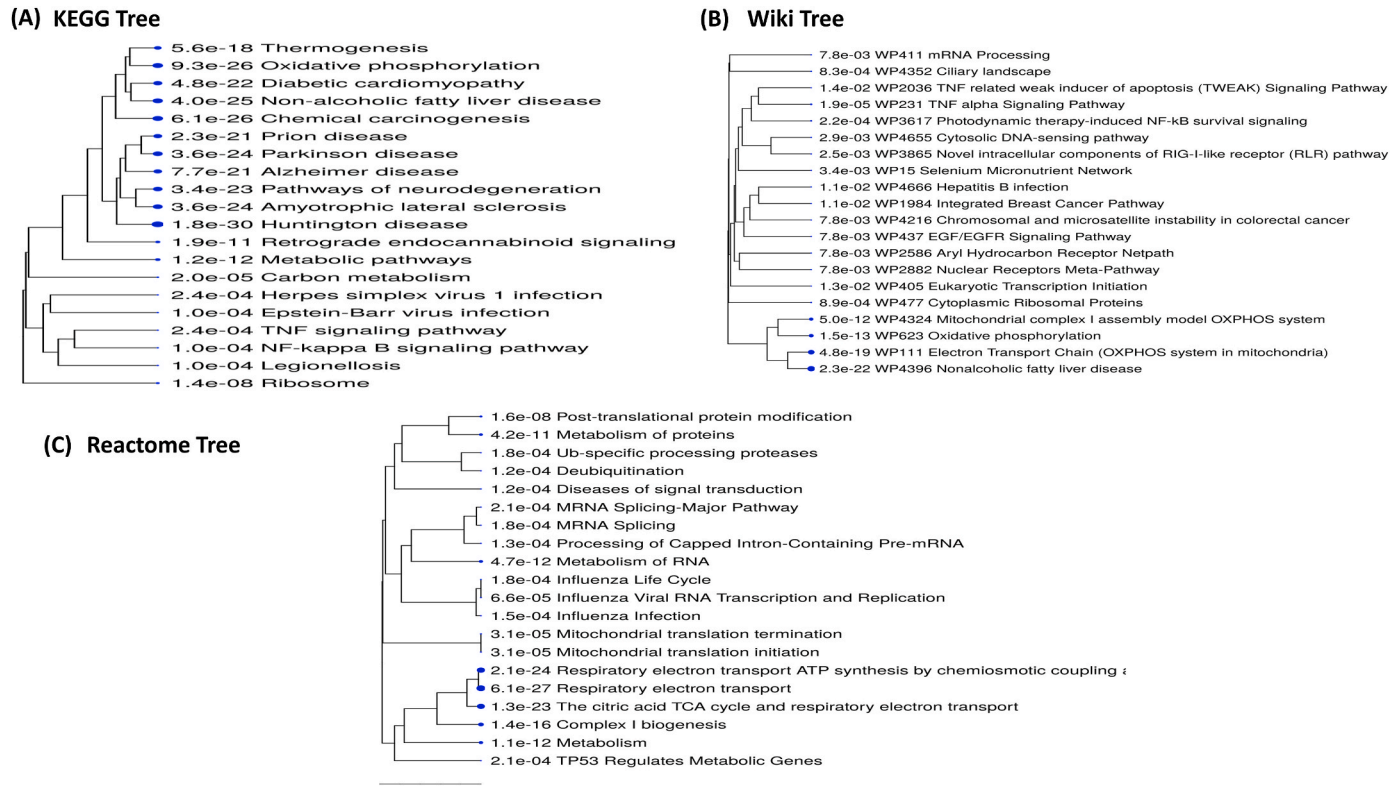

Fig. 6. A hierarchical clustering tree summarizing the correlation among significant pathways listed in the Enrichment tab. Pathways with many shared genes are clustered together. Bigger dots indicate more significant *P*-values.

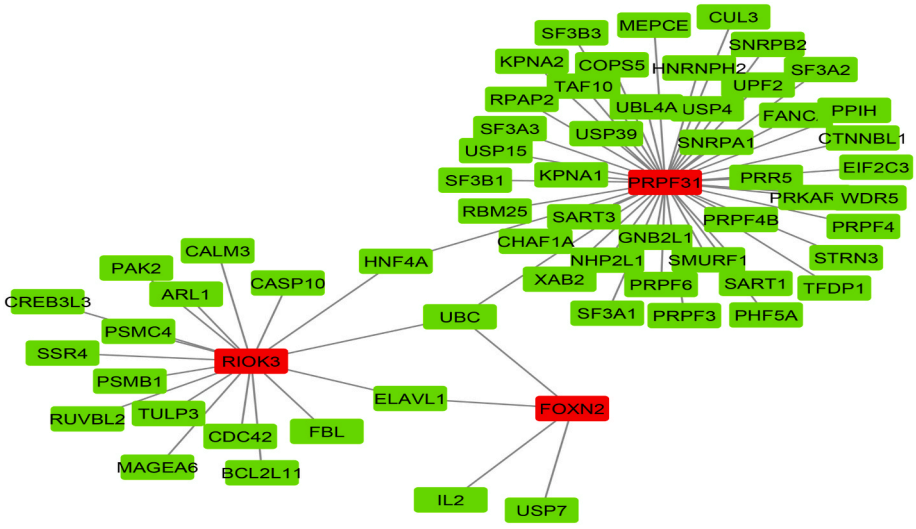

Fig. 7. Protein-protein interaction network analysis of Covid-19, CKD, and CF patients' mutually up-regulated DEGs (red color). The genes having a strong relationship to the common genes are highlighted in light green. The network is made up of 64 nodes, 65 edges, and 3 seeds. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Exploration of hub genes and their topological characteristics. Genes that have a greater value have a greater relevance in connecting regulatory molecules.

Hub gene	Betweenness and centrality	Stress	BottleNeck	Degree
FOXN2	275.7	402	4	4
HNF4A	673.7	1376	16	2
UBC	1009.3	1822	5	3
RIOK3	1619.3	3032	15	17
PRPF31	3489.0	4922	64	44

3.5. GRN demonstration based on overlapping up regulated DEGs

GRN is regarded as a map or blueprint of molecular interaction that may be used to generate novel biological hypotheses about molecular interaction, such as gene transcription regulation, which can then be evaluated in a wet lab using techniques like gene expression assays [44, 45]. We constructed the miRNA and TF co-regulatory network because a large number of genes are regulated by TF in the transcriptional and post-transcriptional steps via miRNA [46]. This network comprised of 8

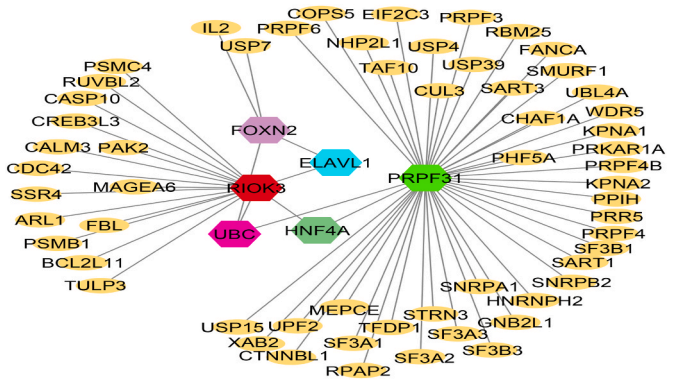

Fig. 8. Identification of hub genes from the PPI network. Six hub genes (PRPF31, FOXN2, RIOK3, UBC, HNF4A, and ELAVL) have been shown here in different colours. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

TFs (SRF, NFYA, GABPA, YY1, FAP2C, SP1, TFAP2A, and E2F1) and 45 miRNAs (Fig. 10). TFs and miRNA networks of the upregulated DEGs in the three disease categories were closely interconnected.

3.6. Protein chemical interactions (CPIs) and drug prediction

The CPIs play a vital role in the regulation of metabolism and biological processes. The information in CPIs is critical for understanding disease mechanisms and developing therapeutic remedies. Using the Network Analyst online tool, we designed a CPIs network by inserting PRPF31, FOXN2, and RIOK3 genes (Fig. 11). The drug compounds have been recommended from the DSigDB database using the Enrichr web platform. The drug chemicals were predicted according to the identified three upregulated DEGs. Four drugs, namely Hesperetin, Dorzolamide, Neostigmine bromide, and Ampyrone, were targeted for RIOK3 and PRPF31 genes, whereas only ZINC CTD 00007011 was for FOXN2 and RIOK3 (Table 3).

4. Discussion

Recent reports have proven that SARS-CoV-2 infects the human lungs, impacting their functioning and eventually affecting people with CF and CKD. This research aims to determine DEGs and their interactions among the COVID-19 patients, CF, and CKD, as well as to identify the biomarkers. We have worked with COVID-19, CF, and CKD transcriptomics datasets to identify DEGs and their key pathways. The number of reported DEGs was 17,228 for CF and 19,564 for CKD. Among the three datasets, 849 DEGs were determined to be mutual. In GO terms, the top 20 functions have been mentioned for the biological, cellular, and molecular functions. The ten most enriched biological terms were: mitochondrial electron transport, aerobic electron chain, mitochondrial ATP synthesis coupled electron transport, respiratory electron transport chain, NADH dehydrogenase complex assembly, mitochondrial respiratory chain complex I assembly, oxidative phosphorylation, mitochondrial respiratory chain complex assembly, and cellular respiration. The cellular ontologies are involved in mitochondrial respiratory chain complex I, NADH dehydrogenase complex, mitochondrial respirasome, oxidoreductase complex, and inner mitochondrial membrane protein. Mitochondrial activity is attributed to a number of cellular activities, including cellular defense systems; the virus is very likely to exploit its dynamics and function. Most of the GO terms in this study are involved in mitochondria. Many recent studies have demonstrated that host mitochondria may play an important role in COVID-19 infection, which is assumed to be one of the key mechanisms for COVID-19 diseases [47–50]. Although mitochondrial ATP is essential for cellular homeostasis; it is also required for viral replication within the host [51,52]. Many single-stranded RNA viruses have been found to affect host mitochondrial dynamics [53–56]. By interacting with the host mitochondria, SARS-CoV-2 manipulates immune responses to avoid innate immunity [54]. SARS-CoV-2 encodes a protein, namely open reading frame 3a (ORF3a), which has been discovered to bind mitochondrial ubiquitin-specific peptidase 30 (USP30), a mitochondrial deubiquitinase engaged in mitophagy regulation and homeostasis [55]. With the help of USP30, SARS-CoV-2 modulates mitochondrial activity that leads to host immunosuppression [57]. SARS-CoV-2 induces neutrophil extracellular trap (NET), an inflammatory response involving mitochondrial biogenesis, fusion, fission, and releasing mitochondrial DNA (mtDNA) into the cytoplasm [58,59]. The

Table 2
Module identification according to modularity. Modularity is a measure that quantifies the complexity of edge arrangements.

Rank	Nodes	Edges	Modularity	InDeg	OutDeg
1	43	42	21	42	2
2	16	15	5	15	3
3	5	4	1.33	4	3

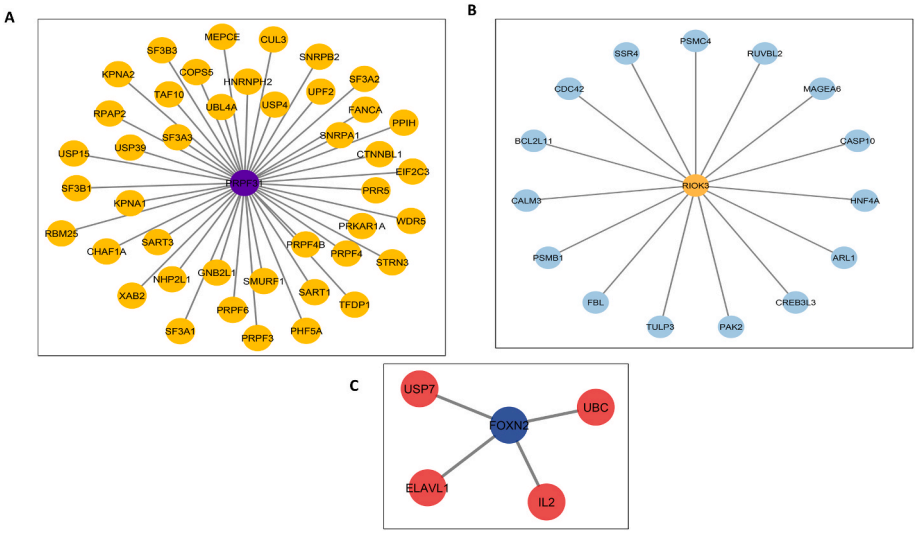

Fig. 9. Analysis of the module interaction network reveals the highly interconnected hub gene and its related genes. The network is ranked by modularity score.

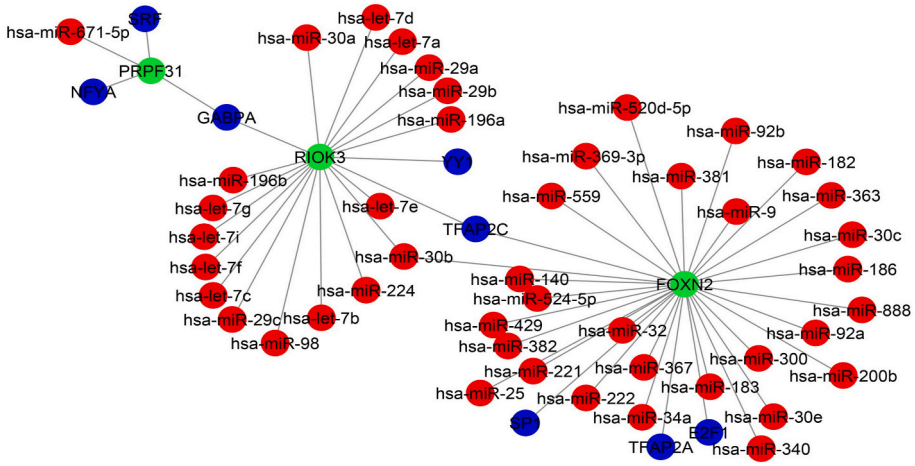

Fig. 10. Transcription factor (TF) and miRNA interaction network. The network is made up of 56 nodes and 56 edges. The miRNA structure is characterized by a red circle, while the TF network is displayed by a blue circle. The network is connected by light green circles that represent central nodes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

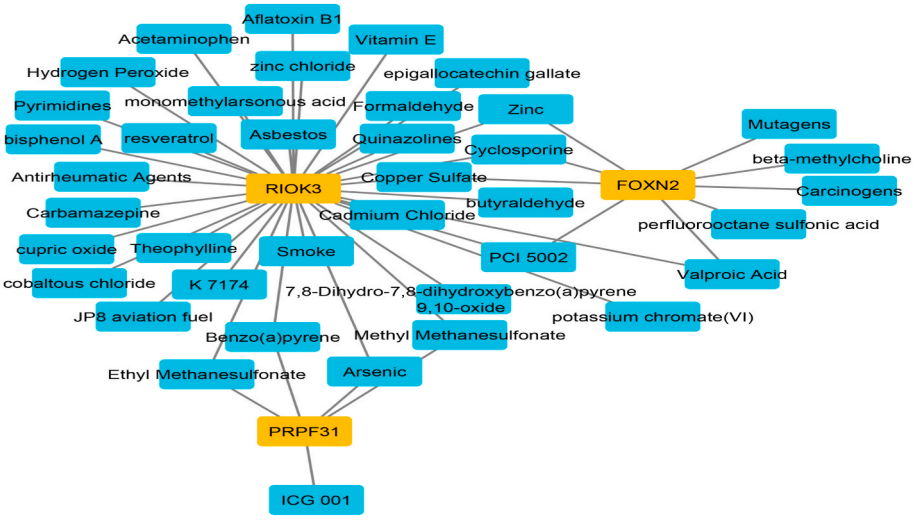

Fig. 11. Protein-Chemical network analysis. The network is formed by three hub genes (yellow) and the chemical is denoted by pest colour. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

innate immune response and inflammation are triggered by this mtDNA, a well-known phenomenon that has been observed during SARS-CoV mediated infection [60–62]. When mtDNA levels rise, the damage and severity of the sickness can progress to multiorgan failure, which is the leading cause of mortality [63]. We have also created three hierarchical pathways, such as KEGG, Reactome, and Wikipathway. In the KEGG, eleven pathways are more significant among the top 20 pathways. Furthermore, Reactome showed five significant pathways, whereas Wiki had six. KEGG pathway databases store higher order functional information for systematic analysis of DEGs function. KEGG pathway databases are increasingly employed in the field of system biology. There are two advantages to this type of pathway analysis. One is to simplify the experiment by collecting thousands of DEGs from high-throughput technologies into a few hundred pathways; another is to improve the experiment's explanatory power by identifying the most impacted pathways under the given conditions [64,65]. Our findings revealed three upregulated DEGs, namely PRPF31, FOXN2, and RIOK3. The PPIs network, gene–miRNA, TF–gene, protein–drug, and protein–chemical interactions were constructed based on these DEGs. These networks revealed a broad range of proteomic information. The PPIs network had 64 nodes and 65 edges. This sort of network could be used in many studies to predict disease genes by taking into account disease loci [66], gene-disease phenotypic connections [67–70], and disease-specific alteration of gene expression [71]. It allows the development of drugs with more specificity and minimal side effects. RIOK3, an upregulated gene in our dataset, is expressed at modest levels in a range of human organs, but it is substantially expressed in lymphoid and myeloid cells, which play an important role in immune surveillance [72]. One study showed that knocking down RIOK3 makes cells more vulnerable to MHV-68 and influenza A virus replication, implying that RIOK3-dependent pathway is important for antiviral defense against a wide range of viruses [73]. Secondly, FOXN2 has been identified as a potential option for the therapy of SARS-CoV-2 infection [74]. We aimed to determine hub genes that act as signaling relays for other proteins' networks. In this investigation, six genes (PRPF31, FOXN2, RIOK3, UBC, HNF4A, and ELAVL) were identified as the hub genes. The reported hub genes can help to identify possible candidate medications because they play a key role in the interaction between COVID-19 and the patient with CF and CKD. A drug target protein has its own three topological unique qualities, such as eccentricity, modularity, and coreness [75]. Our reported hub genes possess these three traits (Table 1), which could be a possible therapeutic target for COVID-19 prevention with

Table 3
Predictive drug compounds based on the targeting RIOK3, FOXN2, & PRPF31 genes.

Names of Drugs	P-value	Adjusted P-value	Odds Ratio	Genes
Hesperetin PC3 DOWN	0.0004	0.034	168.19	RIOK3; PRPF31
Dorzolamide HL60 DOWN	0.0004	0.034	167.47	RIOK3; PRPF31
Deptropine HL60 DOWN	0.00140	0.065	90.36	RIOK3; PRPF31
Neostigmine bromide PC3 DOWN	0.00310	0.065	59.72	RIOK3; PRPF31
Quercetin MCF7 DOWN	0.00345	0.065	453.98	RIOK3
Ethotoin HL60 DOWN	0.00360	0.065	434.22	PRPF31
Hydrocotarnine HL60 DOWN	0.00434	0.065	356.59	RIOK3
Ampyrone HL60 DOWN	0.00445	0.065	49.34	RIOK3; PRPF31
GW843682 LINCS	0.00449	0.065	344.28	RIOK3
XMD13-2 LINCS	0.00464	0.065	332.78	RIOK3
Gly-His-Lys PC3 UP	0.00464	0.065	332.78	PRPF31
Axitinib FDA	0.00584	0.065	262.62	RIOK3
AG-013736 Kinome Scan	0.00584	0.065	262.62	RIOK3
GSK461364 LINCS	0.00674	0.065	226.74	RIOK3
LY-333531 Kinome Scan	0.00733	0.065	207.80	RIOK3
CP-863187 PC3 DOWN	0.00748	0.065	203.55	RIOK3
SP600125 LINCS	0.00778	0.065	195.55	RIOK3
Etynodiol HL60 UP	0.00942	0.065	160.77	FOXN2
ZINC CTD 00007011	0.01910	0.065	22.39	RIOK3; FOXN2

comorbidities (CF and CKD). It suggests that a drug target protein might be able to interact with some hub proteins, which pass on their biological stimulation to other proteins in the same family. These topological features can help researchers understand how drug target proteins work and test new therapeutic approaches. In terms of the regulation of these three upregulated genes, we designed a TF–miRNA co-regulatory network, which measures the performance of TF-genes and miRNAs in the network. The regulation of this network relies on 45 miRNAs and 8 TF-gene interactions. GABPA is a significant TF that plays a crucial role in regulating genes involved in various biological processes, such as embryonic development, cell differentiation, cell cycle, and mitochondrial biogenesis [76–80]. GABPA (also known as nuclear respiratory factor 2), a nuclear E26 transformation-specific transcription factor (ETS), that binds and activates mitochondrial genes involved in electron transport and oxidative phosphorylation [81]. Another TF in the network is SP1, one of the most studied TFs regulating a wide range of genes involved in broad biological processes [82]. We have identified three modules from the PPIs network (Table 2). We also proposed 20 drugs from the Drug Signatures Database (DSigDB) using the Enrichr web platform based on the shared upregulated DEGs (Table 3). Among the 20 drugs, hesperetin has the highest level of enrichment. This drug has been shown to suppress the replication of a variety of viruses in vitro, including SARS-CoV [83]. Hesperetin can bind to ACE-2 with an estimated ΔG (kcal/mol) −8.3, with binding sites at Tyr613, Ser611, Arg482, and Glu479, implying that hesperetin may prevent the infection [84]. Hesperetin inhibits the SARS-CoV-2 virus from binding to the host's ACE-2 enzyme, restricts virus replication after its penetration of the host cell, and counteracts the immune system's pro-inflammatory reactions. However, Hasan MT et al. reported that Imiquimod (IMQ) could be a potential therapeutic agent to treat COVID-19 and CF [85]. In our study, the transcriptome analysis of SARS-CoV-2, CF, and CKD was based on small samples. The greater the number of samples, the more concordant genes will be uncovered, resulting in a significant transcriptome response in the future.

5. Conclusion

We reported the interrelated pathways and significant genes for the first time by using transcriptome analysis among patients with COVID-19, CF, and CKD. A total of 849 genes have been expressed mutually in the whole dataset. Three genes (PRPF31, FOXN2, and RIOK3) are upregulated that could be a biomarker for the patient with CF, CKD, and COVID-19. Six hub genes (PRPF31, FOXN2, RIOK3, UBC, HNF4A, and ELAVL) can help to identify possible candidate medications because they have three topological features, including eccentricity, modularity, and coreness. Finally, we have suggested some medications that can reduce the risk of fatality and hospitalization. There was a brief discussion of three significant upregulated genes that are expected to accelerate the pace of development of therapeutics against COVID-19, CF, and CKD. For the confirmation of our projected medications for the treatment of these three diseases, wet lab experiments are required to evaluate and validate their effectiveness. We believe that the results obtained in this study could serve as a guide for future work in the laboratory.

Author contribution

This study was conceptualised and designed by Golap Babu and Fahim Alam Nobel. Both drafted and reviewed the manuscript critically.

Compliance with ethical standards

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: Not required/not applicable for this article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Holmes KV. SARS coronavirus: a new challenge for prevention and therapy. J Clin Invest 2003;111(11):1605–9. https://doi.org/10.1172/JCI18819.
[2] Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203(2):631–7. https://doi.org/10.1002/path.1570.
[3] Chi X, Yan R, Zhang J, et al. A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. Science 2020;369(6504):650–5. https://doi.org/10.1126/science.abc6952.
[4] Zolin A, Orenti A, Naehrlich L, Jung A, van Rens J. ECFS patient registry annual report 2020. 2022. https://www.ecfs.eu/projects/ecfs-patient-registry/annual-reports.
[5] Khan TZ, Wagener JS, Bost T, Martinez J, Accurso FJ, Riches DW. Early pulmonary inflammation in infants with cystic fibrosis. Am J Respir Crit Care Med 1995;151(4):1075–82. https://doi.org/10.1164/ajrccm/151.4.1075.
[6] Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. Lancet 2018;392(10159):2052–90. https://doi.org/10.1016/S0140-6736(18)31694-5.
[7] Jha V, Prasad N. CKD and infectious diseases in Asia Pacific: challenges and opportunities. Am J Kidney Dis 2016;68(1):148–60. https://doi.org/10.1053/j.ajkd.2016.01.017.
[8] Wang YN, Ma SX, Chen YY, et al. Chronic kidney disease: biomarker diagnosis to therapeutic targets. Clin Chim Acta 2019;499:54–63. https://doi.org/10.1016/j.cca.2019.08.030.

[9] Flight W, Jones A. The diagnosis and management of respiratory viral infections in cystic fibrosis. Expet Rev Respir Med 2017;11(3):221–7. https://doi.org/10.1080/17476348.2017.1288102.
[10] Hoek RA, Paats MS, Pas SD, et al. Incidence of viral respiratory pathogens causing exacerbations in adult cystic fibrosis patients. Scand J Infect Dis 2013;45(1):65–9. https://doi.org/10.3109/00365548.2012.708942.
[11] Wevers BA, van der Hoek L. Renin-angiotensin system in human coronavirus pathogenesis. Future Virol 2010;5(2):145–61. https://doi.org/10.2217/fvl.10.4.
[12] da Silva Filho LV, Zerbinati RM, Tateno AF, et al. The differential clinical impact of human coronavirus species in children with cystic fibrosis. J Infect Dis 2012;206(3):384–8. https://doi.org/10.1093/infdis/jis274.
[13] Colombo C, Cipolli M, Daccò V, et al. Clinical course and risk factors for severe COVID-19 among Italian patients with cystic fibrosis: a study within the Italian Cystic Fibrosis Society. Infection 2021:1–9. https://doi.org/10.1007/s15010-021-01737-z.
[14] Colombo C, Battezzati PM, Lucidi V, et al. Influenza A/H1N1 in patients with cystic fibrosis in Italy: a multicentre cohort study. Thorax 2011;66(3):260–1. https://doi.org/10.1136/thx.2010.157032.
[15] Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020;26(7):1017–32. https://doi.org/10.1038/s41591-020-0968-3.
[16] Wu T, Zuo Z, Kang S, et al. Multi-organ dysfunction in patients with COVID-19: a systematic review and meta-analysis. Aging Dis 2020;11(4):874–94. https://doi.org/10.14336/AD.2020.0520.
[17] Chung EYM, Palmer SC, Natale P, et al. Incidence and outcomes of COVID-19 in people with CKD: a systematic review and meta-analysis. Am J Kidney Dis 2021;78(6):804–15. https://doi.org/10.1053/j.ajkd.2021.07.003.
[18] Diao B, Wang C, Wang R, Feng Z, Tan Y, Wang H, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Nat Commun 2021;12(1):2506. https://doi.org/10.1038/s41467-021-22781-1.
[19] Serfozo P, Wysocki J, Gulua G, et al. Ang II (angiotensin II) conversion to angiotensin-(1-7) in the circulation is POP (Prolyloligopeptidase)-Dependent and ACE2 (Angiotensin-Converting enzyme 2)-independent. Hypertension 2020;75(1):173–82. https://doi.org/10.1161/HYPERTENSIONAHA.119.14071.
[20] Ye M, Wysocki J, William J, Soler MJ, Cokic I, Batlle D. Glomerular localization and expression of Angiotensin-converting enzyme 2 and Angiotensin-converting enzyme: implications for albuminuria in diabetes. J Am Soc Nephrol 2006;17(11):3067–75. https://doi.org/10.1681/ASN.2006050423.
[21] Conesa A, Madrigal P, Tarazona S, et al. A survey of best practices for RNA-seq data analysis [published correction appears in Genome Biol. 2016;17(1):181]. Genome Biol 2016;17:13. https://doi.org/10.1186/s13059-016-0881-8.
[22] Gentleman R, Carey VJ, Huber W, Irizarry RA, Dudoit S, editors. Bioinformatics and computational biology solutions using R and Bioconductor (Published 6 December 2006).doi:10.1111/j.1541-0420.2006.00596_2.x.
[23] Wichert S, Fokianos K, Strimmer K. Identifying periodically expressed transcripts in microarray time series data. Bioinformatics 2004;20(1):5–20. https://doi.org/10.1093/bioinformatics/btg364.
[24] Subramanian A, Kuehn H, Gould J, Tamayo P, Mesirov JP. GSEA-P: a desktop application for gene set enrichment analysis. Bioinformatics 2007;23(23):3251–3. https://doi.org/10.1093/bioinformatics/btm369.
[25] Yang QX, Wang YX, Li FC, et al. Identification of the gene signature reflecting schizophrenia's etiology by constructing artificial intelligence-based method of enhanced reproducibility. CNS Neurosci Ther 2019;25(9):1054–63. https://doi.org/10.1111/cns.13196gene.
[26] Ashburner M, Ball CA, Blake JA, et al. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat Genet 2000;25(1):25–9. https://doi.org/10.1038/75556.
[27] Aken BL, Achuthan P, Akanni W, et al. Ensembl 2017. Nucleic Acids Res 2017;45(D1):D635–42. https://doi.org/10.1093/nar/gkw1104.
[28] Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. Nucleic Acids Res 2000;28(1):27–30. https://doi.org/10.1093/nar/28.1.27.
[29] Yang Q, Li B, Tang J, et al. Consistent gene signature of schizophrenia identified by a novel feature selection strategy from comprehensive sets of transcriptomic data. Briefings Bioinf 2020;21(3):1058–68. https://doi.org/10.1093/bib/bbz049.
[30] Slenter DN, Kutmon M, Hanspers K, Riutta A, Windsor J, Nunes N, Mélius J, Cirillo E, Coort SL, Digles D, Ehrhart F. WikiPathways: a multifaceted pathway database bridging metabolomics to other omics research. Nucleic Acids Res 2018;46(D1):D661–7. https://doi.org/10.1093/nar/gkx1064.
[31] Fabregat A, Jupe S, Matthews L, Sidiropoulos K, Gillespie M, Garapati P, Haw R, Jassal B, Korninger F, May B, Milacic M. The reactome pathway knowledgebase. Nucleic Acids Res 2018;46(D1):D649–55. https://doi.org/10.1093/nar/gkx1132.
[32] Szklarczyk D, Gable AL, Lyon D, et al. STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res 2019;47(D1):D607–13. https://doi.org/10.1093/nar/gky1131.
[33] Ewing RM, Chu P, Elisma F, et al. Large-scale mapping of human protein-protein interactions by mass spectrometry. Mol Syst Biol 2007;3:89. https://doi.org/10.1038/msb4100134.
[34] Ben-Hur A, Noble WS. Kernel methods for predicting protein-protein interactions. Bioinformatics 2005;21(Suppl 1):i38–46. https://doi.org/10.1093/bioinformatics/bti1016.
[35] Navlakha S, Gitter A, Bar-Joseph Z. A network-based approach for predicting missing pathway interactions. PLoS Comput Biol 2012;8(8):e1002640. https://doi.org/10.1371/journal.pcbi.1002640.
[36] Chen B, Fan W, Liu J, Wu FX. Identifying protein complexes and functional modules–from static PPI networks to dynamic PPI networks. Briefings Bioinf 2014;15(2):177–94. https://doi.org/10.1093/bib/bbt039.
[37] Zeng E, Ding C, Narasimhan G, Holbrook SR. Estimating support for protein-protein interaction data with applications to function prediction. Comput Syst Bioinformatics Conf 2008;7:73–84.
[38] Szklarczyk D, Franceschini A, Wyder S, et al. STRING v10: protein-protein interaction networks, integrated over the tree of life. Nucleic Acids Res 2015;43(Database issue):D447–52. https://doi.org/10.1093/nar/gku1003.
[39] Shannon P, Markiel A, Ozier O, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 2003;13(11):2498–504. https://doi.org/10.1101/gr.1239303.
[40] Chin CH, Chen SH, Wu HH, Ho CW, Ko MT, Lin CY. cytoHubba: identifying hub objects and sub-networks from complex interactome. BMC Syst Biol 2014;8(Suppl 4):S11. https://doi.org/10.1186/1752-0509-8-S4-S11. Suppl 4.
[41] Liu ZP, Wu C, Miao H, Wu H. RegNetwork: an integrated database of transcriptional and post-transcriptional regulatory networks in human and mouse. Database 2015;2015:bav095. https://doi.org/10.1093/database/bav095.
[42] Yoo M, Shin J, Kim J, et al. DSigDB: drug signatures database for gene set analysis. Bioinformatics 2015;31(18):3069–71. https://doi.org/10.1093/bioinformatics/btv313.
[43] Barrett T, Wilhite SE, Ledoux P, et al. NCBI GEO: archive for functional genomics data sets-update. Nucleic Acids Res 2013;41(Database issue):D991–5. https://doi.org/10.1093/nar/gks1193.
[44] Bussemaker HJ, Li H, Siggia ED. Regulatory element detection using correlation with expression. Nat Genet 2001;27(2):167–71. https://doi.org/10.1038/84792.
[45] Basso K, Margolin AA, Stolovitzky G, Klein U, Dalla-Favera R, Califano A. Reverse engineering of regulatory networks in human B cells. Nat Genet 2005;37(4):382–90. https://doi.org/10.1038/ng1532.
[46] Irigoyen N, Firth AE, Jones JD, Chung BY, Siddell SG, Brierley I. High-resolution analysis of coronavirus gene expression by RNA sequencing and ribosome profiling. PLoS Pathog 2016;12(2):e1005473. https://doi.org/10.1371/journal.ppat.1005473.
[47] Singh KK, Chaubey G, Chen JY, Suravajhala P. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. Am J Physiol Cell Physiol 2020;319(2):C258–67. https://doi.org/10.1152/ajpcell.00224.2020.
[48] Edeas M, Saleh J, Peyssonnaux C. Iron: innocent bystander or vicious culprit in COVID-19 pathogenesis? Int J Infect Dis 2020;97:303–5. https://doi.org/10.1016/j.ijid.2020.05.110.
[49] Guzzi PH, Mercatelli D, Ceraolo C, Giorgi FM. Master regulator analysis of the SARS-CoV-2/human interactome. J Clin Med 2020;9(4):982. https://doi.org/10.3390/jcm9040982.
[50] Kloc M, Ghobrial RM, Kubiak JZ. The role of genetic sex and mitochondria in response to COVID-19 infection. Int Arch Allergy Immunol 2020;181(8):629–34. https://doi.org/10.1159/000508560.
[51] Silva da Costa L, Pereira da Silva AP, Da Poian AT, El-Bacha T. Mitochondrial bioenergetic alterations in mouse neuroblastoma cells infected with Sindbis virus: implications to viral replication and neuronal death. PLoS One 2012;7(4):e33871. https://doi.org/10.1371/journal.pone.0033871.
[52] Jang KJ, Jeong S, Kang DY, Sp N, Yang YM, Kim DE. A high ATP concentration enhances the cooperative translocation of the SARS coronavirus helicase nsP13 in the unwinding of duplex RNA. Sci Rep 2020;10(1):4481. https://doi.org/10.1038/s41598-020-61432-1.
[53] Kim SJ, Syed GH, Khan M, et al. Hepatitis C virus triggers mitochondrial fission and attenuates apoptosis to promote viral persistence. Proc Natl Acad Sci U S A 2014;111(17):6413–8. https://doi.org/10.1073/pnas.1321114111.
[54] Shi CS, Qi HY, Boularan C, et al. SARS-coronavirus open reading frame-9b suppresses innate immunity by targeting mitochondria and the MAVS/TRAF3/TRAF6 signalosome. J Immunol 2014;193(6):3080–9. https://doi.org/10.4049/jimmunol.1303196.
[55] Chatel-Chaix L, Cortese M, Romero-Brey I, et al. Dengue virus perturbs mitochondrial morphodynamics to dampen innate immune responses. Cell Host Microbe 2016;20(3):342–56. https://doi.org/10.1016/j.chom.2016.07.008.
[56] Barbier V, Lang D, Valois S, Rothman AL, Medin CL. Dengue virus induces mitochondrial elongation through impairment of Drp1-triggered mitochondrial fission. Virology 2017;500:149–60. https://doi.org/10.1016/j.virol.2016.10.022.
[57] Srinivasan K, Pandey AK, Livingston A, Venkatesh S. Roles of host mitochondria in the development of COVID-19 pathology: could mitochondria be a potential therapeutic target? Mol Biomed 2021;2(1):38. https://doi.org/10.1186/s43556-021-00060-1.
[58] Singh KK, Chaubey G, Chen JY, Suravajhala P. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. Am J Physiol Cell Physiol 2020;319(2):C258–67. https://doi.org/10.1152/ajpcell.00224.2020.
[59] Schönrich G, Raftery MJ. Neutrophil extracellular traps Go viral. Front Immunol 2016;7:366. https://doi.org/10.3389/fimmu.2016.00366.
[60] White MJ, McArthur K, Metcalf D, et al. Apoptotic caspases suppress mtDNA-induced STING-mediated type I IFN production. Cell 2014;159(7):1549–62. https://doi.org/10.1016/j.cell.2014.11.036.
[61] Rongvaux A, Jackson R, Harman CC, et al. Apoptotic caspases prevent the induction of type I interferons by mitochondrial DNA. Cell 2014;159(7):1563–77. https://doi.org/10.1016/j.cell.2014.11.037.
[62] West AP, Khoury-Hanold W, Staron M, et al. Mitochondrial DNA stress primes the antiviral innate immune response. Nature 2015;520(7548):553–7. https://doi.org/10.1038/nature14156.
[63] Aswani A, Manson J, Itagaki K, et al. Scavenging circulating mitochondrial DNA as a potential therapeutic option for multiple organ dysfunction in Trauma Hemorrhage. Front Immunol 2018;9:891. https://doi.org/10.3389/fimmu.2018.00891. 2018 May 8.

[64] Glazko GV, Emmert-Streib F. Unite and conquer: univariate and multivariate approaches for finding differentially expressed gene sets. Bioinformatics 2009;25 (18):2348–54. https://doi.org/10.1093/bioinformatics/btp406.
[65] Khatri P, Sirota M, Butte AJ. Ten years of pathway analysis: current approaches and outstanding challenges. PLoS Comput Biol 2012;8(2):e1002375. https://doi.org/10.1371/journal.pcbi.1002375.
[66] Oti M, Snel B, Huynen MA, Brunner HG. Predicting disease genes using protein-protein interactions. J Med Genet 2006;43(8):691–8. https://doi.org/10.1136/jmg.2006.041376.
[67] Fraser HB, Plotkin JB. Using protein complexes to predict phenotypic effects of gene mutation. Genome Biol 2007;8(11):R252. https://doi.org/10.1186/gb-2007-8-11-r252.
[68] Köhler S, Bauer S, Horn D, Robinson PN. Walking the interactome for prioritization of candidate disease genes. Am J Hum Genet 2008;82(4):949–58. https://doi.org/10.1016/j.ajhg.2008.02.013.
[69] Lage K, Karlberg EO, Størling ZM, et al. A human phenome-interactome network of protein complexes implicated in genetic disorders. Nat Biotechnol 2007;25(3): 309–16. https://doi.org/10.1038/nbt1295.
[70] Wu X, Jiang R, Zhang MQ, Li S. Network-based global inference of human disease genes. Mol Syst Biol 2008;4:189. https://doi.org/10.1038/msb.2008.27.
[71] Karni S, Soreq H, Sharan R. A network-based method for predicting disease-causing genes. J Comput Biol 2009;16(2):181–9. https://doi.org/10.1089/cmb.2008.05TT.
[72] Su AI, Wiltshire T, Batalov S, et al. A gene atlas of the mouse and human protein-encoding transcriptomes. Proc Natl Acad Sci U S A 2004;101(16):6062–7. https://doi.org/10.1073/pnas.0400782101.
[73] Feng J, De Jesus PD, Su V, et al. RIOK3 is an adaptor protein required for IRF3-mediated antiviral type I interferon production. J Virol 2014;88(14):7987–97. https://doi.org/10.1128/JVI.00643-14.
[74] Salgado-Albarrán M, Navarro-Delgado EI, Del Moral-Morales A, et al. Comparative transcriptome analysis reveals key epigenetic targets in SARS-CoV-2 infection. NPJ Syst Biol Appl 2021;7(1):21. https://doi.org/10.1038/s41540-021-00181-x.
[75] Feng Y, Wang Q, Wang T. Drug target protein-protein interaction networks: a systematic perspective. BioMed Res Int 2017;2017:1289259. https://doi.org/10.1155/2017/1289259.
[76] Ristevski S, O'Leary DA, Thornell AP, Owen MJ, Kola I, Hertzog PJ. The ETS transcription factor GABPalpha is essential for early embryogenesis. Mol Cell Biol 2004;24(13):5844–9. https://doi.org/10.1128/MCB.24.13.5844-5849.2004.
[77] Manukjan G, Ripperger T, Venturini L, et al. GABP is necessary for stem/progenitor cell maintenance and myeloid differentiation in human hematopoiesis and chronic myeloid leukemia. Stem Cell Res 2016;16(3):677–81. https://doi.org/10.1016/j.scr.2016.04.007.
[78] Yu S, Cui K, Jothi R, et al. GABP controls a critical transcription regulatory module that is essential for maintenance and differentiation of hematopoietic stem/progenitor cells. Blood 2011;117(7):2166–78. https://doi.org/10.1182/blood-2010-09-306563.
[79] Yang ZF, Mott S, Rosmarin AG. The Ets transcription factor GABP is required for cell-cycle progression. Nat Cell Biol 2007;9(3):339–46. https://doi.org/10.1038/ncb1548.
[80] Yang ZF, Drumea K, Mott S, Wang J, Rosmarin AG. GABP transcription factor (nuclear respiratory factor 2) is required for mitochondrial biogenesis. Mol Cell Biol 2014;34(17):3194–201. https://doi.org/10.1128/MCB.00492-12.
[81] Yang ZF, Drumea K, Mott S, Wang J, Rosmarin AG. GABP transcription factor (nuclear respiratory factor 2) is required for mitochondrial biogenesis. Mol Cell Biol 2014;34(17):3194–201. https://doi.org/10.1128/MCB.00492-12.
[82] O'Connor L, Gilmour J, Bonifer C. The role of the Ubiquitously expressed transcription factor Sp1 in Tissue-specific transcriptional regulation and in disease. Yale J Biol Med 2016;89(4):513–25.
[83] Kaul TN, Middleton Jr E, Ogra PL. Antiviral effect of flavonoids on human viruses. J Med Virol 1985;15(1):71–9. https://doi.org/10.1002/jmv.1890150110.
[84] C. Chen H, Du Q. Potential natural compounds for preventing SARS-CoV-2 (2019-nCoV) infection. doi:10.20944/preprints202001.0358.v3.
[85] Hasan MT, Abdulrazak LF, Alam MK, et al. Discovering common pathophysiological processes between COVID-19 and cystic fibrosis by differential gene expression pattern analysis. BioMed Res Int 2022;2022:8078259. https://doi.org/10.1155/2022/8078259.