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Unveiling the Biomarkers of Cancer and COVID-19 and Their Regulations in Different Organs by Integrating RNA-Seq Expression and Protein−Protein Interactions

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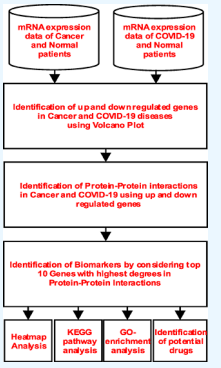
ABSTRACT: Cancer and COVID-19 have killed millions of people worldwide. COVID-19 is even more dangerous to people with comorbidities such as cancer. Thus, it is imperative to identify the key human genes or biomarkers that can be targeted to develop novel prognosis and therapeutic strategies. The transcriptomic data provided by the next-generation sequencing technique makes this identification very convenient. Hence, mRNA (messenger ribonucleic acid) expression data of 2265 cancer and 282 normal patients were considered, while for COVID-19 assessment, 784 and 425 COVID-19 and normal patients were taken, respectively. Initially, volcano plots were used to identify the up- and down-regulated genes for both cancer and COVID-19. Thereafter, protein−protein interaction (PPI) networks were prepared by combining all the up- and down-regulated genes for each of cancer and COVID-19. Subsequently, such networks were analyzed to identify the top 10 genes with the highest degree of connection to provide the biomarkers. Interestingly, these genes were all up-regulated for cancer, while they were down-regulated for COVID-19. This study had also identified common genes between cancer and COVID-19, all of which were up-regulated in both the diseases. This analysis revealed that *FN1* was highly up-regulated in different organs for cancer, while *EEF2* was dysregulated in most organs affected by COVID-19. Then, functional enrichment analysis was performed to identify significant biological processes. Finally, the drugs for cancer and COVID-19 biomarkers and the common genes between them were identified using the Enrichr online web tool. These drugs include lucanthone, etoposide, and methotrexate, targeting the biomarkers for cancer, while paclitaxel is an important drug for COVID-19.



INTRODUCTION

According to the W.H.O. information, cancer is the second leading cause of death worldwide. However, an early detection can result in a lower mortality rate. When a person is afflicted with cancer, the normal cells change to tumorous ones; therefore, identification of the genes that are involved in this transformation is very crucial for effective treatment. Though there are many methods that have been proposed for the investigation of cancer, human genome sequencing developed by the Human Genome Project was a landmark in the development of cheaper techniques but with a higher throughput to obtain a comprehensive knowledge of the entire genomes.[1] The new techniques in the Human Genome Project have been included in next-generation sequencing (NGS)[2] as well. In this regard, gene expression from microarray data has been used for a long time for the identification of biomarkers in cancer. However, it is usually very noisy.[3] On the other hand, RNA sequencing (RNA-seq) can find a very low level expression of genes; thus, its development as part of the NGS technology is very important as it can produce expression data with very low noise.[4] There are many studies in the literature such as refs 5−67, which have used RNA-seq data for the analysis of various types of cancer. RNA-seq can rapidly sequence and analyze transcriptomic data to identify potential biomarkers in cancer, a possible biomarker type being mRNA.[8] mRNA is a type of RNA molecule that is able to carry genetic information from the DNA nucleus to the ribosome, where the amino acid sequence of the protein products of gene expression is specified by the mRNA's sequence. However, due to the complex and high dimensional nature of the data, it is a non-trivial task to analyze the same.[8] In this regard, tools such as BioExpress[9] and Oncomine[10] are proposed in order to search for biomarkers.

Meanwhile, COVID-19, the disease caused by SARS-CoV-2, has been disrupting our lives for more than 2 years now. By August 2022, almost 6.5 million people have died worldwide due to this virus. This can be attributed to the fact that SARS-CoV-2 has several variants due to its genetic mutations.[11−13] Moreover, COVID-19 is especially detrimental to people suffering from comorbidities such as cancer and neurological diseases. Thus, identifying biomarkers in COVID-19 is a very significant step in finding an effective treatment for the same, and the contribution of transcriptome analysis is noteworthy here as well. In ref,[14] Hasan et al. considered two RNA-seq data sets and one

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Table 1. Statistics for the Cancer Data Set

cancer type	abbreviation of cancer type	organ	number of genes	tumor/cancer	normal
bladder urothelial carcinoma	BLCA	bladder	18539	56	11
breast invasive carcinoma	BRCA	breast	18637	778	100
head and neck squamous cell carcinoma	HNSC	head and neck	18692	263	31
esophageal carcinoma	ESCA	esophagus	21657	185	13
liver hepatocellular carcinoma	LIHC	liver	18015	17	9
kidney renal clear cell carcinoma	KIRC	kidney	18691	469	68
lung squamous cell carcinoma	LUSC	lung	18936	223	17
stomach adenocarcinoma	STAD	stomach	21239	274	33

microarray data set of COVID-19 for peripheral blood mononuclear cells (PBMCs) to identify the biomarkers. Through their analysis, they concluded that blood cells can be used to diagnose COVID-19 as well as to develop corresponding drugs. Auwul et al.[15] have analyzed PBMC GSE152418 and CRA002390 data sets using gene co-expression analysis. Through their analysis, they identified four key gene modules and a hub gene signature using module membership statistics and PPI networks. They have also identified drugs by considering drug−gene interaction analysis. Hasankhani et al.[16] have performed weighted gene co-expression network analysis (WGCNA) on RNA-seq data from PBMC for healthy persons and 17 mild and severe COVID-19 patients. The co-expression analysis revealed that 72% of modules that were identified in healthy samples were altered by SARS-CoV-2. In their work, many transcriptional regulatory factors with important immunoregulatory roles in SARS-CoV-2 infection were also identified, which included *NFKB*1, *HIF*1*A*, *AHR*, and *TP*53. Sagulkoo et al.[17] proposed a multi-level biological network analysis framework to provide candidate drugs targeting the key genes using the drug−gene interaction network and structural analysis as well as key gene identification via protein−protein interaction (PPI) network analysis and survival analysis based on differentially expressed genes (DEGs) in leukocyte transcriptomic profiles. Their analysis revealed *CDC*25*A*, *GUSB*, *MYBL*2, and *SDAD*1 as key genes in severe COVID-19. Medini et al.[18] have analyzed RNA-seq data sets for three blood data sets with 48 healthy and 119 afflicted patients and two respiratory tract data sets with 157 healthy and 524 affected patients. In their work, they have found reduced mtDNA (mitochondrial DNA) gene expression in blood. To assess the impact of SARS-CoV-2, Park et al.[19] have used shotgun metatranscriptomics (total RNA-seq) to profile human tissues in 39 patients who have succumbed to COVID-19. Their study revealed a marked disruption of cellular and transcriptional programs among COVID-19 and normal patients.

Motivated by the literature, in this work, we considered mRNA expression data of 2265 cancer and 282 normal patients for 16088 human genes common among different organs such as bladder, breast, head and neck, esophagus, liver, kidney, lung, and stomach, while for COVID-19, mRNA expression data of 784 COVID-19 and 425 normal patients across 14412 human genes for nasopharynx, blood, respiratory tract, lung, heart, liver, intestine, stomach, eye, kidney, brain, pancreas, and uterus were taken into consideration. In order to identify the corresponding up- and down-regulated genes, respective volcano plots were created for both cancer versus normal and COVID-19 versus normal cases. Thereafter, the top 10 genes with the highest degrees (biomarkers) were identified using PPIs by combining the respective up- and down-regulated genes. For both cancer and COVID-19 afflicted patients, the identification of these biomarkers is important for early detection as well as effective treatment for the diseases. The identified biomarkers for cancer were *FN1*, *UBE2C*, *CCNB1*, *CDK1*, *MAD2L1*, *AURKA*, *TOP2A*, *TPX2*, *NUSAP1*, and *KIF11*, while for COVID-19, such biomarkers were *EEF2*, *NDUFB7*, *NHP2*, *RPL9*, *MRPL15*, *RPS5*, *RPS15*, *UQCRQ*, *RPL35*, and *RPS9*. Furthermore, the regulation of the different biomarkers in the organs affected by cancer and COVID-19 are reported through heatmaps. Moreover, the pathway analysis of these biomarkers is reported using KEGG, while their biological significance is shown through gene ontology (GO) enrichment analysis. Several enriched pathways for the biomarkers of cancer include the p53 signaling pathway and human immunodeficiency virus 1 infection, while for COVID-19, the induced pathways include coronavirus disease, diabetic cardiomyopathy, Parkinson disease, and Alzheimer disease. This study has also identified up-regulated genes such as *CXCL10*, *CXCL9*, and *IDO1* to be the common genes between cancer and COVID-19. Finally, drugs targeting the identified biomarkers as well as the common genes are reported for both cancer and COVID-19 using the Enrichr online web tool.[20,21] In this regard, lucanthone, etoposide, and methotrexate were some of the drugs targeting the biomarkers for cancer, while paclitaxel targets the biomarkers for COVID-19. Thus, this work summarizes the biomarkers that can be investigated further to combat both cancer and COVID-19.

MATERIALS AND METHODS

In this section, the data preparation is elaborated at first, which is then followed by the discussion on the pipeline of the proposed work.

Data Preparation. In this work, initially, mRNA expression data of 2265 cancer and 282 normal patients were collected from

Table 2. Statistics for the COVID-19 Data Set

GEOID	organ	number of genes	COVID-19	normal
GSE163151	blood	21952	145	113
GSE164332	brain	57996	9	7
GSE164073	eye	25222	9	9
GSE162736	heart	23194	24	24
GSE159201	intestine	33550	12	12
GSE173707	kidney	24975	9	9
GSE151803	liver	22316	12	9
GSE147507	lung	20748	21	29
GSE152075	nasopharynx	19744	430	54
GSE165890	pancreas	22057	6	6
GSE156063	respiratory tract	15811	93	141
GSE153684	stomach	26501	9	9
GSE171995	uterus	19715	5	3

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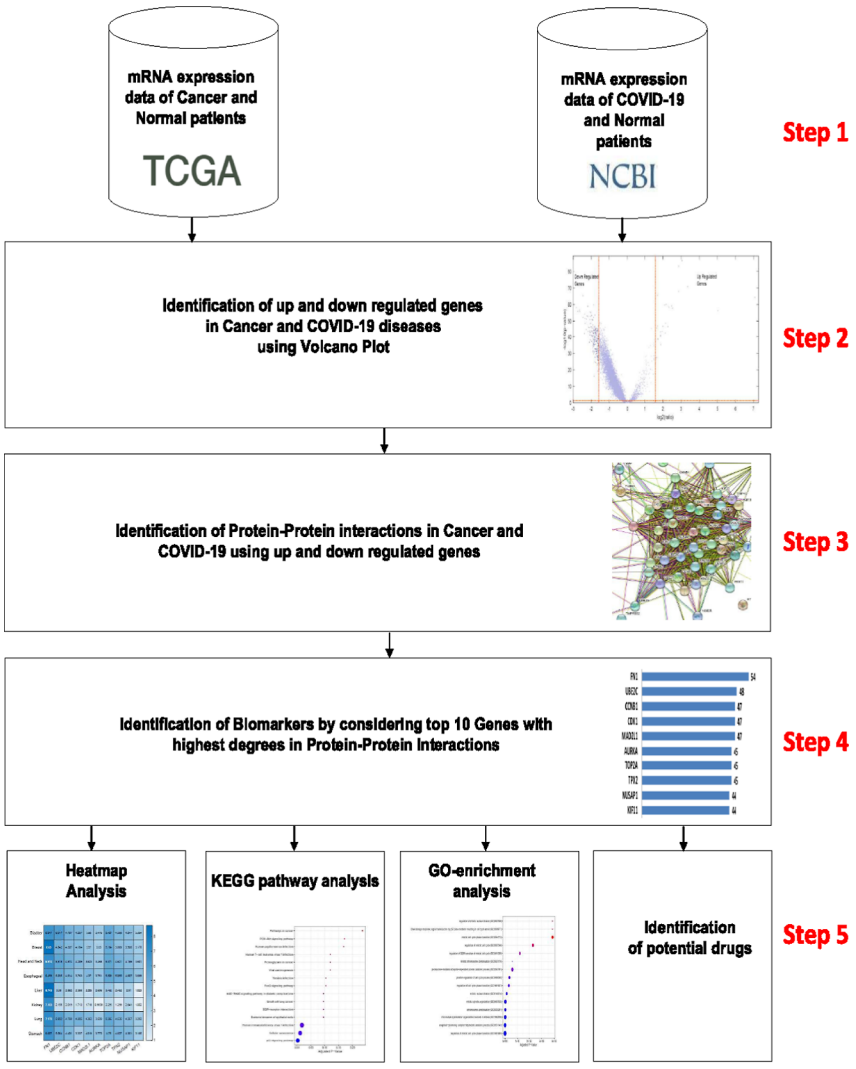

Figure 1. Pipeline of the Work.

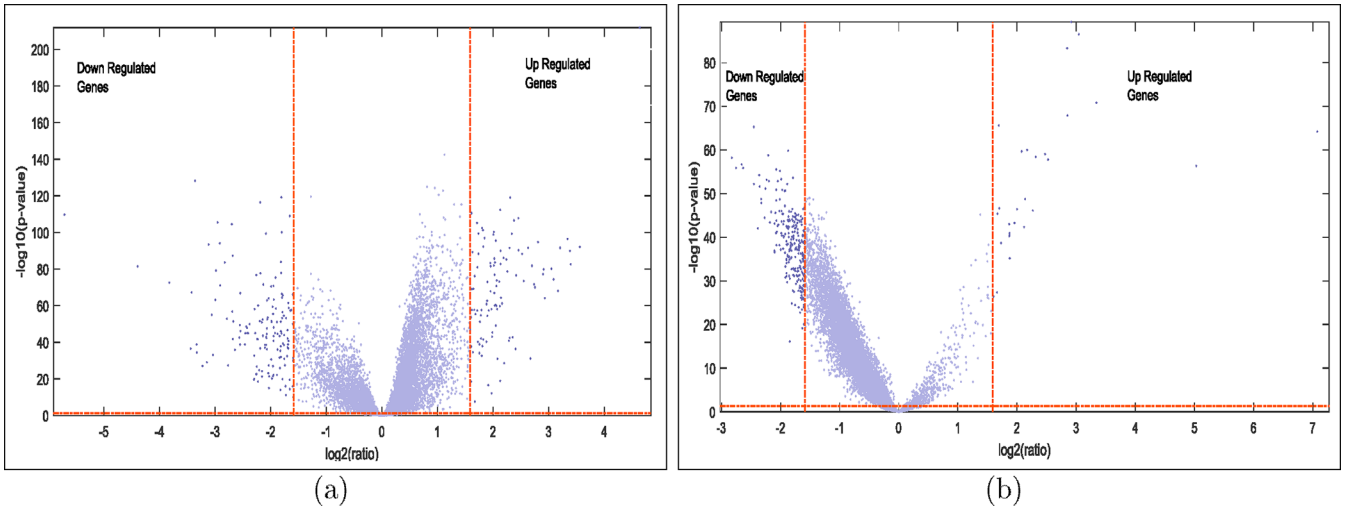

Figure 2. Volcano plots for (a) cancer vs normal and (b) COVID-19 vs normal cases, where the *p*-value is less than 0.05 and the FC value is greater than 3.

the cancer Genome Atlas (TCGA),[22] while mRNA expression data for 784 COVID-19 and 425 normal patients were downloaded from gene expression omnibus (GEO) of NCBI.[23] The eight organs considered for cancer were bladder, breast, head and neck, esophagus, liver, kidney, lung, and stomach, while for COVID-19, the 13 considered organs were

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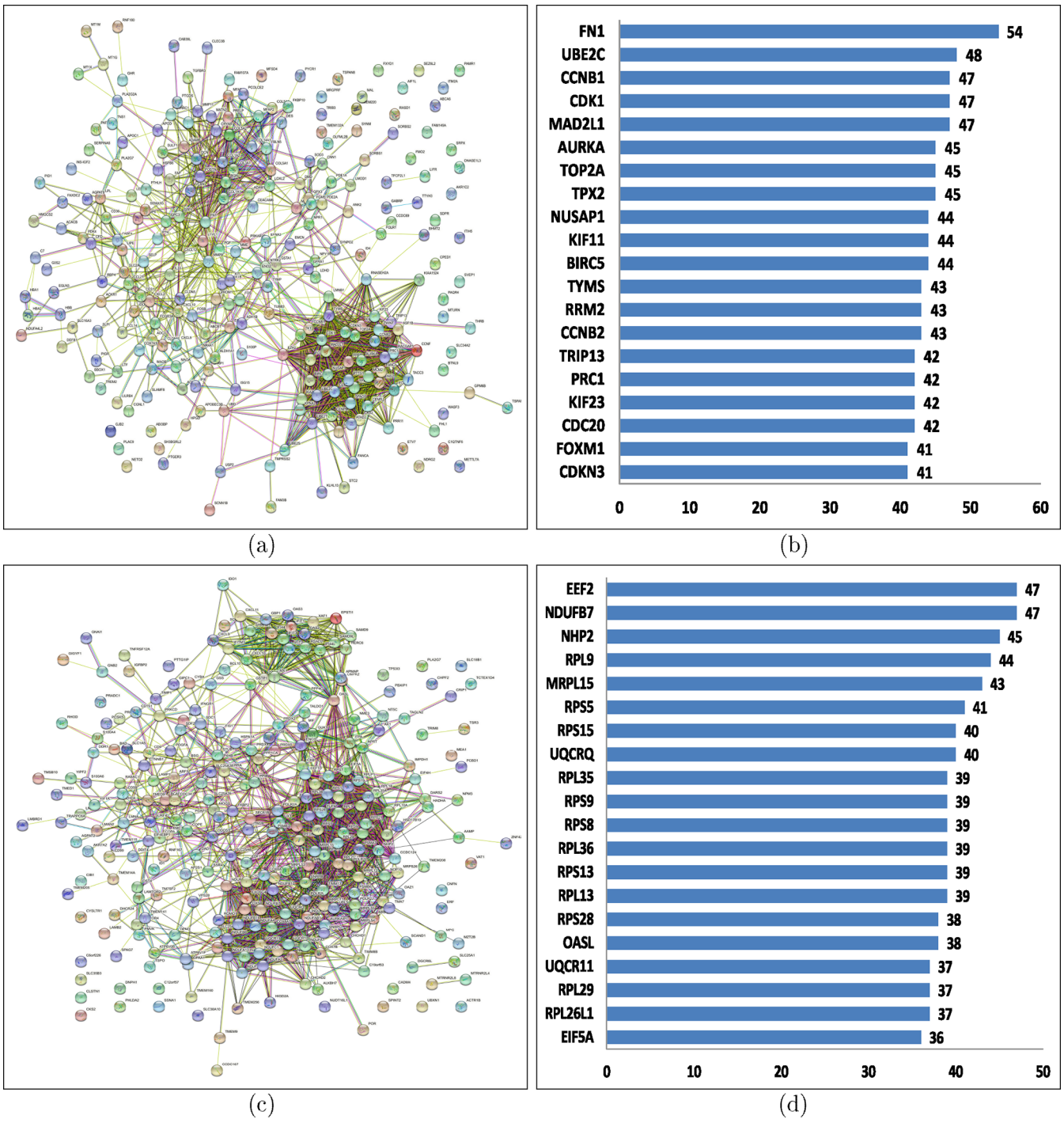

Figure 3. (a) PPI network and (b) top 20 genes for cancer and (c) PPI network and (d) top 20 genes for COVID-19.

nasopharynx, blood, respiratory tract, lung, heart, liver, intestine, stomach, eye, kidney, brain, pancreas, and uterus. This resulted in 16088 and 14412 genes for cancer and COVID-19, respectively. The statistics for cancer data are reported in Table 1, while that for COVID-19 are presented in Table 2. The expression data of COVID-19 were also used to prepare COVID19db by Zhang et al.[24] All the expression data are provided in the Supporting Information as excel files. Please note that in this work, the malignant tumors were considered and referred to as cancer throughout the manuscript.

Pipeline of the Work. The primary motivation of this work is to identify the human genes as biomarkers that are mostly affected by different types of cancer and COVID-19 diseases. The pipeline of the work is provided in Figure 1. The pipeline provides the different steps involved in the identification of biomarkers. In this regard, mRNA expression data of 2265 cancer and 282 normal patients were considered with 16088 genes, while mRNA expression data for 784 COVID-19 and 425 normal patients were considered with 14412 genes (Step 1). Then, in Step 2, the corresponding up- and down-regulated genes were identified using volcano plots on these expression data of cancer and COVID-19. Thereafter, the corresponding PPIs were identified using STRING database3 by combining the up- and down-regulated genes for each of cancer and COVID-19

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cases (Step 3). Based on the degree, the top 10 genes were then selected as biomarkers for each of the case in Step 4. Once the biomarkers were identified, their regulations were analyzed in the different organs for both cancer and COVID-19. Moreover, their corresponding pathways were explored using KEGG, while their biological significance had been reported through GO enrichment analysis. Finally, FDA-approved drugs targeting the biomarkers for both cancer and COVID-19 were identified using the Enrichr4 tool. The aforementioned analysis was explored in Step 6.

RESULTS

This work was executed according to the pipeline shown in Figure 1. To carry out the experiments in this work, MATLAB R2021a was used on an Intel Core i5-8250U CPU @ 1.80 GHz machine with 8 GB RAM and Windows 10 operating system. Initially, we had used mRNA expression data of cancer and COVID-19 patients along with the corresponding normal individuals to identify the respective up- and down-regulated genes using the volcano plot, where the *p*-value was less than 0.05 and the log fold change (FC) value was greater than 3. This resulted in 107 and 151 up- and down-regulated genes for cancer, respectively, while for COVID-19, the statistics was 28 and 256, respectively. The volcano plots for cancer versus normal and COVID-19 versus normal cases are shown in Figure 2a,b, respectively. Based on the FC values derived from the volcano plot, the top 10 up- and down-regulated genes for cancer versus normal and COVID-19 versus normal cases are reported in Supporting Information, Tables S1 and S2, respectively. As can be seen from Table S1, *MMP11* with a *p*-value of 1.30×10^{-212} and an FC value of 24.82 is the top ranked up-regulated gene for the cancer versus normal case, while the corresponding top ranked down-regulated gene is *ADH1B* with a *p*-value of 2.21E-110 and an FC value of −52.24. On the other hand, *MTRNR2L8* with a *p*-value of 6.49×10^{-65} and an FC value of 134.59 and *RPS21* with a *p*-value of 6.18×10^{-59} and an FC value of −7.06 are the top ranked up- and down-regulated genes for the COVID-19 versus normal case, respectively. The total list of up- and down-regulated genes for both cancer and COVID-19 are provided in the Supporting Information, Table S3.

Once the up- and down-regulated genes were identified, they were combined together, and their PPIs were evaluated for both cancer and COVID-19. This led to the identification of 219 genes for cancer and 257 genes for COVID-19. The total list is provided in the Supporting Information, Table S3. Among these 219 and 257 genes for cancer and COVID-19, based on the highest degree, the respective top 10 genes were considered as biomarkers for each. The respective PPIs are shown in Figure 3a,c, while the top 20 genes based on the degree are shown in Figure 3b,d. Please note that if there was any tie in the degree, the corresponding gene with the smaller *p*-value was taken to break the tie. For example, as can be observed from Figure 3b, *NUSAP1*, *KIF11*, and *BIRC5* were all tied to be a part of the top 10 candidates with the degree of 44. However, their *p*-values were 1.89×10^{-95}, 1.01E-90, and 2.84×10^{-83}, respectively. As in this work, we consider only 10 biomarkers, and *NUSAP1* and *KIF11* were chosen, while BIRC5 was discarded based on its *p*-value. The biomarkers identified for cancer and COVID-19 are, respectively, reported in Tables 3 and 4. The top 10 biomarkers for cancer are *FN1*, *UBE2C*, *CCNB1*, *CDK1*, *MAD2L1*, *AURKA*, *TOP2A*, *TPX2*, *NUSAP1*, and *KIF11*, while those for COVID-19 are *EEF2*, *NDUFB7*, *NHP2*, *RPL9*, *MRPL15*, *RPS5*, *RPS15*, *UQCRQ*, *RPL35*, and *RPS9*. *FN1* or Fibronectin 1, which is an up-regulated gene with a degree of 54, a *p*-value 1.00×10^{-43}, and an FC value of 3.94, is the top most biomarker in cancer. It is known to be involved in various types of tumors and is up-regulated in many cancer types.[25] The top most biomarker for

Table 3. Top 10 Genes as Biomarkers for Cancer

genes	degree	regulation	*p*-value	FC value
FN1	54	up	1.00×10^{-43}	3.94
UBE2C	48	up	9.21×10^{-93}	11.76
CCNB1	47	up	7.05×10^{-87}	4.55
CDK1	47	up	5.58×10^{-91}	5.48
MAD2L1	47	up	4.50×10^{-101}	4.03
AURKA	45	up	9.60×10^{-120}	4.93
TOP2A	45	up	1.28×10^{-90}	10.40
TPX2	45	up	4.19×10^{-97}	10.10
NUSAP1	44	up	1.89×10^{-95}	6.99
KIF11	44	up	1.00×10^{-90}	4.38

Table 4. Top 10 Genes as Biomarkers for COVID-19

genes	degree	regulation	*p*-value	FC value
EEF2	47	down	1.83×10^{-44}	−3.58
NDUFB7	47	down	1.37×10^{-56}	−6.73
NHP2	45	down	9.52×10^{-41}	−3.63
RPL9	44	down	2.93×10^{-29}	−3.16
MRPL15	43	down	1.24×10^{-29}	−3.05
RPS5	41	down	6.98×10^{-39}	−4.04
RPS15	40	down	5.78×10^{-33}	−3.24
UQCRQ	40	down	2.29×10^{-33}	−3.37
RPL35	39	down	2.35×10^{-52}	−5.10
RPS9	39	down	2.54×10^{-51}	−3.81

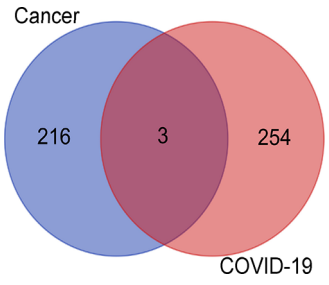

Figure 4. Venn diagram to show the number of common genes between cancer and COVID-19.

Table 5. Common Genes between Cancer and COVID-19

	cancer				COVID			
common genes	degree	regulation	*p*-value	FC value	degree	regulation	*p*-value	FC value
CXCL9	13	Up	3.83×10^{-74}	5.85	15	Up	8.06×10^{-47}	4.80
CXCL10	15	Up	1.56×10^{-82}	6.48	24	Up	1.63×10^{-71}	10.13
IDO1	6	Up	4.46×10^{-46}	3.95	4	Up	4.21×10^{-28}	3.16

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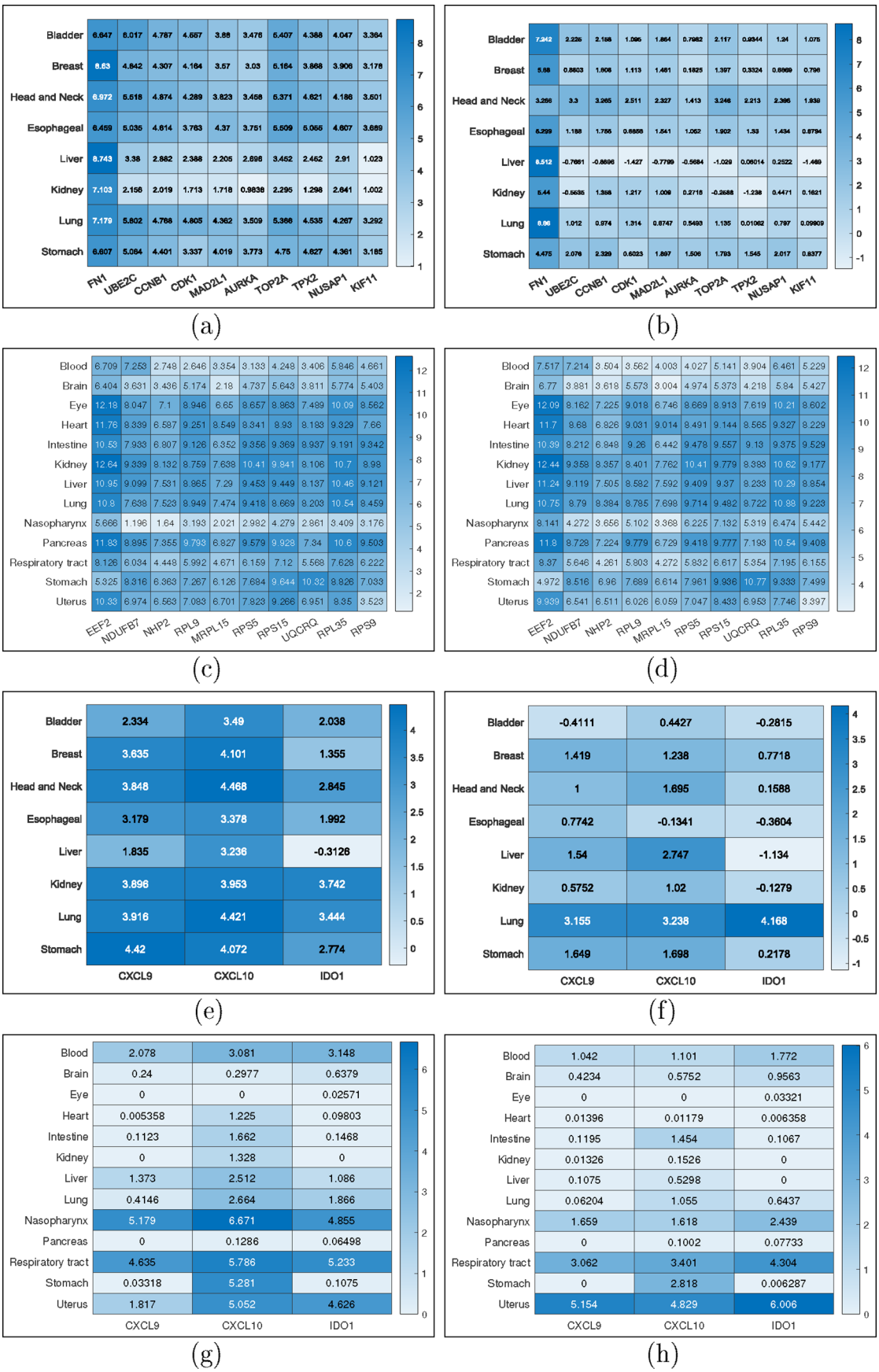

Figure 5. Heatmap to represent the regulation of the biomarkers in different organs for (a) cancer, (b) corresponding normal, (c) COVID-19, and (d) corresponding normal and regulation of common genes for (e) cancer, (f) corresponding normal, (g) COVID-19, and (h) Corresponding normal.

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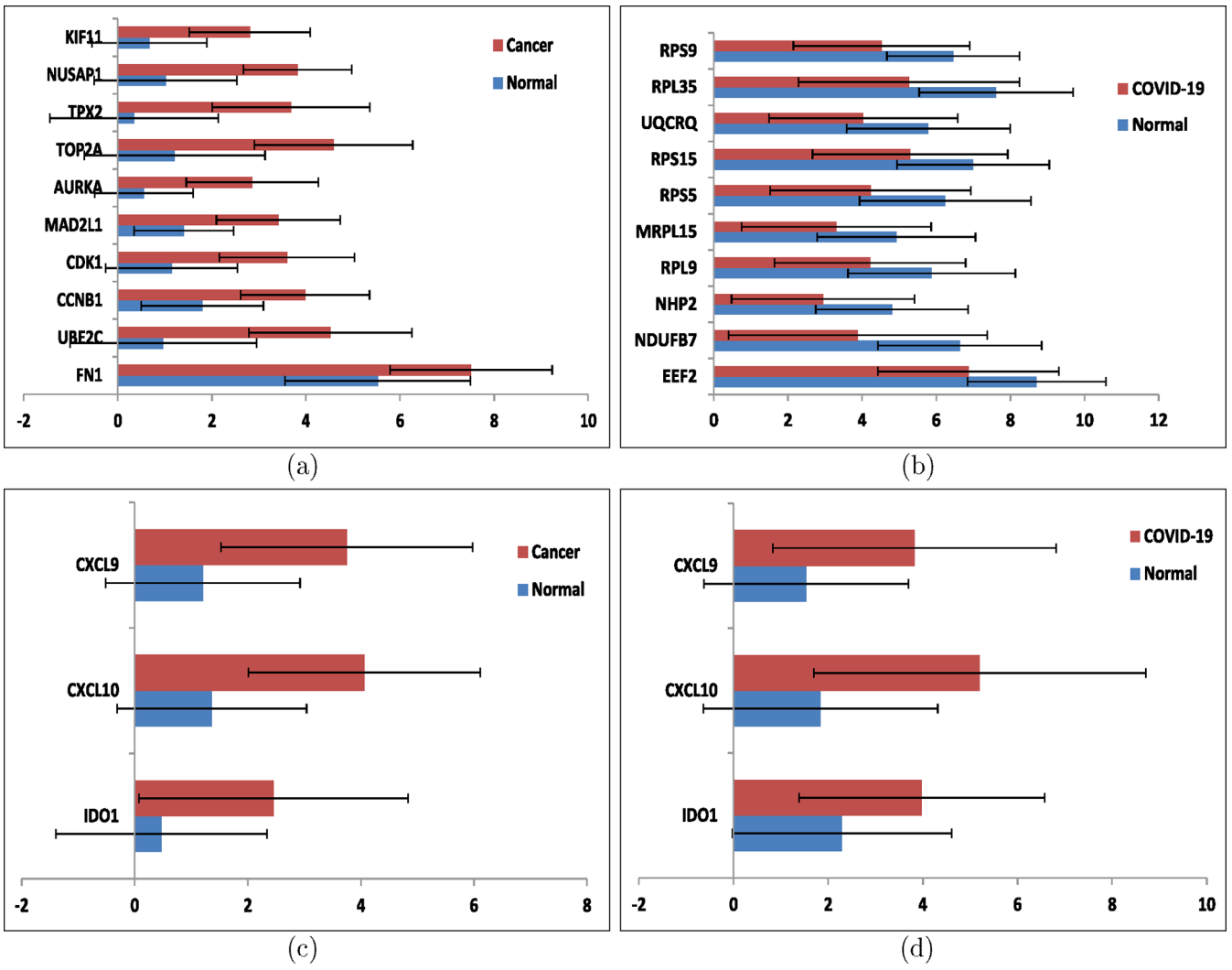

Figure 6. Average expression values for the biomarkers of (a) cancer (b) COVID-19 and common genes for (c) cancer and (d) COVID-19.

COVID-19 is *EEF2*, which is a down-regulated gene and has a degree of 47, a *p*-value 1.83×10^{-44}, and an FC value of −3.58. Figure 4 shows the number of common genes between cancer (219) and COVID-19 (257), while Table 5 reports these common genes; they being *CXCL9*, *CXCL10*, and *ID O 1*. All of these three genes are up-regulated in both cancer and COVID-19.

Based on the average expression values, the regulation of the biomarkers for cancer and corresponding normal patients for the different afflicted organs is represented in Figure 5a,b, respectively, where the colors represent the regulation; a darker color shows that a gene is highly regulated in a particular organ. For example, *FN1* is highly regulated in the breast, head and neck, esophagus, liver, kidney, and stomach of a cancer patient as opposed to a normal individual. On the other hand, such regulation for COVID-19 and corresponding normal patients is shown in Figure 5c,d, respectively. For example, *EEF2* is down-regulated in organs such as the respiratory tract, nasopharynx, liver, brain, and blood of a COVID-19 patient. These observations support our previous discussions on *FN1* and *EEF2*. Moreover, the regulation of the common genes pertaining to cancer and COVID-19 are reported through Figure 5e,h. As can be seen from Figure 5e, *CXCL10* is highly expressed in the lung of cancer patients. This is in line with the observation made by Mahmood et al.[26] Further analysis for the average expression values for the biomarkers of cancer and COVID-19 are provided in Figure 6a,b, respectively, while such an analysis for the common genes is shown in Figure 6c,d. Figure 6a also corroborates the fact that all the biomarkers are up-regulated in cancer and down-regulated in COVID-19, while the three common genes are highly expressed in both cancer and COVID-19.

DISCUSSION

According to ref,[27] DNA damage may be caused by the dysregulation of *EEF2*. Also, the possible association of down regulation of *EEF2* with COVID-19 severity has been mentioned in ref.[28] Please note that biomarkers for COVID-19 such as *EEF2*, *NHP2*, *RPL9*, *MRPL15*, *RPS5*, *RPS15*, *RPL35*, and *RPS9* are all directly interacting with various SARS-CoV-2 proteins such as NSP7, Spike, Envelope, ORF6, ORF7a, ORF7b, ORF9b, and ORF10.[29] As reported in the Results section, the three common genes that are up-regulated in both cancer and COVID-19 are CXCL9, CXCL10, and IDO1. The intratumoral accumulation of CXCL9 and CXCL10, which promotes tumor-infiltrating lymphocytes (TIL) chemotactic recruitment, may enhance TIL-dependent immune intervention in cancer.[30] Following immune checkpoint blockage, CXCL9 has been

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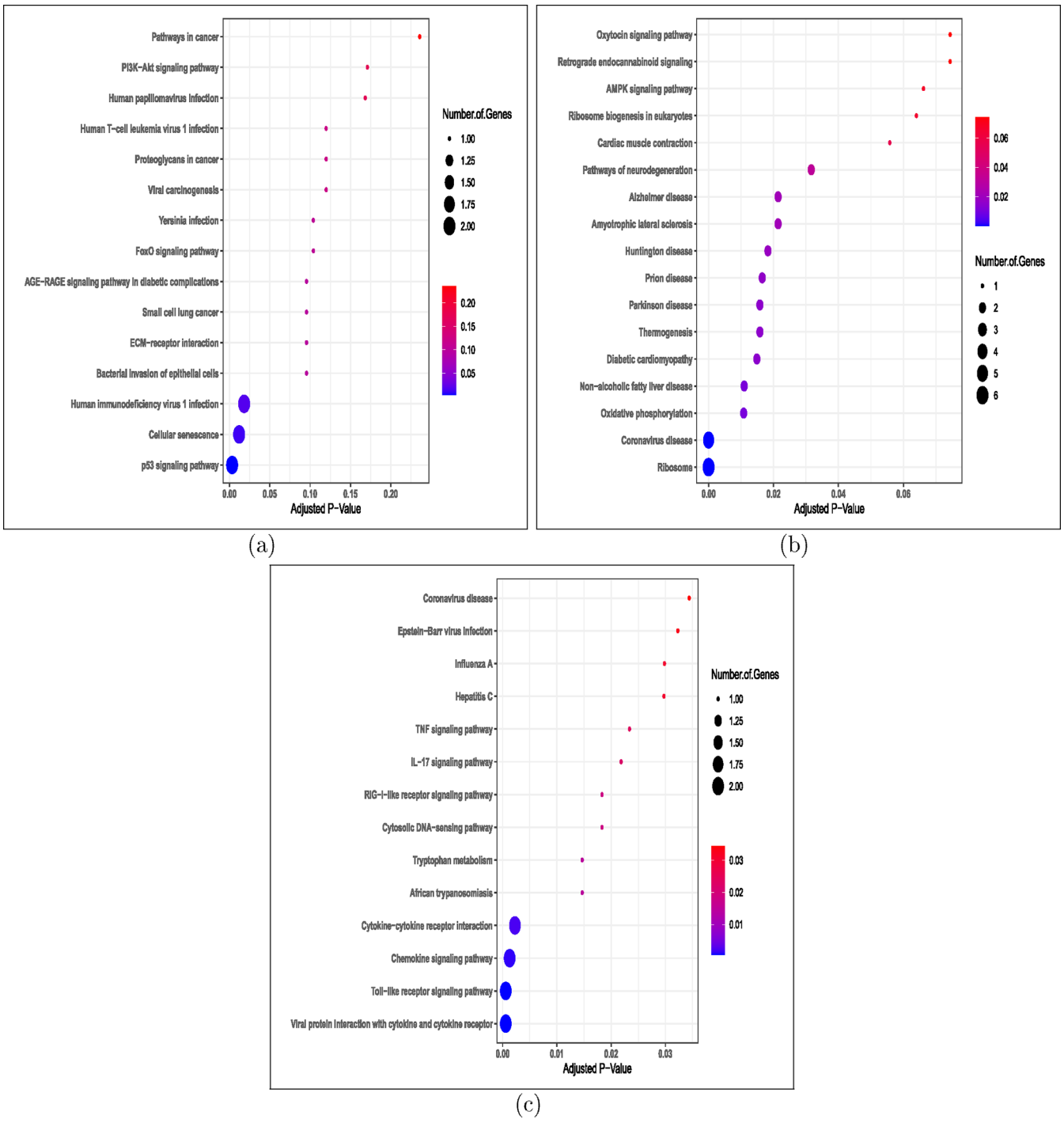

Figure 7. Significant KEGG pathways corresponding to biomarkers for (a) cancer and (b) COVID-19 and (c) common genes between cancer and COVID-19.

demonstrated to be necessary for antitumor immune responses.[31] On the other hand, patients dying from SARS-CoV-2 have shown higher plasma levels of CXCL9.[32,33] *CXCL10* is responsible for immune responses in the lung and COVID-19 infection.[26] On the other hand, *ID O 1* can be considered to be an ideal target for cancer immunotherapy.[34]

KEGG Pathway Analysis. Some important pathways for the different biomarkers of cancer and COVID-19 and the common genes between them are shown in Figure 7a−c, respectively. These results were collected from the Enrichr tool. The bubbles in the plots represent the number of genes (biomarkers) associated with each pathway; a smaller bubble represents a lower number of biomarkers, while a larger bubble indicates the opposite, and the colors are based on the corresponding adjusted *p*-value. As can be seen from Figure 7a, biomarkers for cancer are enriched in pathways, which include the *p53 signaling pathway* (*CCNB1* and *CDK1*), *human immunodeficiency virus 1 infection* (*CCNB1* and *CDK1*), and so on, with the corresponding adjusted *p*-values of 3.33×10^{-3} and 1.82×10^{-2}, respectively. Biomarkers for COVID-19 are enriched in pathways such as *coronavirus disease* (*RPS15, RPS9, RPS5, RPL35,* and *RPL9*), *diabetic cardiomyopathy* (*NDUFB7* and

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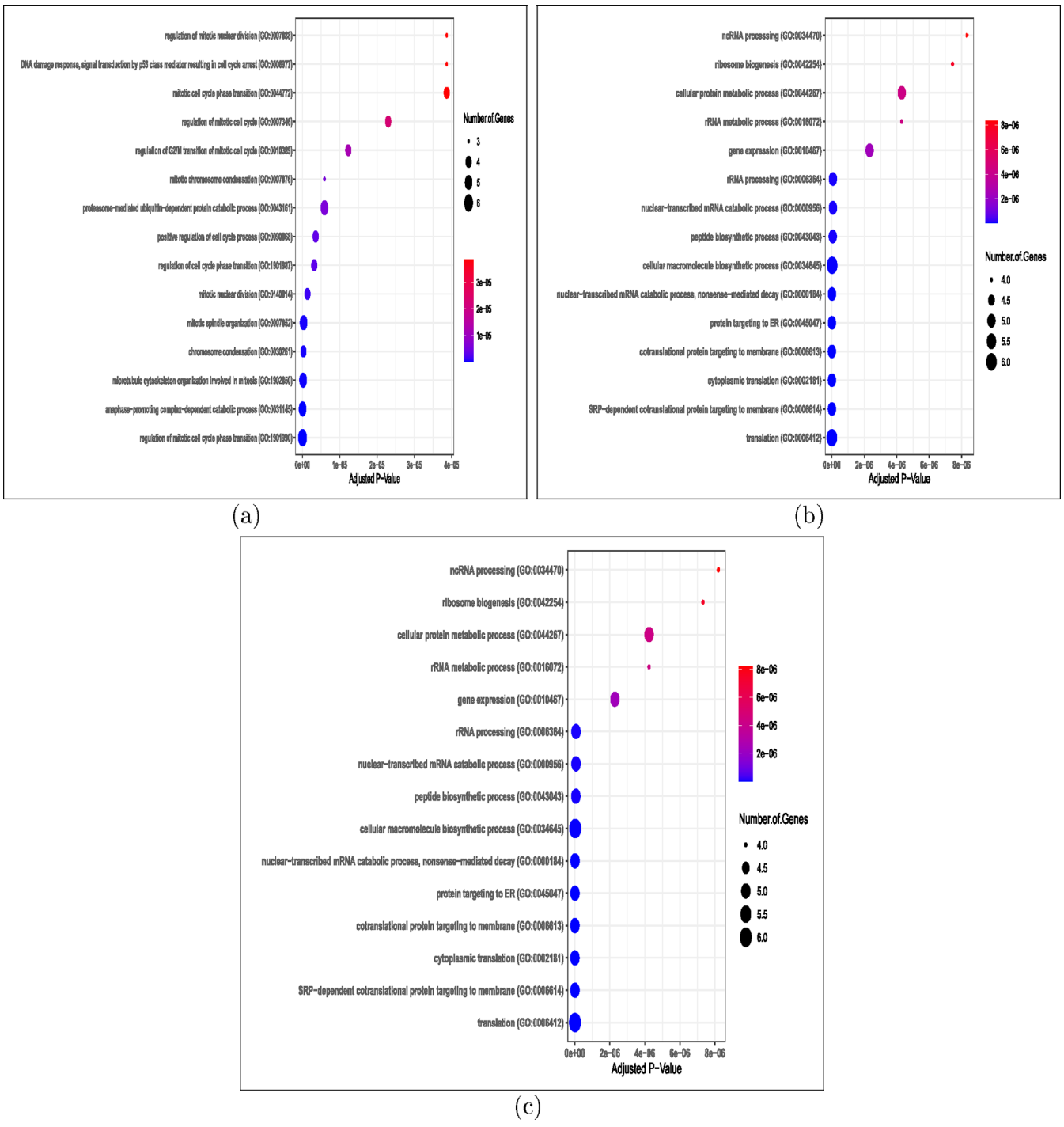

Figure 8. Significant GO biological processes corresponding to biomarkers for (a) cancer and (b) COVID-19 and (c) common genes between cancer and COVID-19.

UQCRQ), *Parkinson disease* (*NDUFB7* and *UQCRQ*), *Huntington disease* (*NDUFB7* and *UQCRQ*), *Alzheimer disease* (*NDUFB7* and *UQCRQ*), *pathways of neurodegeneration* (*NDUFB7* and *UQCRQ*), and so on with the corresponding adjusted *p*-values of 4.11×10^{-7}, 1.48×10^{-2}, 1.57×10^{-2}, 1.82×10^{-2}, 2.14×10^{-2}, and 3.16×10^{-2}, respectively. These results highlight that COVID-19 can aggravate the pathways for other diseases as well, leading to comorbidity. On the other hand, the common genes target pathways such as the *chemokine signaling pathway* (*CXCL10, CXCL9*), *African trypanosomiasis* (*ID O 1*), *IL-17 signaling pathway*, *TNF signaling pathway*, *Hepatitis C*, *Influenza A*, *Epstein−Barr virus infection*, *coronavirus disease*, and so on (all triggered by *CXCL10*) with the corresponding adjusted *p*-values of 1.27×10^{-3}, 1.46×10^{-2}, 2.18×10^{-2}, 2.33×10^{-2}, 2.97×10^{-2}, 2.98×10^{-2}, 3.23×10^{-2}, and 3.43×10^{-2}, respectively. Among these, chemokine, IL-17, and TNF signaling pathways are all pathways in cancer, while coronavirus disease is a pathway in COVID-19.

GO Enrichment Analysis. GO enrichment analysis was performed to understand the significance of the different interacting human genes in biological activities. Similar to KEGG pathways, the GO enrichment results were collected

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Table 6. Details of Drugs Corresponding to Biomarkers for Cancer and COVID-19

disease	human genes	drugs	drug bank ID	treatment
cancer	FN1 , UBE2C, CCNB1, CDK1, MAD2L1,	lucanthone	DB04967	inhibits post-radiation DNA repair in tumor cells. it is also shown to be toxic to glioma cells by inhibiting autophagy.[43]
	AURKA , TOP2A, TPX2, NUSAP1, KIF11	etoposide	DB00773	testicular and small cell lung tumors.
		methotrexate	DB00563	a wide variety of cancers.
		trifluridine	DB00432	chemotherapy for certain types of metastatic gastrointestinal cancers.
		resveratrol	DB02709	herpes simplex virus types 1 and 2, found to have potential anticancer properties.
		belinostat	DB05015	relapsed or refractory peripheral T-cell lymphoma (PTCL).
		thalidomide	DB01041	newly diagnosed multiple myeloma and erythema nodosum leprosum.
		ciclopirox	DB01188	mild to moderate onychomycosis of fingernails and toenails. It can be considered to be a novel chemotherapeutic for the treatment of colorectal cancer.[44]
		vinblastine	DB00570	breast cancer, testicular cancer, neuroblastoma, Hodgkin's and non-Hodgkins lymphoma, mycosis fungoides, histiocytosis, and Kaposi's sarcoma.
COVID-19	EEF2 , NDUFB7, RPL9, MRPL15, RPS5, RPS15, UQCRQ, RPL35, RPS9	disodium selenite	DB11127	potential therapy in the prevention or management of atherosclerosis, reduces COVID-19.[45]
		midecamycin	DB13456	a variety of infections caused by susceptible bacteria.
		amikacin	DB00479	infections caused by more resistant strains of Gram negative bacteria and some Gram positive bacteria. a potent inhibitor of main protease of SARS-CoV-2.[46]
		paclitaxel	DB01229	advanced carcinoma of the ovary and other various cancers including breast and lung cancer. Treatment of COVID.
		metformin hydrochloride	DB00331	glycemic control in type 2 diabetes mellitus
		ambroxol	DB06742	airway secretion clearance therapy, has anti SARS-CoV-2 activity[47]
		clindamycin	DB01190	serious infections caused by susceptible anaerobic, streptococcal, staphylococcal, and pneumococcal bacteria. a potential inhibitor of TMPRSS2 (SARS-CoV-2 uses TMPRSS2 for spike protein priming).[48]
		hydralazine	DB01275	management of essential hypertension or severe hypertension.
		baclofen	DB00181	severe spasticity of cerebral or spinal origin in adult and pediatric patients. shows significant reversal power to the COVID-19 gene signature.[49]
Common	CXCL10, CXCL9, IDO1	imatinib	DB00619	leukemia, myelodysplastic/myeloproliferative disease, systemic mastocytosis, hypereosinophilic syndrome, dermatofibrosarcoma protuberans, and gastrointestinal stromal tumors. may reverse pulmonary capillary leak in COVID-19 patients[40]
		dinoprostone	DB00917	induce labor or abortion as well as treatment of nonmetastatic gestational trophoblastic disease.
		decitabine	DB01262	myelodysplastic syndromes (MDS)
		roflumilast	DB01656	decrease the risk of exacerbations in patients with severe chronic obstructive pulmonary disease (COPD). restricts tumor growth in ovarian cancer.[41] might be beneficial for COVID-19 patients.[50,42]

from the Enrichr tool as well and considered only for the biomarkers. The results of the analysis for the different biomarkers of cancer and COVID-19 and the common genes in terms of biological processes are shown in Figure 8a−c, respectively, while those for cellular and molecular processes are shown in Supporting Information Figures S1 and S2. The detailed analysis for all the GO pathways (biological, molecular, and cellular) are provided in the Supporting Infomation. Some significant biological pathways for biomarkers such as *TPX2, CCNB1, UBE2C, CDK1, MAD2L1, AURKA, NUSAP1*, and *KIF11* in cancer are as follows: *regulation of mitotic cell cycle phase transition (GO:1901990)*, *anaphase-promoting complex-dependent catabolic process (GO:0031145)*, and *microtubule cytoskeleton organization involved in mitosis (GO:1902850)* with adjusted *p*-values of 2.93×10^{-8}, 3.24×10^{-8}, and 1.84×10^{-7}, respectively. For COVID-19, such pathways for biomarkers such as *RPS15, RPS9, RPS5, RPL35, EEF2*, and *RPL9* are as follows: *translation (GO:0006412)*, *SRP-dependent cotranslational protein targeting to membrane (GO:0006614)*, and *cytoplasmic translation* (GO:0002181) with an adjusted *p*-value of 8.02×10^{-9} for all and some significant pathways for the common genes are *positive regulation of calcium ion transmembrane transport (GO:1904427)*, *positive regulation of release of sequestered calcium ion into cytosol (GO:0051281)*, and *positive regulation of calcium ion transport into cytosol (GO:0010524)* with the adjusted *p*-value of 1.73×10^{-4}.

Drug-Targeting Biomarkers. There are many drugs that are prescribed for cancer patients, while drugs to combat COVID-19 is still under development. In this regard, drug repurposing can be a viable alternative for effective identification

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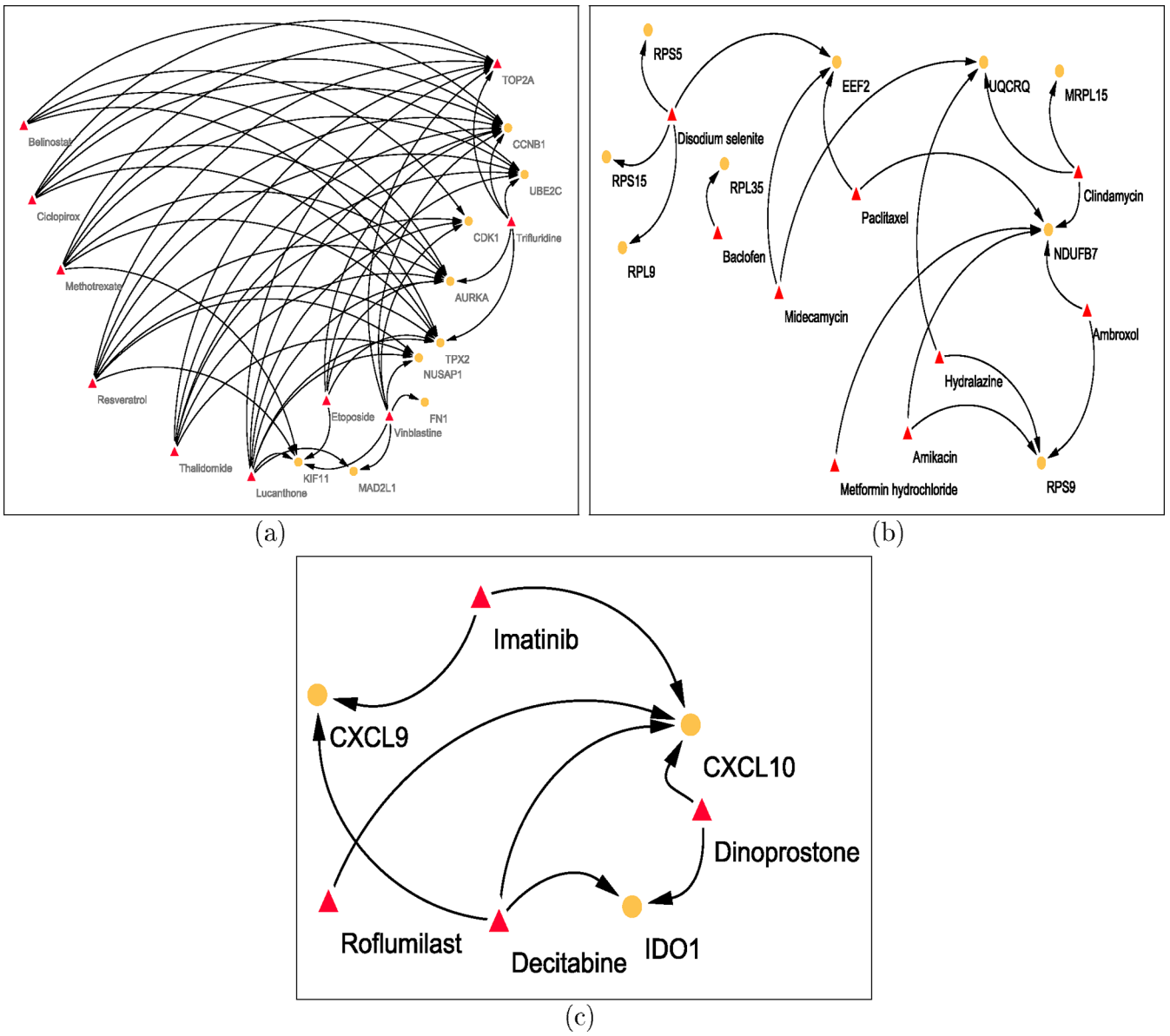

Figure 9. Drug−protein interactions between (a) cancer and (b) COVID-19 and (c) common proteins (genes) between cancer and COVID-19. In the figures, the triangles represent the drugs, while the proteins are represented by circles.

of a drug for COVID-19, and as such, the biomarkers can be considered as good target candidates. For both cancer and COVID-19, the drugs that interact with the biomarkers were identified using DSigDB in the Enrichr tool. The results for the corresponding drugs are reported in Table 6 along with the relevant drug IDs as collected from Drug Bank and the possible treatments. The corresponding drug−protein interactions are shown in Figure 9.Figure 6.

As can be seen from Table 6, lucanthone, etoposide, methotrexate, trifluridine, resveratrol, belinostat, ciclopirox, and vinblastine are few of the drugs that are used for treating several types of cancer and related to the identified biomarkers as well. On the other hand, a drug such as paclitaxel, which targets the biomarkers of COVID-19 such as EEF2 and NDUFB7, is not only used for cancer but is also used for the treatment of COVID. Al-Motawa et al.[35] have also provided a scientific rationale for repurposing paclitaxel for the treatment of COVID-19. In the past, paclitaxel has also been judged for antiviral activity, especially for viral helicase.[36−39] Drugs such as imatinib and decitabine targeting the common proteins (genes) of both cancer and COVID-19, which are used for the treatment of cancer, are also under trial for the treatment of COVID-19[40] as well. Roflumilast, which is another drug targeting the common proteins (genes), is used for decreasing the risk of exacerbations in patients with severe chronic obstructive pulmonary disease (COPD) and is also under trial for treating cancer[41] and COVID-19.[42]

CONCLUSIONS

Both cancer and COVID-19 have been responsible for many deaths around the globe. Though various types of cancer have been prevalent for a very long time, SARS-CoV-2, the virus causing COVID-19, has been around for more than 2 years now. In this work, we have identified the human genes as biomarkers that can be targeted for cancer and COVID-19 diseases. Though we conducted the experiments with mRNA expression data of cancer and COVID-19 to identify the up- and down-regulated genes, our main focus in this work was to identify the biomarkers

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using the PPI network as they are the ones that are connected to most of the other human proteins and consequently aid in the progression of a disease. Thus, we identified 10 biomarkers for both cancer and COVID-19 with the highest degrees and have also shown the regulation of each biomarker in the corresponding human organs affected by cancer and COVID-19. We have also reported the corresponding KEGG pathways and the results of GO enrichment analysis for the biomarkers. Finally, the different drugs targeting the biomarkers of cancer and COVID-19 are also reported in this work. Such drugs including lucanthone, etoposide, methotrexate, trifluridine, resveratrol, belinostat, ciclopirox, and vinblastine are targeting the biomarkers of cancer. As per the literature, these drugs are already in use for several types of cancer. Similarly, for the biomarkers of COVID-19, the identified drug paclitaxel is under trial as per the literature. Therefore, we hope that the identified biomarkers may help the ongoing research in cancer and COVID-19.

■ ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The ethical approval or individual consent was not applicable.

■ AVAILABILITY OF DATA AND MATERIALS

The Supporting Information of this work is available at "http://www.nitttrkol.ac.in/indrajit/projects/Cancer-COVID-19-Biomarkers/".

Consent for Publication. Not applicable.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04389.

Top 10 up- and down-regulated genes for cancer versus normal, top 10 up- and down-regulated genes for COVID-19 versus normal, link and description of Supporting Information files, significant GO cellular processes corresponding to biomarkers for (a) cancer and (b) COVID-19, significant GO molecular processes corresponding to biomarkers for (a) cancer and (b) COVID-19 and (c) common genes between cancer and COVID-19, up- and down-regulated genes for cancer, up- and down-regulated genes for COVID-19, genes identified from the PPI of cancer data, and genes identified from the PPI of COVID-19 data (PDF)

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Notes

The authors declare no competing financial interest.

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