Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Global multi-omics and systems pharmacological strategy unravel the multi-targeted therapeutic potential of natural bioactive molecules against COVID-19: An in silico approach

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ABSTRACT

Understanding the immunological behavior of COVID-19 cases at molecular level is essential for therapeutic development. In this study, multi-omics and systems pharmacology analyses were performed to unravel the multi-targeted mechanisms of novel bioactives to combat COVID-19. Immuno-transcriptomic dataset of healthy controls and COVID-19 cases was retrieved from ArrayExpress. Phytocompounds from ethnobotanical plants were collected from PubChem. Differentially expressed 98 immune genes associated with COVID-19 were derived through NetworkAnalyst 3.0. Among 259 plant derived compounds, 154 compounds were targeting 13 COVID-19 immune genes involved in diverse signaling pathways. In addition, pharmacological properties of these phytocompounds were compared with COVID-19 drugs prescribed by WHO, and 25 novel phytocompounds were found to be more efficient with higher bioactive scores. The current study unravels the virogenomic signatures which can serve as therapeutic targets and identified phytocompounds with anti-COVID-19 efficacy. However, further experimental validation is essential to bring out these molecules as commercial drug candidates.

1. Introduction

Certain viruses belong to Coronaviridae family regularly present in the human population, for example, rhinoviruses which cause mild respiratory infections, a certain type of viruses such as severe acute respiratory syndrome associated coronavirus (SARS-CoV) and the Middle East respiratory syndrome associated coronavirus (MERS-CoV) cause a lethal respiratory syndrom in humans [1,2]. The emergence of novel corona virus (2019-nCoV) has evolved as a serious global threat due to highest transmission from human to human [3,4]. Because of the global spread, the World Health Organization (WHO) officially declared coronavirus disease (COVID-19) as a pandemic disease on March 11, 2020. A new virus 2019-nCoV was identified to be a type of beta coronavirus and as it is closely related to SARS-CoV with 76% genome similarity and it was renamed as SARS-CoV2 by the International Committee on Taxonomy of Viruses [5]. COVID-19 caused by SARS-CoV2 is spreading at an alarming rate across continents and it certainly impacted the health and wealth of the entire world. This viral pandemic is an imminent threat to the human population. The current COVID-19 pandemic condition is that there is no approved drug available to date to treat this disease and the only measure which is being taken is the prevention of disease spread by social distancing [6,7]. Thus, the need of the hour for this world is to identify the potential drug molecules to treat the condition and to understand the in-depth molecular mechanisms and switches involved in virus entry into a host cell to prevent the transmission and infection.

The spike protein of SARS-CoV2 is almost structurally identical to that of SARS-CoV and the entry of SARS-CoV2 into host cells is mediated by the binding of S proteins to the angiotensin-converting enzyme-2 (ACE2) receptor present on the host cell surface followed by mem-

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brane fusion [8–10]. The spike protein has two functional subunits namely S1 involved in receptor binding and S2 involved in membrane fusion [11]. In addition, there is a need for spike protein priming which is mediated by the proteolytic activity of transmembrane protease serine 2 (TMPRSS2) to expose the functional subunits [12]. But role of these receptor molecules with their interacting immune responsive genes remain unexplored. The scientific efforts taken so far to overcome the pandemic of COVID-19 are focusing more on ACE2 receptor inhibitors, TMPRSS2 inhibitors and the development of spike protein vaccines. But none of the studies conclusively cataloged the status of phytomolecules and their respective human immune responsive target genes.

Medicinal plants are the best reservoir of huge numbers of pharmacologically active bioactive compounds and used as a curative medicine for multiple diseases from ancient period. These are all the backbone of traditional medicine; approximately 3.3 billion people in developing countries are still using them on an ordinary basis [13]. These reservoirs contain plenty of pharmaceutical ingredients that can be used in the process of new drug development. Medicinal plants play a crucial role in the development of human cultures around the world. In accordance with the IUCN (International Union for Conservation of Nature) report, nearly 80,000 flowering plant species were worn for medicinal purposes. *Justicia adhatoda*, *Ocimum sanctum*, *Solanum trilobatum*, *Andrographis paniculata*, *Eucalyptus Sp.*, *Alpinia officinarum* and *Plectranthus amboinicus* are some of the essential medicinal plants in traditional Indian medicines. These plants were used in traditional Ayurvedic medicines to treat the various respiratory tract diseases such as pharyngitis, bronchitis, sinusitis, asthma, cough, tuberculosis [14–22]. In addition, these plants are also used to treat skin diseases, wound healing, diabetes, dysentery, digestive and cardiovascular diseases. The selected medicinal plants also possess a wide variety of pharmacological activities including antiviral, adaptogenic, antioxidant, anticancer, analgesic, anti-tussive, anti-inflammatory, antimicrobial, and immune-modulator [14–22].

In spite of the pivotal role of Indian traditional medicine, how the phytomolecules will work and what are their significant immune responsive human targets are still a major bottleneck. The main goal of this present study is to explore the significant immunological mechanism and the pharmaceutical properties and activities of bioactive compounds from *J. adhatoda, O. sanctum, S. trilobatum, A. paniculata, Eucalyptus Sp., A. officinarum* and *P. amboinicus* against COVID-19, major issues addressed in the current study are as follows: (i) which human immune responsive genes are differentially regulated in COVID-19? (ii) Which bioactive phytomolecules are involved in the immune regulatory functions for the treatment of this deadly COVID-19 infection? (iii) Which human COVID-19 immune responsive genes are closely associated and modulated by the phytomolecules to accomplish the immunobiological activity and the purpose of curing the respiratory (COVID-19) viral disease? With the advancement of systems pharmacology and pivotal analytical tools such as immuno-transcriptomics, cheminformatics, interactomics analyses allow us to unravel the molecular mechanisms of traditional Indian medicines in treating this deadly infection. Hence, the present study reveals in-depth information into the immunological mechanisms of bioactive molecules and their pharmacological roles. Immuno-transcriptomic profiling identifies the differentially expressed genes associated with COVID-19. Cheminformatics analysis was performed to filter the novel bioactive compounds with essential pharmacological activities and also the dependability of compound – human immune target interactions were predicted. The obtained COVID-19 immunological targets were then imported on to the specialized databases to find out their immunological mechanisms and signaling pathways of active phytocompounds. We hope that the help of human systems pharmacology and the investigation of immunological mechanisms of traditional Indian medicines will significantly promote the development of new drugs and for the treatment of COVID-19 and other respiratory diseases in mere future.

2. Materials and methods

A global multi-omics and systems pharmacology integrated approaches have been applied for the very first time to unravel the significant curative efficacy of potential therapeutic molecules from ethnobotanical plants to combat deadly COVID-19 consisting of: (i) target mining and functional enrichment analysis to identify the phytocompounds – COVID-19 direct immune target network; (ii) systemic network edifice and analysis to demonstrate the molecular machinery of phytocompounds derived from Indian traditional medicinal plants in treating COVID-19; (iii) functional gene ontology and STRING interaction for COVID-19 immune responsive gene targets will pave the way for diverse biological pathway analysis to reveal the functional mode of key players in multiple nodes from an immunological pathway level.

2.1. In silico mining of immune responsive genes in healthy controls and COVID-19 cases from human transcriptome

The human immuno- transcriptomic dataset of healthy controls and COVID-19 cases (*E*-MTAP-8871) was collected/ retrieved from ArrayExpress database (www.ebi.ac.uk/arrayexpress/). The retrieved dataset was manually curated using MS Excel. Further, this human immuno- transcriptomic data was imported into the Gene Expression Table of NetworkAnalyst 3.0 tool [23]. The dataset was uploaded using (.txt or .zip) input file format and that can be plotted in Excel file with microarray data intensities (gene expression values), corresponding immune responsive genes or healthy controls and COVID-19 cases or samples or time series in columns and rows with gene name. Each column was named as per the type of specific samples and or cases. Filtering and normalization were performed to remove data that are simply erroneous and to ensure that the expression distribution of each sample is similar across the entire experiment, respectively. Followed by differential gene expression analysis was carried out to identify the significant immune responsive genes using Limma statistical model with adjusted *P*-value 0.05 and Log2 fold change is 1.0. The identified significant immune responsive genes (official gene symbol) were used to study the over-representation analysis (ORA) functional enrichment and tissue specific (whole blood) protein-protein interaction (PPI) analysis through inbuilt KEGG and DifferentialNet databases of NetworkAnalyst 3.0, respectively. It will pave the way to impute the potential human drug targets for further analysis.

2.2. Collection of pharmacologically active phytomolecules

The comprehensive information on 259 pharmacologically active compounds from *J. adhatoda, O. sanctum, S. trilobatum, A. paniculata, Eucalyptus Sp., A. officinarum* and *P. amboinicus* were collected from web sources and literature [14–22]. A list of pharmacologically active phytomolecules was given in Table 1.

2.3. Retrieval of phytochemical information and human target imputations

In total, 259 pharmacologically active plant derived compounds and their canonical SMILES from *J. adhatoda, O. sanctum, S. trilobatum, A. paniculata, Eucalyptus Sp., A. officinarum* and *P. amboinicus* were obtained from the PubChem database [24]. The identified plant derived active compounds with their respective canonical SMILES were searched against *Homo sapiens* in SwissTargetPrediction tool to retrieve the compounds with their corresponding human targets especially on immune responsive genes (www.swisstargetprediction.ch/).

2.4. Computational mining of human targets and encoding features

Identified significant human immune responsive genes/ targets were imported onto the NCBI-Gene database and/or Expression atlas for retrieving the molecular features such as official gene symbol with

Table 1
Plant active compounds and its abbreviations.

S. No	Compounds	Abbreviations
Justicia adhatoda		
1.	Undecanal	UD
2.	Anisotine	AS
3.	Peganine	PN
4.	Arachidic acid	ARA
5.	Octanal	OCT
6.	Tetradecane	TD
7.	5-Octadecenal	5-OD
8.	Scopolamine	SL
9.	Tetradecanol	TD
10.	Megastigmatrieno-ne B	MGM B
11.	Ascorbic acid	AA
12.	Scopoline	SCP
13.	Docosanoic acid	DA
14.	17-Octadecynoic acid	17-OCA
15.	Taraxerol	TX
16.	beta-Carotene	β-CT
17.	beta-Sitosterol	β-SS
18.	9,12-Octadecadienoic acid	9,12-ODA
19.	Vasicine	VS
20.	Betaine	BT
21.	Vasicinol	VSC
22.	Vasicinolone	VSN
23.	1-Octene	1-OC
24.	1-Pentadecanol	1-PD
25.	(-)-Verbenone	(-)-VB
26.	Cerotic acid	CA
27.	Eicosane	ES
28.	Phytol	PT
29.	Heptacosane	HEC
30.	Tricosane	TRC
31.	Pentacosane	PEC
32.	8,11-Octadecadienoic acid	8,11-OCA
33.	Palmitic acid	PA
34.	Caryophyllene oxide	CAO
35.	Vasicinone	VSC
36.	Isomethyl-alpha-ionone	IAI
37.	Deoxyvasicinone	DOV
38.	Hentriacontane	HC
39.	Tetracontane	TC
40.	Nonacosane	NC
41.	Heneicosane	HC
42.	Vasicol	VC
43.	Fenretinide	FRT
44.	Tetracosanoic acid	TTA
45.	Dodecane	DD
46.	beta-Eudesmol	β-ED
47.	Vasicoline	VSC
48.	Linoleic acid	LA
49.	Vasicolinone	VSL
50.	Lyoniside	LYN
Ocimum sanctum		
1.	Aromadendrene oxide	ADO
2.	Apigenin	AG
3.	Benzaldehyde	BA
4.	Borneol	BN
5.	Bornyl acetate	BA
6.	Campesterol	CP
7.	Caryophyllene oxide	CO
8.	Carvacrol	CC
9.	Cineole	CN
10.	Cirsilineol	CSL
11.	Cirsimaritin	CSM
12.	Cubenol	CB
13.	alpha-terpineol	α-TP
14.	Citral	CT
15.	D-Limonene	D-LM
16.	beta-Elemene	β-EM
17.	Eucalyptol	ECL
18.	Camphor	CP
19.	Eugenol	EG
20.	Eicosane	EC
21.	Germacrene D	GD
22.	Heptanol	HT
23.	Linalol	LL
24.	Linoleic acid	LA
25.	Luteolin	LT
26.	Methyleugenol	MTE
27.	Butyl benzoate	BB
28.	Ocimarin	OM
29.	Oleanolic acid	OLA
30.	Oleic acid	OA
31.	Palmitic acid	PA
32.	Phytol	PT
33.	Rosmarinic acid	ROA
34.	Sabinene	SB
35.	Stearic acid	SA
36.	Selinene	SL
37.	Stigmasterol	SS
38.	Thymol	TM
39.	Ursolic acid	UA
40.	Vanillic acid	VA
41.	Viridiflorol	VDF
42.	Xylose	XL
43.	1-Octen-3-OL	1-OCT-3-OL
44.	α-Camphene	α-CP
45.	alpha-Myrcene	α-MRC
46.	alpha-Pinene	α-PN
47.	α-Bisabolene	α-BB
48.	α-humulene	α-HM
49.	Linolenic acid	LLA
50.	α-thujene	α-TJ
51.	β-caryophyllene	β-CP
52.	β-gurjunene	β-GJ
53.	β-Pinene	β-PN
54.	ß-carotene	β-CT
55.	β-guaiene	β-GE
56.	β-bisabolene	β-BB
57.	ß-sitosterol	β-SS
58.	(E)-beta-ocimene	(E)- β-OM
59.	3-Furaldehyde	3-FA
Solanum trilobatum		
1.	Sobatum	SB
2.	Solasodine	SSD
3.	Solanine	SN
4.	Tomatidine	TM
5.	Disogenin	DG
6.	β-Solamargine	β-SM
7.	Campesterol	CS
8.	Sitosterol	SS
9.	Soladunalinidine	SDL
Andrographis paniculata		
1.	Andrographolide	ADG
2.	Neoandrographoli-de	NAG
3.	Isoandrographolide	IAG
4.	Andrographiside	AGP
5.	Andrograpanin	AG
6.	Andrographolacto-ne	AGL
7.	Bisandrographolide A	BAG
8.	Apigenin	AG
9.	7-O-methylwogonin	7-O-MW
10.	Onysilin	OS
11.	Andrographidine A	AGA
12.	Andrographidine C	AGC

(*continued on next page*)

Table 1 (*continued*)

S. No	Compounds	Abbreviations
13.	Luteolin	LT
14.	14-Deoxyandrograph-olide	14- DOA
15.	14-Deoxy 11, 12-didehydroandro-grapholide	14-D-11,12-DAG
16.	14-Deoxy-11-hydroxyandrogra-pholide	14-D-11-HAG
17.	14-Deoxy-12-hydroxyandrogra-pholide	14-D-12-HAG
18.	3-O-beta-D-glucopyranosyl 14, 19-dideoxyandrogra-pholide	3-O β-D-G14,19-DDAG
19.	8, 17-Epoxy-14-deoxyandrographo-lide	8,17-E-14-DAG
20.	3,4-Dicaffeoylquinic acid	3,4-DA
Alpinia officinarum		
1.	Chrysin	CS
2.	Pinocembrin	PC
3.	Tectochrysin	TC
4.	Galangin	GAL
5.	Acacetin	AC
6.	Kaempferide	KPF
7.	Isorhamnetin	IR
8.	Apigenin	AG
9.	3-O-methylgalangi-n	3-0-MG
10.	Kaempferol	KAF
11.	Quercetin	QC
12.	Rutin	RT
13.	Yakuchinone A	YCA
14.	Hexahydrocurcum-in	HHC
15.	Hannokinol	HK
16.	Nootkatone	NK
17.	Luteolin	LT
18.	Izalpinin	IP
19.	Pinobaksin	PB
20.	5-hydroxy-1,7-di-phenyl-3-hepta-none - 3,5-dihydrox-y-1,7-diphenylhep-tane	5-H-1,7-D-3-H
21.	1,7-diphenylhep-t-4-en-3-one	1,7-DP-4-E3O
22.	Zingerone	ZG
23.	1'-acetoxychavicol acetate	1'-ACA
24.	β-sitosterol	β-SS
25.	p-Coumaryl alcohol	p-CA
26.	1,5-bis-(4-hydroxy-phenyl)-2-(hydrox-ymethyl)-4-pen-ten-1-ol	1,5-B-4H-2HE-4-P-1
27.	1,5-bis-(4-hydroxy-phenyl)-1-methox-y-2-(methoxyme-thyl) -4-pentene	1,5-B-4H-1M-2-4P
28.	1,5-bis-(4-hydroxy-phenyl)-1-ethox-y-2-(methoxyme-thyl)-4-pentene	1,5-B-4H-1E-2-M-4-P
29.	1,5-bis-(4-hydroxy-phenyl)-1-[3-(4-a-cetoxyphe-nyl)-2-propenox-y]-2-(methoxyme-thyl)-4-pentene	1,5-B-4H-1-3-4A-2P-2-M-4-P
30.	1,5-bis-(4-hydroxy-phenyl)-2-(methox-ymethyl)-4-pen-ten-1-ol	1,5-B-4H-2-ME-4-P-1
Plectranthus amboinicus		
1.	Carvacrol	CC
2.	Thymol	TM
3.	Eugenol	EG
4.	Chavicol	CVC
5.	1,8-Cineole	1,8-CN
6.	β-Caryophyllene	β-CP
7.	p-Cymene	p-CM
8.	Caryophyllene oxide	CPO
9.	α-Terpinene	α-TP
10.	Spathulenol	STL
11.	Ethyl Salicylate	ES
12.	Terpinen-4-ol	TP-4-ol
13.	α-Terpinolene	α-TPL
14.	Squalene	SQL
15.	Oleic acid	OA
16.	Phytol	PT
17.	β-Cedrene epoxide	β-CE
18.	Tetradecanal	TTD
19.	α-Humulene	α-HM
20.	β-Copaen-4-α-ol	β-CP-4-α-ol
21.	β-Selinene	β-SL
22.	α-Terpineol	α-TP
23.	γ-Terpinene	γ-TP
24.	β-Himachalene oxide	β-HO
25.	Undecanal	UD
26.	α-Calacorene	α-CC
27.	Methyl chavicol	MC
28.	Patchoulane	PC
29.	Terpine-4-ol	TP-4-ol
30.	trans-Caryophyllene	tr-CP
31.	α-Cadinol	α-CD
32.	1-Octen-3-ol	1-OCT-3-ol
33.	(Z)-1,3-Hexadiene	(Z)-1,3,-HD
34.	(Z)-3-Hexenol	(Z)-3-HX
35.	α-Muurolene	α-MR
36.	(E,E)-α-Farnesene	(E,E)-α-FS
37.	Camphor	CP
38.	δ-3-Carene	δ-3-CR
39.	Linalool	LL
40.	Nerol acetate	NA
41.	Geranyl acetate	GA
42.	3-Carene	3-CR
43.	Caffeic acid	CA
44.	Gallic acid	GA
45.	p-Coumaric acid	p-CA
46.	Rosmarinic acid	ROA
47.	Salvianolic acid A	SAA
48.	Chrysoeriol	CS
49.	Durohydroquinone	DHQ
50.	Dihydro carveol	DHC
51.	Cirsimaritin	CSM
52.	Eriodictyol	ED
53.	Luteolin	LT
54.	Rutin	RT
55.	Salvigenin	SG
56.	Thymoquinone	TQ
57.	Methyl carvacrol	MC
58.	Methyl octanoate	MO
59.	β-Sesquiphellandrene	β-SQP
60.	Quercetin	QC

(*continued on next page*)

Table 1 (*continued*)

S. No	Compounds	Abbreviations
61.	Methyl eugenol	ME
62.	Ocimene	OM
63.	Geraniol	GN
64.	Germacrene D	GCD
Eucalyptus Sp.		
1.	α- pinene	α- PN
2.	1,8-cineol	1,8-CN
3.	α-Terpineol	α-TP
4.	p-Cymene	p-CM
5.	γ-Terpinene	γ-TP
6.	Trans-Pinocarveol	tr-PC
7.	α-Terpinyl acetate	α-TA
8.	Globulol	GB
9.	Limonene	LN
10.	Guaiene	GE
11.	Spathulenol	STL
12.	Terpinene-4-ol	TP-4-Ol
13.	Aromadendrene	AM
14.	Cryptone	CP
15.	Verbenone	VB
16.	Phellandral	PL
17.	p-Cymen-8-ol	P-CM-8-ol
18.	Caryophyllene oxide	CPO
19.	Epiglobulol	EG
20.	Viridiflorol	VIF
21.	Carvacrol	CV
22.	α-Eudesmol	α- ED
23.	β-Eudesmol	β-ED

their full name, exact position of the targets, chromosome number and orthologs of differentially expressed immune responsive genes [25].

2.5. Compound Target Network (C-T-N) construction

C-T-N was constructed to battle the COVID-19 by illuminating the multi-target therapeutic features of the pharmacologically active plant derived compounds. In this molecular interactome, promising immune target proteins and active phytocompounds interacted if the protein is targeted by the phytomolecule. Molecular interactome was visualized by Cytoscape v3.7.2 [26]. In the obtained interactome, node depicts compounds and targets whereas edges denote the molecular interactions between them.

2.6. Identification of features of the phytomolecules

Phytocompounds with their respective canonical SMILES were subjected to Molinspiration (www.molinspiration.com/cgi-bin/properties) [27] tool to obtain the significant calculation on pharmacologically active compounds with their molecular features. In addition to that, the imputation of the bioactive score for the vital targets such as Kinase inhibitor activity (Ki), GPCR ligand activity (GPCR), protease inhibitor activity (Pi), number of violations (nvio), enzymes and nuclear receptors (Ncr) was predicted.

2.7. Drug and phytomolecule comparison

Identified pharmacologically active molecules with their respective molecular and bioactive features were compared with commercially available WHO suggested drugs for the treatment of COVID-19. This comparative analysis was done to unveil the active compounds with the help of nvio, GPCR, Ki, Ei, Pi and Ncr properties.

2.8. Gene Ontology (GO) enrichment analysis

Differentially expressed genes (DEGs) with their encoding gene symbols were uploaded to the GOnet database (https://tools.dice-database.org/GOnet/) [28] to attain ontology against *H. sapiens* with significant threshold q-value level is < 0.05. Immune responsive genes were also pigeonholed as per GO molecular function (MF) and biological process (BP) according to the functional enrichment classification of the GOnet database.

2.9. Immune responsive and human COVID-19 receptor genes network analysis

Forty-two human COVID-19 receptors and essential immunity genes were collected from the literature [29]. The list of these genes and their functions were given in Table S1. Protein- protein interactions (PPI) analysis of these COVID-19 receptors, essential immunity genes and identified significantly active immune responsive genes (official gene symbols) were done by STRING *v*10.5 with a high confidence score of 0.7. Further, the PPI network enrichment analysis was executed through a significant value of 0.01. This signalome was used to delineate the physical and functional role of the candidate's involved [30].

3. Results

3.1. Immune responsive genes from meta–analysis of human immuno-transcriptome

The immuno-transcriptomic dataset contains 579 immune responsive genes of which 549 genes were commonly found in meta–-differential (up, down and non-significant) expression (Fig. 1) and the remaining 30 genes were unmatched. Heatmap profiling revealed that 98 immune responsive genes were differentially expressed in COVID-19 cases at various time points when compared to healthy controls (Fig. 2). Further, these significant genes were involved in tissue specific (whole blood) PPI network. This network had 1228 nodes, 1616 edges and 80 seed proteins (Fig. 3 and Table S2) and the pathway based ORA enrichment network showed the involvement in various biological pathways (Fig. 4 and Table S3).

3.2. Phytomolecule information retrieval

A 259 number of phytochemicals were employed as a query in PubChem database to fetch and retrieve the canonical SMILES (Table S4). This obtained SMILES information was used for further biomolecular analyses.

3.3. Identification of pharmacologically active compounds interacting with human targets

Pharmacologically active phytomolecules targeting human immune receptors were imputed through SwissTargetPrediction tool. Among 259 phytomolecules, 154 compounds were significantly targeting 13 out of 98 human immune responsive genes/ receptors which were differentially expressed between healthy controls and COVID-19 cases. A detailed list of phytochemicals and significant human immune responsive gene information are provided in Table S5.

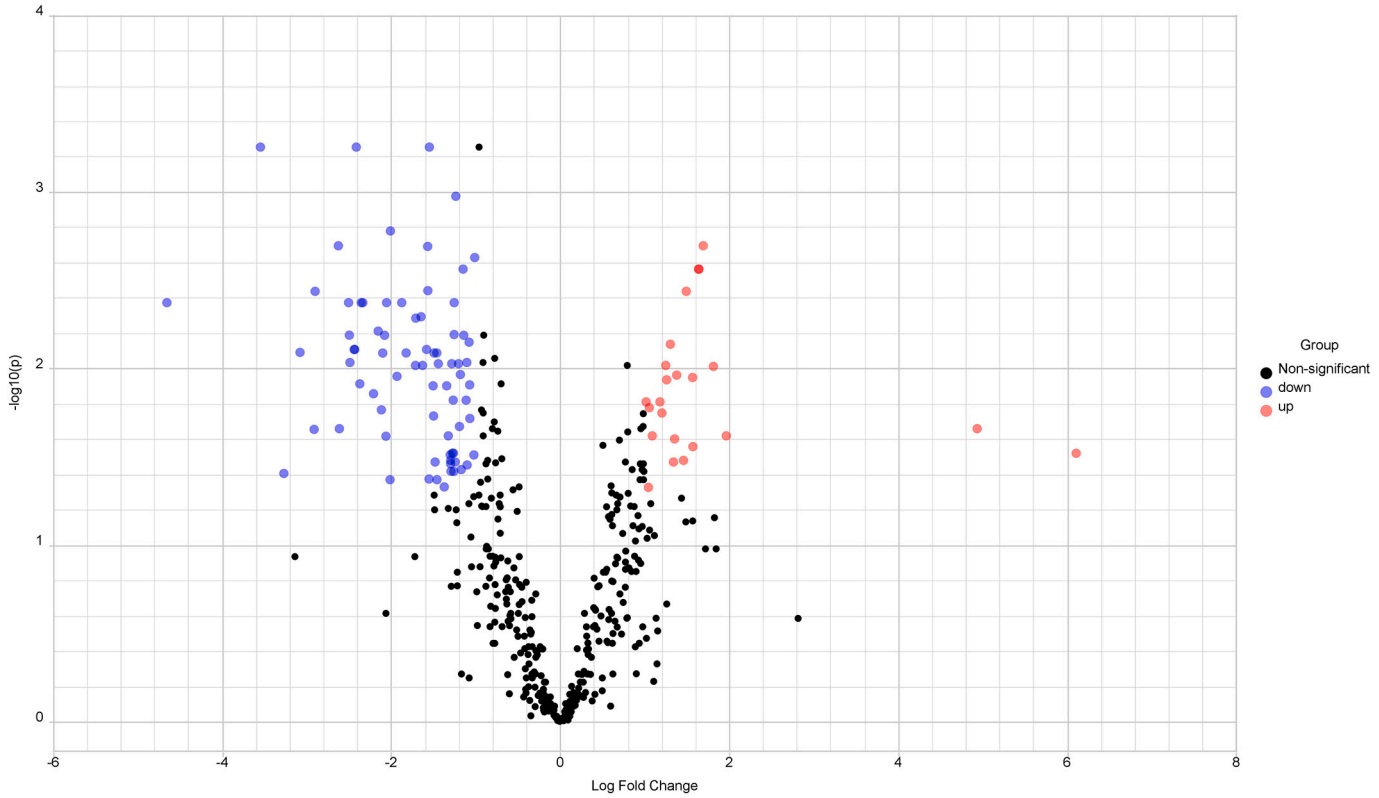

Fig. 1. Volcano Plot for human immune differential gene expression. Scattered points encode genes. The x-axis is $\log_2$ fold change values of gene expression levels between healthy controls and COVID-19 cases, whereas the y-axis is adjusted *P*-value based on $-\log_{10}$. Red color dots - upregulation, blue color dots - down regulation represents differentially expressed immune genes based on significant thresholds (i) adjusted *P*-value < 0.05 and (ii) $\log_2$ fold change level is 1.0 and black color dots – non significant immune responsive genes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.4. Properties of human immune responsive genes

One hundred fifty four numbers of potential compounds significantly targets the 13 human immune responsive genes. These immune receptors with their corresponding information such as chromosome number, physical position and full name of the genes and orthologs details were retrieved and given in Table 2. These immune responsive genes with their attributes will pave the way to delineate their detailed molecular function.

3.5. Functional GO enrichment analysis

Significant COVID-19 immune responsive gene targets with their corresponding molecular features were analyzed by gene symbols using the GOnet tool which revealed the involvement of these immune proteins in various molecular functions and biological processes. The target immune responsive genes with their corresponding proteins were imputed to be involved in crucial biological regulation of inflammatory response, innate immune response, positive regulation of interferon-α, interlekin-1-β and cytokine secretion, apoptotic process, response to virus, leukocyte and B-Cell proliferation, negative regulation of signal transduction (Fig. 5). In molecular functions, human immune targets were involved in phosphatase and chemokine binding, G-protein-coupled chemoattractant receptor and peptide receptor activity (Fig. 6).

3.6. C-T-N analysis

Fig. 7 showed the C-T-N based cross-talk between 154 active compounds and 13 significant human immune responsive gene targets. Molecular cross-talk between the active compounds and potential immune targets unveiled the multi-target strategy which is the significant feature of herbal medicine. As for the 13 significant human immune targets, 154 phytochemicals (Table S5) had high probability, which revealed the essential therapeutic ability of each natural bioactive molecules present in traditional Indian medicinal plants such as *J. adhatoda, O. sanctum, S. trilobatum, A. paniculata, Eucalyptus Sp., A. officinarum* and *P. amboinicus* for combating COVID-19 infection by transducing the transcriptional reprogramming and/or modulating the signals of these possible immune responsive proteins/genes.

3.7. Molecular interactome analysis

Forty-two numbers of human COVID-19 immune regulators and identified 13 immune responsive genes that are differentially expressed between healthy controls and COVID-19 cases demonstrated molecular cross-talks from *H. sapiens*. The interactome had 452 edges and 55 nodes (Fig. 8). The proteins of the human COVID-19 responsive immune genes with their molecular cross-talks had an average nodal degree of 16.4 in the tightly connected proteins/ immune genes. PPI enrichment of these human COVID-19 responsive immune genes had a *P*-

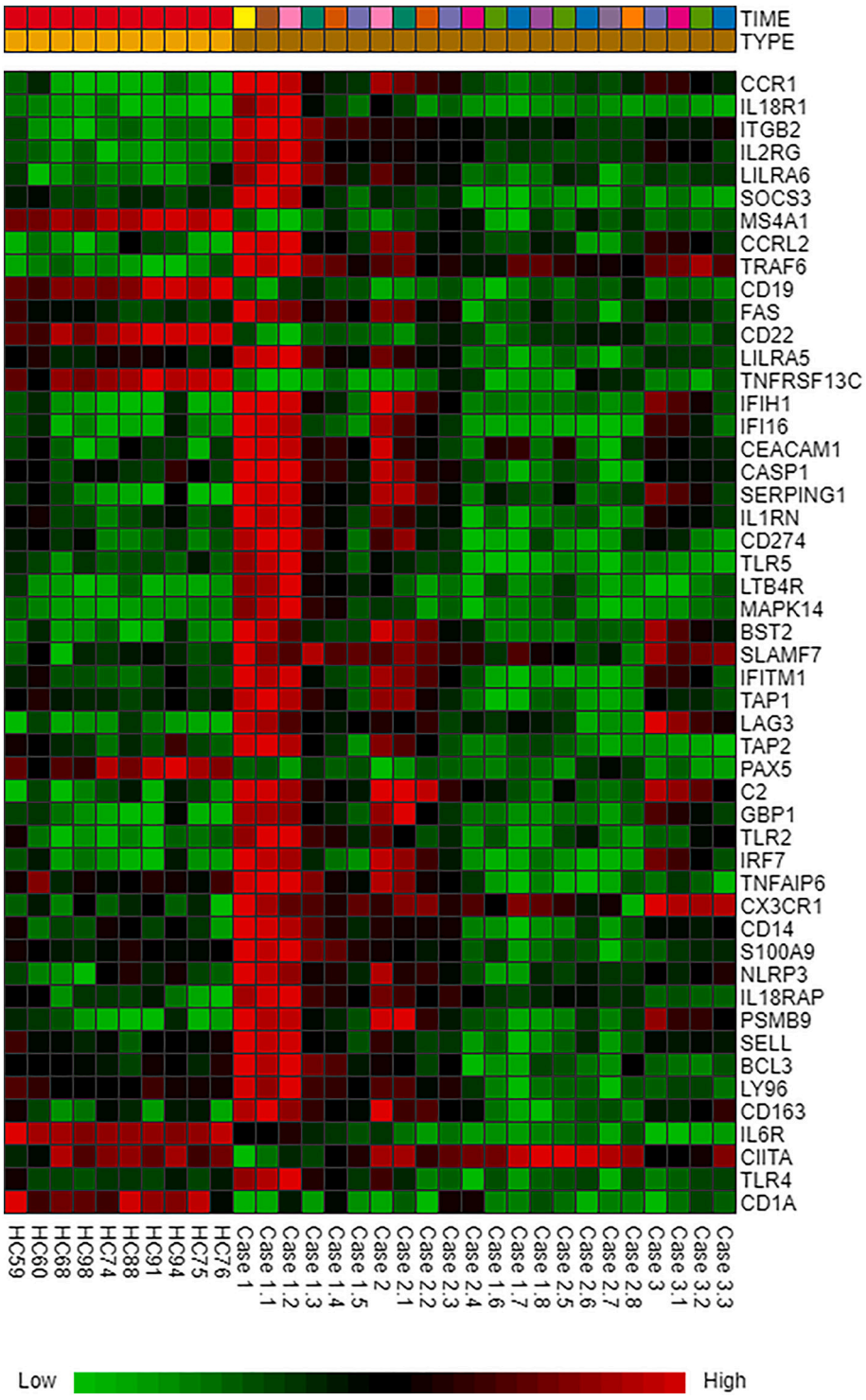

Fig. 2. Heatmap profiling denoting the top 98 genes which are differentially expressed between human healthy controls and COVID-19 cases. Green color, down regulation; Red color, up regulation; Black color, non significant expression. Dataset: E-MTAB-8871- Time: In Days (0, 4,5, 6, 7, 8, 9, 10, 11, 12, 13, 18 and 19) and Type: Healthy Controls and COVID-19 cases. The colored scale bar at bottom represents relative expression, where green and red colors represent down regulation and up regulation, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

value score of < 0.01. In addition, this interaction showed that the complexity and functionalities of human COVID-19 responsive immune genes, with their cross-talks provide potential targets for therapy against COVID-19 infection.

3.8. Features of natural bioactive molecules and novel compounds

One fifty-four numbers of natural bioactive molecules with their calculated pharmaceutical properties such as GPCR, Pi, Ki, Ncr, Ei, nVio

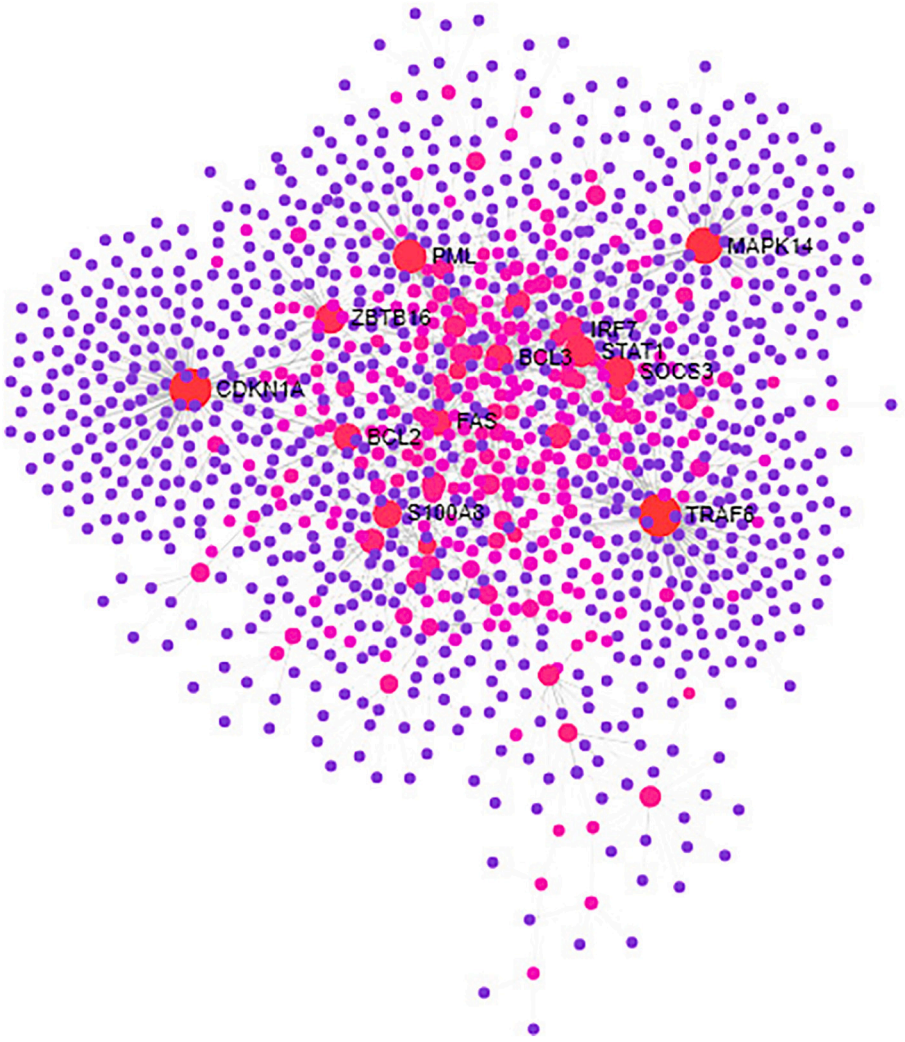

Fig. 3. Tissues Specific protein protein interaction. Red color represents differentially expressed human immune responsive genes/nodes, blue color indicates interacting partners present in human whole blood tissue type. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

were collected and given in Table 3. Based on the number of violations and enzyme inhibitor activity, a feature score above 0.5 were considered as a significant level. Further, the WHO prescribed commercial drugs for the treatment of COVID-19 pandemic were compared with the pharmaceutical properties of natural bioactive compounds and 25 potential compounds were found to be more efficacious than the WHO prescribed drugs and are listed in Table 4.

4. Discussion

The ongoing COVID-19 pandemic completely disrupted the global homeostasis. The unavailability and ineffectiveness of anti-COVID-19 medicines to deal with this noxious infection make it an urgent need to identify the novel drugs/compounds that are efficacious in the control and treatment of this deadly infection. The effectiveness of traditional Indian medicines was well known for over 1000 years of practice [31]. Despite the fact that the pharmaceutical ingredients of medicinal plants have been extorted and purified for unsullied drug development, this method still ends up in failure due to the higher violation of chemical components and functional drug regulation. Indian traditional medicines were proven to be effective to treat viral diseases such as herpes simplex virus (HSV), measles, influenza, viral carcinogenesis, Hepatitis, coxsackievirus, HIV, etc. [32,33]. It can be also seen as a major complexity and is confronting another complexity, which essentially throw more light in the understanding of the entire human physiological system by controlling the molecular cross-talk between all the immunological key elements within the species. On the other hand, the exact mechanism of the immune responsive targets and biological pathways of herbal medicines remains poorly understood [31]. Hence, in this pilot study, we employed immuno-transcriptomics, cheminformatics, interactomics and integrated pharmacology strategy for the first time to unravel the COVID-19 immune targets and their associated signaling pathways, pharmacological roles of *J. adhatoda, O. sanctum, S. trilobatum, A. paniculata, Eucalyptus Sp., A. officinarum* and *P. amboinicus* derived bioactive compounds in the treatment of COVID-19 at molecular system level. In addition, the exploration of plant derived natural bioactive molecules for the management of viral diseases can provide a vital source of therapeutic molecules. Furthermore, the medicinal plant

Fig. 4. Gene set enrichment network analysis. The number of human immune responsive genes falling in each KEGG pathway category is directly proportional to the node size. The nodes are color shaded according to the significance level (adjusted *P*-value < 0.05).

Table 2
Molecular attributes of human immune responsive genes and their orthologs.

S. No	Human Gene Name	Full name	Chr. No	Start	End	Orthologs (*Mus musculus*)	Chr. No	Start	End
1.	TLR4	toll like receptor 4	9	117704403	117724735	Tlr4	4	66827584	66930284
2.	STAT1	signal transducer and activator of transcription 1	2	190968989	191014250	Stat1	1	52119440	52161865
3.	SELL	selectin Lymphocyte	1	169690667	169711620	Sell	1	164061982	164084181
4.	PSMB9	proteasome 20S subunit beta 9	6	32854192	32859851	Psmb9	17	34181987	34187764
5.	CD22	CD22 molecule	19	35329169	35347361	Cd22	7	30865402	30880342
6.	CCR1	C-C motif chemokine receptor 1	3	46201711	46208313	Ccr1	9	123962124	123968692
7.	CCR5	C-C motif chemokine receptor 5	3	46370142	46376206	Ccr5	9	124121543	124147699
8.	LTB4R	leukotriene B4 receptor	14	24311502	24318036	–	–	–	–
9.	MAPK14	mitogen-activated protein kinase 14	6	36027677	36122964	Mapk14	17	28691329	28748406
10.	CSF1R	colony stimulating factor 1 receptor	5	150053291	150113372	Csf1r	18	61100598	61132149
11.	BCL2	BCL2 apoptosis regulator	18	63123346	63320280	Bcl2	1	106538178	106714274
12.	CASP1	caspase 1	11	105025443	105035591	Casp1	9	5298508	5307290
13.	NLRP3	NLR family pyrin domain containing 3	1	247416163	247448823	Nlrp3	11	59541568	59566956

derived active molecules are less toxic when compared to the modern/ synthetic drugs which cause numerous side effects. Besides, the findings of the present study will also prescribe the natural and novel bioactive molecules for treating the COVID-19 by altering and or stimulating the immune functional regulations.

This study mainly aimed to identify and understand the host gene expression pattern response to COVID-19/ respiratory viral infections. To the best of our knowledge, this is the first investigation to perform immuno-transcriptomic profiling between healthy controls and COVID-19 cases using publicly available transcriptomic dataset and processed

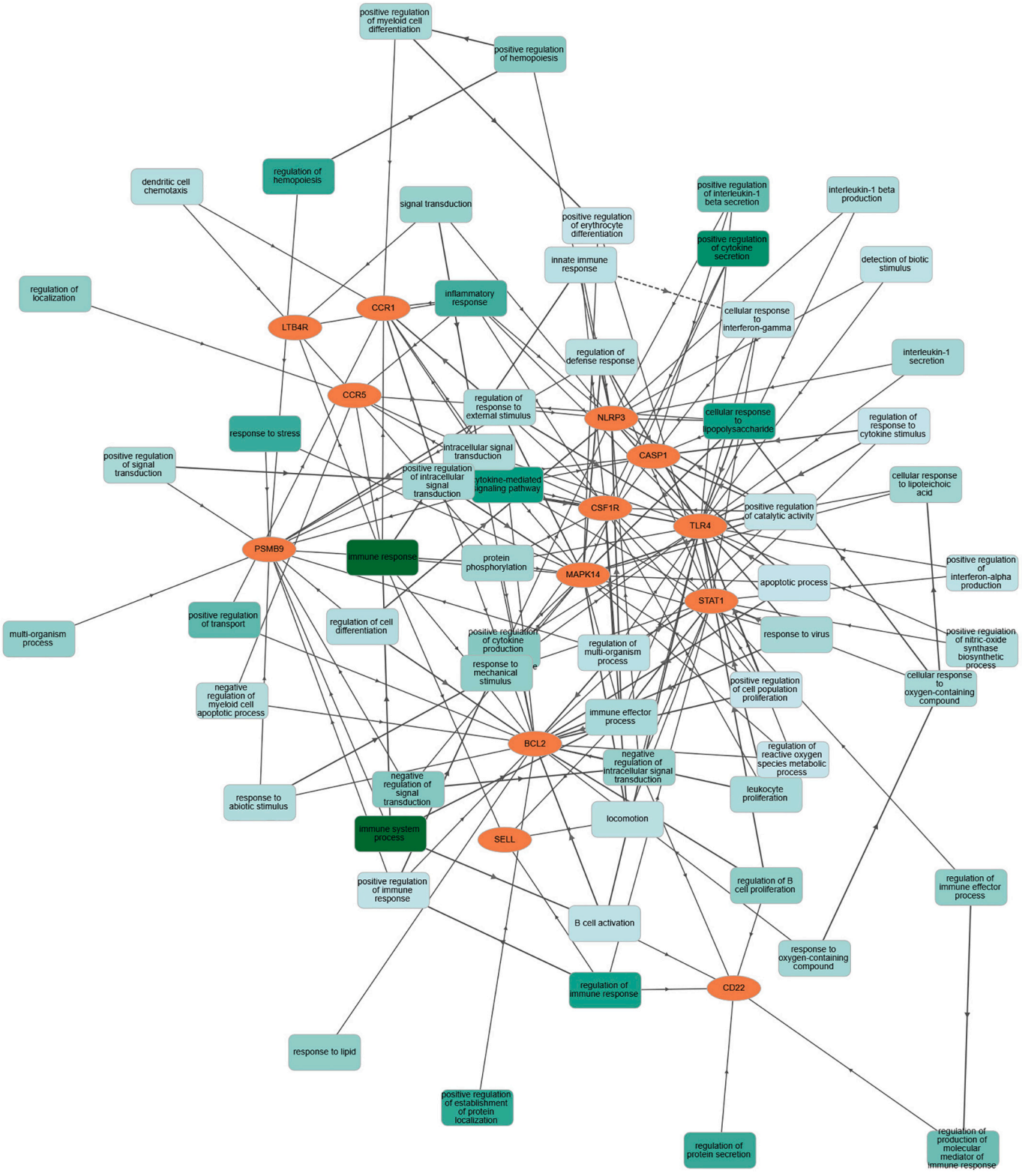

Fig. 5. Classification human targets with their biological processes. Orange color encodes human COVID-19 immune targets; green color represents diverse biological processes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

by NetworkAnalyst 3.0 [23]. Heatmap was derived in accordance to the microarray intensities of the COVID-19 immune responsive genes and based on the intensity values of 98 immune responsive genes differentially expressed between the healthy controls and COVID-19 cases at various time points. The identified genes were chosen for subsequent analysis.

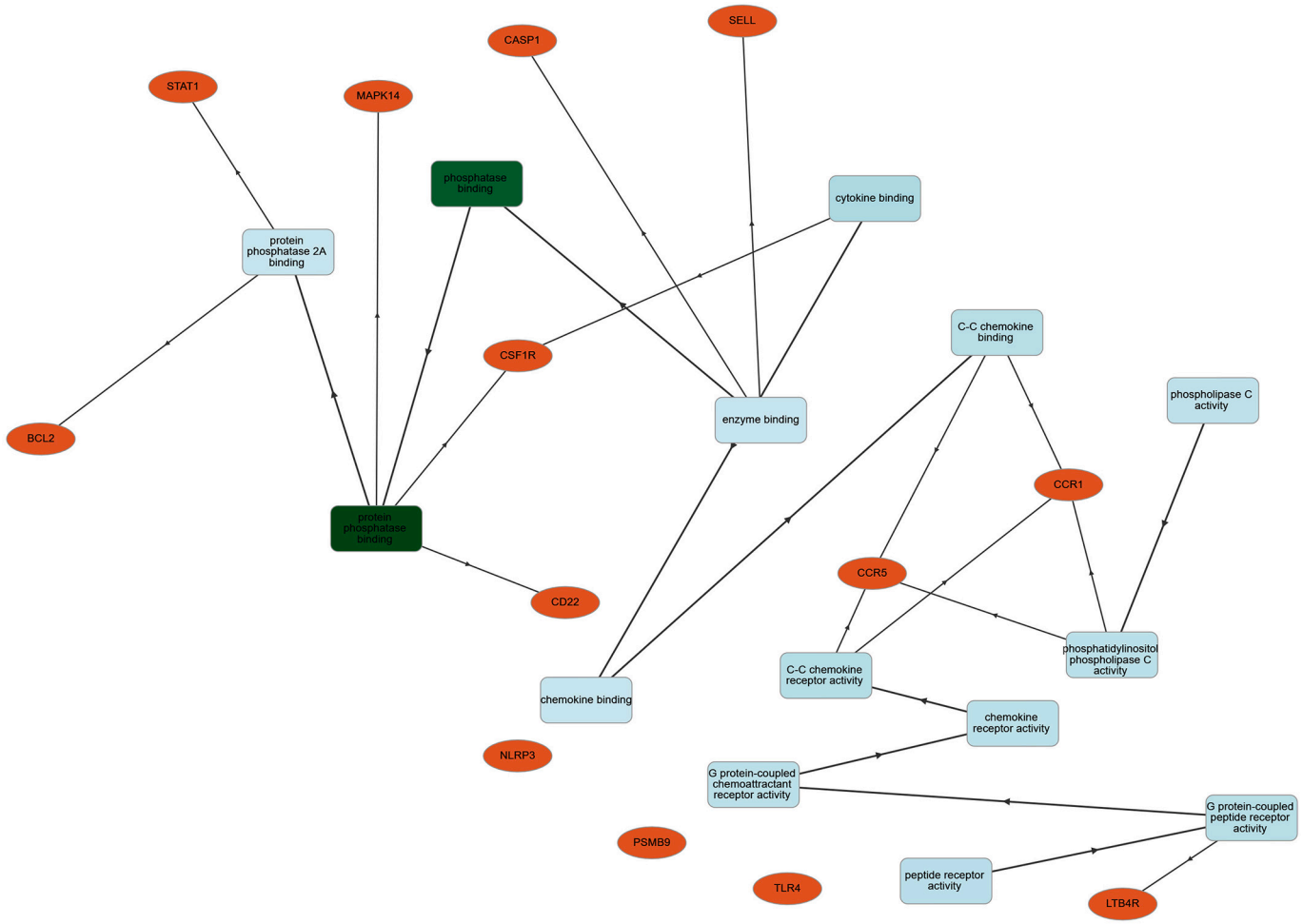

Fig. 6. Classification human targets with encoding molecular functions. Orange color encodes human COVID-19 immune targets; green color represents significant molecular functions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

On the other hand, with the help of cheminformatics, PubChem and interactomics databases, 259 natural bioactive compounds were identified. Among 259, 154 active compounds strongly interacted with 13 out of 98 differentially expressed COVID-19 immune responsive genes by drug targeting. Notably, these genes were predicted to be involved in various biological/ immunological activities against COVID-19 and have not been reported so far, demonstrating the ability of SwissTargetPrediction and GOnet enrichment evaluation methods. Further, ORA functional and GO enrichment of identified genes that are more specific to COVID-19 were delineated. The analysis of principle compounds that actively targeting the differentially expressed human immune responsive genes through COVID-19 disease highlighted the role of 13 genes (TLR4, STAT1, SELL, PSMB9, CD22, CCR1, CCR5, LTB4R, MAPK14, CSF1R, BCL2, CASP1, and NLRP3). For example, TLR4 (Toll-like receptor 4) protein is being the efficient innate immune receptor that plays a pivotal role in pathogen recognition and activates pro-inflammatory responses. Hence, the cross-talk between the spike protein of SARS-CoV2 and TLR4 might be one of the reasons behind the immuno-pathological expression of COVID-19 [34]. STAT1 immune player is associated with host responses to viral infections and stimulates the type I interferon signaling. But in the case of SARS-CoV2 fled the host interferon dynamism and its ORF6 protein can obstructs the regulation of STAT1-activated genes [35]. NLRP3 (NBS, LRR, and pyrin domain-containing 3) inflammasome complex interacts with apoptosis-associated speck-like protein carrying a caspase activation (ASC) and plays a role in the regulation of immune response, apoptosis and inflammation. Thus, the SARS-CoV2 viroporins (*E*-protein, ORF3a and ORF8a) are inducing this receptor NLRP3 via lysosomal disruption and ion redistribution mechanisms. It leads to the production of cytokines namely tumor necrosis factor (TNF), IL-1β, IL-6 causing severe tissue inflammation during respiratory problems caused by COVID-19 [36]. Notably, all these 13 COVID-19 genes are linked with other viral infections and have maximum interaction. By selecting closely related genes, an ORA enrichment and STRING network analysis were employed to identify the deeper insights about the function of these genes. It was lucid from the results that the immunological and genetic pathways associated with Influenza A, Hepatitis B and C, Viral myocarditis, Malaria, Rheumatoid arthritis, Measles, tuberculosis, pertussis, viral carcinogenesis and AGE-RAGE signaling mechanism were of significance. The correlation between host immune response to pertussis, Malaria, tuberculosis, Rheumatoid arthritis and COVID-19 has been a wonder to date. Hypothetically, drugs commercially available for the treatment of pertussis, Malaria, tuberculosis and Rheumatoid arthritis may have therapeutic efficacy against COVID-19 [37,38]. Our results revealed that the interaction in the immune response between these infections and the COVID-19 is highly significant at the molecular level.

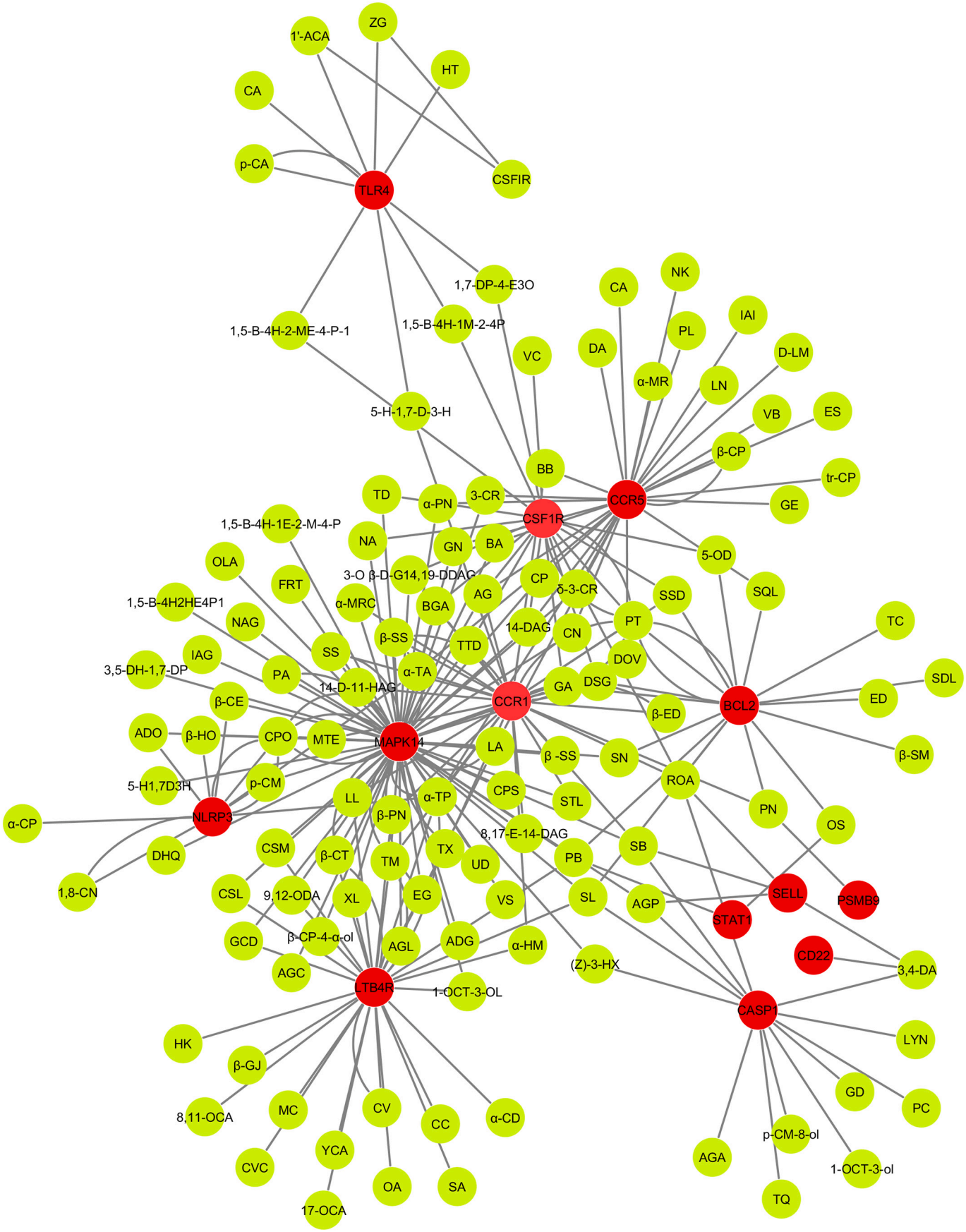

Fig. 7. Compound target network (C-T-N). Green color represents compounds and red color indicates human COVID-19 immune targets. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

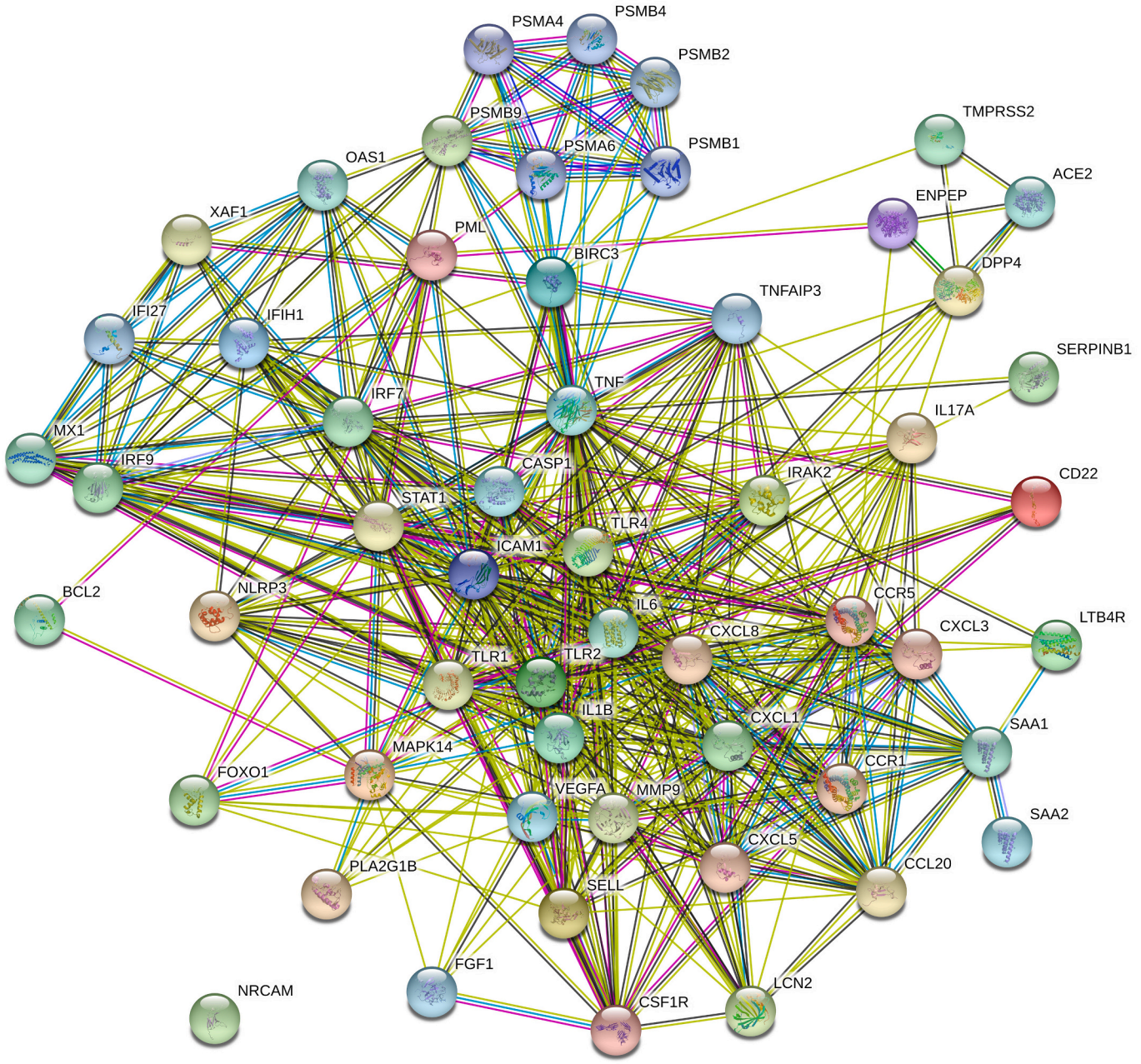

Fig. 8. Human COVID-19 immune target genes and their molecular interaction. Human immune responsive genes and their cross-talks showing tightly interacting functional components. Colored lines between the seed proteins indicates various types of interacting elements/ signals. Green color- gene neighbourhood; blue color - gene co-occurrence; pink color - experimentally determined/ Post translational modifications; black color - coexpression. Nodes filled with ribbon like structure represents the availability of protein 3D structural information is predicted or known. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

As described earlier, the identified 13 genes were involved in the regulation of various immunological pathways such as Toll-like receptor, IL-17, TNF, NF-kappa B (Nuclear Factor-Kappa B/ NF-kB), MAPK, NOD- like receptor signaling pathway, RIG-I-like receptor signaling pathway, B and T cell receptor signaling pathways, Antigen processing and presentation (Fig. 9). In addition, these genes had a strong association with COVID-19 as per ORA functional and GO enrichment and significantly related to TNF and NF-kappa B signaling pathways. The TNF receptors are the key players involved in apoptosis and inflammation. The cross-talk between viral proteins and intracellular components of the TNF receptors demonstrated the critical ability of viral replication machinery to evade the immunological responses [39]. The NF-kB pathway is highly related to pro-oxidant and pro-inflammatory responses and is particularly involved in the inflammatory reactions in acute lung diseases/ injuries. The mechanism of NF-kB activation was projected as a pivotal adjuvant treatment for deadly COVID-19 infection [40].

Cytoscape analysis results revealed the molecular interaction of

Table 3
Phytocompounds and its pharmaceutical features.

S.No	Compound	GPCR lg	Ki	Ncr	Pi	Ei	nvio
	Justicia adhatoda **(Family:Acanthaceae)**						
1.	17-Octadecynoic acid	0.22	−0.11	0.42	0.23	0.47	1
2.	1-Pentadecanol	−0.24	−0.35	−0.22	−0.31	0.03	1
3.	5-Octadecenal	0.08	−0.22	0.04	0.11	0.30	1
4.	8,11-Octadecadienoic acid	0.29	−0.16	0.31	0.12	0.38	1
5.	9,12-Octadecadienoic acid	0.29	−0.16	0.31	0.12	0.38	1
6.	β-Carotene	−0.04	−0.15	0.40	−0.06	0.17	2
7.	β-Eudesmol	−0.02	−0.62	0.60	−0.10	0.48	0
8.	β-Sitosterol	0.14	−0.51	0.73	0.07	0.51	1
9.	Caryophyllene oxide	−0.08	−0.86	0.62	0.00	0.57	0
10.	Cerotic acid	0.14	−0.09	0.20	0.16	0.14	1
11.	Deoxyvasicinone	−0.98	−0.75	−1.39	−1.22	−0.09	0
12.	Docosanoic acid	0.17	−0.10	0.23	0.17	0.17	1
13.	Eicosane	−0.04	−0.14	−0.05	−0.11	0.03	1
14.	Fenretinide	−0.08	−0.18	0.67	−0.18	0.31	1
15.	Isomethyl-alpha-ionone	−0.50	−0.91	−0.01	−0.96	0.13	0
16.	Linoleic acid	0.29	−0.16	0.30	0.12	0.38	1
17.	Lyoniside	0.14	−0.18	−0.20	0.07	0.23	3
18.	Palmitic acid	0.02	−0.33	0.08	−0.04	0.18	1
19.	Phytol	0.11	−0.32	0.35	0.00	0.31	1
20.	Scopolamine	0.58	0.06	0.11	0.28	0.35	0
21.	Scopoline	0.07	−0.62	−1.02	−0.55	0.35	0
22.	Taraxerol	0.21	−0.20	0.54	0.00	0.49	1
23.	Tetradecanol	−0.32	−0.45	−0.32	−0.40	−0.02	1
24.	Undecanal	−0.54	−0.96	−0.70	−0.41	−0.03	1
25.	Vasicine	0.03	−0.43	−0.59	−0.36	0.24	0
26.	Vasicol	−0.13	−0.29	−0.52	0.14	0.16	0
	Ocimum sanctum **(Family: Lamiaceae)**						
1.	1-Octen-3-OL	−1.78	−2.59	−1.68	−1.86	−1.09	0
2.	α-Myrcene	−1.11	−1.65	−0.70	−1.29	−0.22	0
3.	α-terpineol	−0.51	−1.45	−0.02	−0.78	0.14	0
4.	Aromadendrene oxide	−0.41	−1.00	−0.04	−0.00	−0.23	0
5.	Bornyl acetate	−0.32	−1.33	−0.59	−0.44	−0.12	0
6.	Butyl benzoate	−0.80	−1.03	−0.75	−0.94	−0.43	0
7.	Campesterol	0.11	−0.48	0.71	0.01	0.50	1
8.	Carvacrol	−1.02	−1.15	−0.70	−1.25	−0.56	0
9.	Caryophyllene oxide	−0.08	−0.86	0.62	0.00	0.57	0
10.	Cineole	−0.93	−1.60	−1.07	−0.90	−0.15	0
11.	Cirsilineol	−0.09	0.20	0.13	−0.29	0.14	0
12.	Cirsimaritin	−0.09	0.20	0.17	−0.31	0.14	0
13.	D-Limonene	−0.91	−2.01	−0.34	−1.38	−0.21	0
14.	Eugenol	−0.86	−1.14	−0.78	−1.29	−0.41	0
15.	Germacrene D	−0.30	−0.81	0.32	−0.67	0.26	1
16.	Heptanol	−2.90	−3.18	−2.88	−2.92	−2.50	0
17.	Linalool	−0.73	−1.26	−0.06	−0.94	0.07	0
18.	Linoleic acid	0.29	−0.16	0.31	0.12	0.38	1
19.	Methyleugenol	−0.81	−1.06	−0.80	−1.14	−0.43	0
20.	Oleanolic acid	0.28	−0.40	0.77	0.15	0.65	1
21.	Palmitic acid	0.02	−0.33	0.08	−0.04	0.18	1
22.	Phytol	0.11	−0.32	0.35	0.00	0.31	1
23.	Rosmarinic acid	0.17	−0.18	0.57	0.15	0.24	0
24.	Sabinene	−1.15	−1.79	−0.69	−0.78	−0.60	0
25.	Selinene	−0.26	−0.94	0.35	−0.48	0.29	1
26.	β-carotene	−0.04	−0.15	0.40	−0.06	0.17	2
27.	β-sitosterol	0.14	−0.51	0.73	0.07	0.51	1
28.	Stearic acid	0.11	−0.20	0.17	0.06	0.20	1
29.	Stigmasterol	0.12	−0.48	0.74	−0.02	0.53	1
30.	Thymol	−1.05	−1.29	−0.78	−1.34	−0.57	0
31.	Xylose	−0.77	−1.34	−1.61	−0.83	0.25	0
32.	α-Camphene	−1.02	−1.85	−1.15	−1.40	−0.82	0
33.	β-caryophyllene	−0.34	−0.78	0.13	−0.60	0.19	1
34.	β-guaiene	−0.52	−1.04	−0.04	−0.72	−0.24	0
35.	β-Pinene	−0.53	−1.45	−0.50	−0.80	−0.34	0
	Solanum trilobatum **(Family:Solanaceae)**						
1.	Sobatum	0.14	−0.51	0.73	0.07	0.51	1
2.	Solasodine	0.24	−0.66	0.36	0.01	0.60	1
3.	Solanine	−2.38	−3.44	−3.13	−1.82	−2.61	3
4.	Tomatidine	0.32	−0.50	0.28	0.17	0.57	1
5.	Disogenin	0.05	−0.57	0.58	−0.06	0.61	1
6.	β-Solamargine	−2.45	−3.52	−3.22	−1.92	−2.59	3
7.	Campesterol	0.11	−0.48	0.71	0.01	0.50	1
8.	Sitosterol	0.14	−0.51	0.73	0.07	0.51	1
9.	Soladunalinidine	0.40	−0.40	0.09	0.31	0.55	1

(*continued on next page*)

Table 3 (*continued*)

S.No	Compound	GPCR lg	Ki	Ncr	Pi	Ei	nvio
	Andrographis paniculata **(Family:Acanthaceae)**						
1.	14-Deoxy-11-hydroxyandrographolide	0.39	−0.41	0.94	0.15	0.72	0
2.	3,4-Dicaffeoylquinic acid	0.19	−0.01	0.50	0.16	0.40	3
3.	3-O-beta-D-glucopyranosyl 14, 19-dideoxyandrographolide	0.39	−0.28	0.48	0.15	0.68	0
4.	8, 17-Epoxy-14-deoxyandrographolide	0.46	−0.60	0.82	0.41	0.66	0
5.	Andrograpanin	0.43	−0.37	0.76	0.07	0.63	0
6.	Andrographidine A	0.09	−0.19	0.11	0.00	0.29	0
7.	Andrographidine C	0.01	0.06	0.05	−0.07	0.33	0
8.	Andrographiside	0.36	0.08	0.55	0.28	0.80	2
9.	Andrographolactone	0.39	−0.46	0.19	−0.20	0.20	0
10.	Andrographolide	0.32	−0.01	0.94	0.26	0.81	0
11.	Apigenin	−0.07	0.18	0.34	−0.25	0.26	0
12.	Bisandrographolide A	−0.21	−0.92	−0.32	−0.19	−0.25	1
13.	Isoandrographolide	0.32	−0.01	0.94	0.26	0.81	0
14.	Neoandrographolide	0.47	−0.16	0.44	0.21	0.70	0
15.	Onysilin	0.01	−0.22	0.18	−0.16	0.12	0
	Eucalyptus *Sp.*, (Family:Myrtaceae)						
1.	α- pinene	−0.48	−1.50	−0.62	−0.85	−0.34	0
2.	1,8-cineol	−0.93	0.01	−1.60	−1.07	−0.15	0
3.	Terpineol alpha	−0.51	−1.45	−0.02	−0.78	0.14	0
4.	α-Terpinyl acetate	−0.35	−1.14	0.00	−0.50	0.28	0
5.	Limonene	−0.91	−2.01	−0.34	−1.38	−0.21	0
6.	Guaiene	−0.49	−1.27	−0.01	−0.57	−0.14	0
7.	Spathulenol	−0.42	−0.68	0.28	−0.36	0.06	0
8.	Cryptone	−1.10	−2.05	−0.59	−0.93	−0.32	0
9.	Verbenone	−0.76	−1.98	−0.50	−0.86	−0.33	0
10.	Phellandral	−0.78	−1.27	−0.17	−0.59	−0.13	0
11.	p-Cymen-8-ol	−0.49	−1.12	−0.43	−0.95	−0.17	0
12.	Caryophyllene oxide	−0.08	−0.86	0.62	0.00	0.57	0
13.	Carvacrol	−1.02	−1.15	−0.70	−1.25	−0.56	0
14.	β-Eudesmol	−0.02	−0.62	0.60	−0.10	0.48	0
	Alpinia officinarum **(Family:Zingiberaceae)**						
1.	Pinocembrin	−0.00	−0.32	0.37	−0.17	0.21	0
2.	Tectochrysin	−0.14	0.12	0.23	−0.31	0.18	0
3.	Yakuchinone A	0.07	−0.31	0.12	0.01	0.16	0
4.	Hannokinol	0.34	0.13	0.54	0.34	0.45	0
5.	Nootkatone	−0.40	−1.73	0.66	−0.58	0.34	0
6.	Pinobaksin	0.03	−0.10	0.21	−0.00	0.31	0
7.	5-hydroxy-1,7-diphenyl-3-heptanone	0.22	−0.27	0.18	0.30	0.42	0
8.	3,5-dihydroxy-1,7-diphenylheptane	0.30	0.06	0.40	0.32	0.45	0
9.	1,7-diphenylhept-4-en-3-one	0.10	−0.40	0.15	0.09	0.30	0
10.	Zingerone	−0.58	−1.15	−0.59	−0.72	−0.07	0
11.	1'-acetoxychavicol acetate	−0.37	−0.68	−0.12	−0.47	−0.04	0
12.	β-sitosterol	0.14	−0.51	0.73	0.07	0.51	1
13.	p-Coumaryl alcohol	−0.63	−0.93	−0.28	−1.07	−0.09	0
14.	1,5-bis-(4-hydroxyphenyl)-2-(hydroxymethyl)-4-penten-1-ol	0.40	0.15	0.51	0.05	0.48	0
15.	1,5-bis-(4-hydroxyphenyl)-1-methoxy-2-(methoxymethyl) -4-pentene	0.24	−0.02	0.31	0.04	0.32	0
16.	1,5-bis-(4-hydroxyphenyl)-1-ethoxy-2-(methoxymethyl)-4-pentene	0.20	−0.08	0.39	0.00	0.24	0
17.	1,5-bis-(4-hydroxyphenyl)-2-(methoxymethyl)-4-penten-1-ol	0.33	0.06	0.47	0.04	0.37	0
	Plectranthus amboinicus **(Family:Lamiaceae)**						
1.	(Z)-3-Hexenol	−3.04	−3.44	−2.82	−3.13	−2.79	0
2.	1,8-Cineole	−0.93	−1.60	−1.07	−0.90	−0.15	0
3.	1-Octen-3-ol	−1.78	−2.59	−1.68	−1.86	−1.09	0
4.	3-Carene	−1.29	−1.51	−1.28	−1.28	−0.53	0
5.	Caffeic acid	−0.48	−0.81	−0.10	−0.79	−0.09	0
6.	Carvacrol	−1.02	−1.15	−0.70	−1.25	−0.56	0
7.	Caryophyllene oxide	−0.08	−0.86	−0.62	0.00	0.57	0
8.	Chavicol	−0.99	−1.39	−0.81	−1.39	−0.48	0
9.	Durohydroquinone	−0.81	−1.00	−0.69	−0.94	−0.33	0
10.	Eriodictyol	0.07	−0.22	0.46	−0.09	0.21	0
11.	Eugenol	−0.86	−1.14	−0.78	−1.29	−0.41	0
12.	Gallic acid	−0.77	−0.88	−0.52	−0.94	−0.17	0
13.	Geraniol	−0.60	−1.32	−0.20	−1.03	0.28	0
14.	Geranyl acetate	−0.50	−1.11	−0.12	−0.80	0.21	0
15.	Germacrene D	−0.30	−0.81	0.32	−0.67	0.26	1
16.	Methyl chavicol	−0.06	−0.46	0.29	−0.18	0.15	1
17.	Nerol acetate	−0.50	−1.11	−0.12	−0.80	0.21	0
18.	Oleic acid	0.17	−0.22	0.23	0.07	0.27	1
19.	p-Coumaric acid	−0.56	−0.91	−0.12	−0.87	−0.15	0
20.	Phytol	0.11	−0.32	0.35	0.00	0.31	1
21.	Rosmarinic acid	0.17	−0.18	0.57	0.15	0.24	0
22.	Spathulenol	−0.42	−0.68	0.28	−0.36	0.06	0
23.	Squalene	0.04	−0.10	0.19	−0.03	0.16	1
24.	Tetradecanal	−0.24	−0.56	−0.34	−0.15	0.12	1

(*continued on next page*)

Table 3 (*continued*)

S.No	Compound	GPCR lg	Ki	Ncr	Pi	Ei	nvio
25.	Thymol	−1.05	−1.29	−0.78	−1.34	−0.57	0
26.	Thymoquinone	−1.40	−1.27	−1.47	−1.45	−0.40	0
27.	trans-Caryophyllene	−0.34	−0.78	0.13	−0.60	0.19	1
28.	Undecanal	−0.54	−0.96	−0.70	−0.41	−0.03	1
29.	α-Cadinol	−0.09	−0.87	0.39	−0.63	0.40	0
30.	α-Humulene	−0.14	−0.93	0.34	−0.67	0.31	1
31.	α-Muurolene	−0.15	−0.84	0.22	−0.74	0.28	1
32.	α-Terpineol	−0.51	−1.45	−0.02	−0.78	0.14	0
33.	α-Terpinolene	−0.88	−1.61	−0.50	−1.74	−0.26	0
34.	β-Caryophyllene	−0.34	−0.78	0.13	−0.60	0.19	1
35.	β-Cedrene epoxide	−0.10	−1.10	0.12	−0.02	0.48	0
36.	β-Copaen-4-α-ol	−0.19	−0.57	0.45	−0.17	0.27	0
37.	β-Himachalene oxide	−0.33	−0.79	0.63	−0.39	0.43	0
38.	δ-3-Carene	−1.29	−1.51	−1.28	−1.28	−0.53	0

Table 4
Comparison with available drugs and novel bioactive compounds.

S.No	Drugs	GPCR lg	Ki	Ncr	Pi	Ei	nvio
	Drugs for COVID-19 treatment prescribed by WHO						
1	ASC-09 (TMC-310911)	−0.67	−1.57	−1.82	0.18	−1.10	3
2	Camostat	−0.10	−0.32	−0.20	0.07	−0.08	0
3	Chloroquine	0.32	0.38	−0.19	0.05	0.11	1
4	Dapagliflozin	0.15	−0.05	0.09	0.06	0.25	0
5	Famotidine	0.06	−0.80	−1.08	0.22	0.38	1
6	Favipiravir	−0.62	−0.31	−1.50	−0.91	−0.33	0
7	Fluvoxamine	0.33	0.23	0.37	0.26	0.28	0
8	Hydroxychloroquine	0.35	0.44	−0.12	0.12	0.15	0
9	Ivermectin	−2.49	−3.23	−2.94	−1.89	−2.53	2
10	Lopinavir	0.04	−0.55	−0.66	0.42	−0.37	2
11	Nafamostat	0.28	−0.03	−0.16	0.57	0.19	1
12	Nitazoxanide	−0.55	−0.19	−0.73	−0.66	−0.31	0
13	Remdesivir	0.27	0.20	−0.48	0.49	0.38	2
14	Ritonavir	−0.33	−1.02	−1.41	0.35	−0.74	3
15	Umifenovir (arbidol)	−0.19	−0.39	−0.34	−0.46	−0.07	0
	Justicia adhatoda **(Family:Acanthaceae)**						
1	β-Sitosterol	0.14	−0.51	0.73	0.07	0.51	1
2	Caryophyllene oxide	−0.08	−0.86	0.62	0.00	0.57	0
	Ocimum sanctum **(Family: Lamiaceae)**						
1	Campesterol	0.11	−0.48	0.71	0.01	0.50	1
2	Caryophyllene oxide	−0.08	−0.86	0.62	0.00	0.57	0
3	Oleanolic acid	0.28	−0.40	0.77	0.15	0.65	1
4	β-sitosterol	0.14	−0.51	0.73	0.07	0.51	1
5	Stigmasterol	0.12	−0.48	0.74	−0.02	0.53	1
	Solanum trilobatum **(Family:Solanaceae)**						
1	Sobatum	0.14	−0.51	0.73	0.07	0.51	1
2	Solasodine	0.24	−0.66	0.36	0.01	0.60	1
3	Tomatidine	0.32	−0.50	0.28	0.17	0.57	1
4	Disogenin	0.05	−0.57	0.58	−0.06	0.61	1
5	Campesterol	0.11	−0.48	0.71	0.01	0.50	1
6	Sitosterol	0.14	−0.51	0.73	0.07	0.51	1
7	Soladunalinidine	0.40	−0.40	0.09	0.31	0.55	1
	Andrographis paniculata **(Family:Acanthaceae)**						
1	14-Deoxy-11-hydroxyandrographolide	0.39	−0.41	0.94	0.15	0.72	0
2	3-O-beta-D-glucopyranosyl 14, 19-dideoxyandrographolide	0.39	−0.28	0.48	0.15	0.68	0
3	8, 17-Epoxy-14-deoxyandrographolide	0.46	−0.60	0.82	0.41	0.66	0
4	Andrograpanin	0.43	−0.37	0.76	0.07	0.63	0
5	Andrographiside	0.36	0.08	0.55	0.28	0.80	2
6	Andrographolide	0.32	−0.01	0.94	0.26	0.81	0
7	Isoandrographolide	0.32	−0.01	0.94	0.26	0.81	0
8	Neoandrographolide	0.47	−0.16	0.44	0.21	0.70	0
	Eucalyptus *Sp.*, (Family:Myrtaceae)						
1	Caryophyllene oxide	−0.08	−0.86	0.62	0.00	0.57	0
	Alpinia officinarum **(Family:Zingiberaceae)**						
1	β-sitosterol	0.14	−0.51	0.73	0.07	0.51	1
	Plectranthus amboinicus **(Family:Lamiaceae)**						
1	Caryophyllene oxide	−0.08	−0.86	−0.62	0.00	0.57	0

These novel phytocompounds directly targets the human COVID-19 immune receptors.

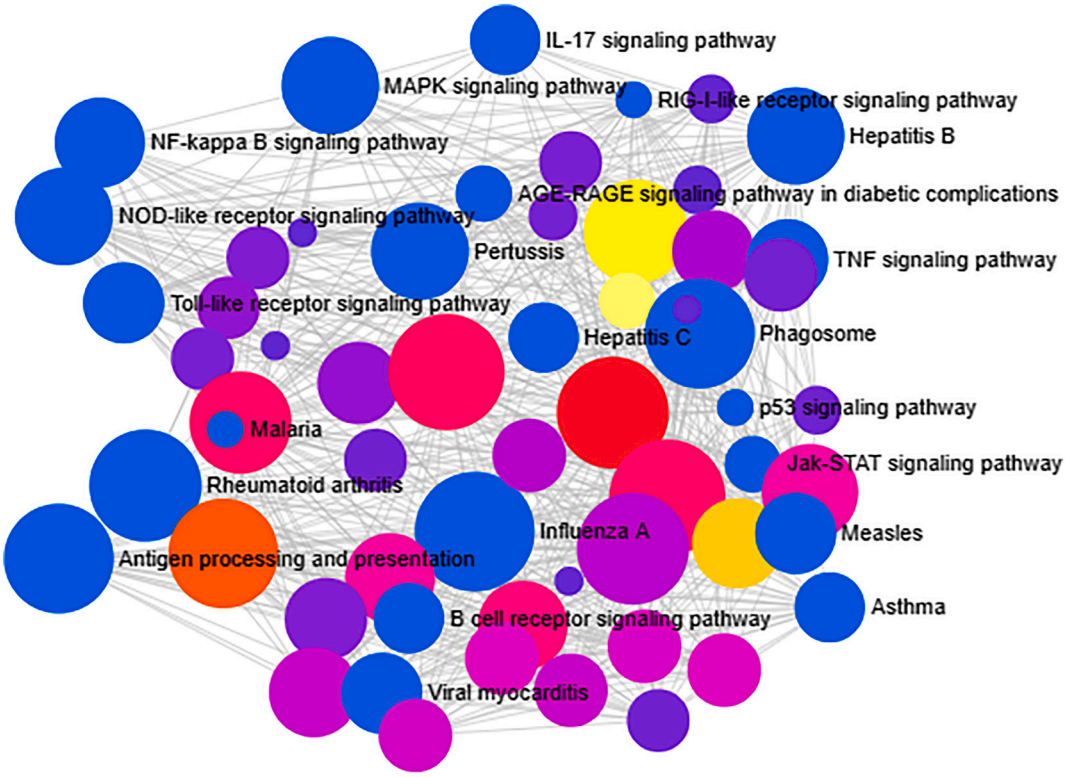

Fig. 9. ORA enrichment analysis of significant immune responsive genes. The number of human immune responsive genes falling in each KEGG pathway category is directly proportional to the node size. The nodes are color shaded according to the significance level (adjusted *P*-value < 0.05).

bioactive compounds and immune responsive genes network. The C-T-N results exhibited that there are 154 bioactive compounds interacting with or targeting the 13 immune responsive genes. It also unveils the diverse mechanism and plausible mode of action used by active phytochemicals to exert their curative effects and makes the traditional Indian medicines more fruitful and efficacious to the society and to come out of this pandemic situation.

Identified natural bioactive compounds that are targeting/ altering the COVID-19 immune response signaling pathways especially on TNF, JAK-STAT, NF-kB, and MAPK pathways by inhibiting or suppressing the 13 key receptors with their functions and could induce the production of anti-COVID-19 antibodies via antigen presenting cells (Fig. 10). Since synthetic drugs are incapable of producing a breakthrough to date in the treatment of this deadly virus disease, it is the need the hour to shift our focus to traditional Indian medicinal plants derived bioactive compounds in confronting this deadly COVID-19 infection.

5. Conclusion

The current findings revealed that the Indian traditional medicinal plants exhibited diverse immunological stimulants to treat/ altering the replication machinery of human COVID-19 infection. Biomedical research in traditional Indian medicinal plants notably on *J. adhatoda, O. sanctum, S. trilobatum, A. paniculata, Eucalyptus Sp., A. officinarum* and *P. amboinicus* is still bottleneck, significantly, our results on novel bioactive compounds with their pharmacological properties, human COVID-19 immune receptors/targets, diverse biological processes and their molecular interactions will pave the way to open the advanced molecular biological and COVID-19 research floodgates with the combination of Ayurveda to modern medicine era. This is the first and foremost holistic study identified several pivotal aspects of the host immune response to COVID-19 infection. Identified immune responsive genes and their associated diverse signaling pathways could be used for unraveling the pathogenesis of COVID-19. These significant genetic factors/immune responsive genes and pathways have been identified which is used to characterize the immune-pathology of human COVID-19 infection. This study hypothesizes that natural bioactive compounds and in combination with other substances, as is recommended by the traditional (according to Ayurveda) and modern medicine system (prescribed by WHO), may result in synergistic effects and need to be investigated further to develop the new drug to treat the COVID-19. In addition, this study suggested that obtained molecular interaction results can be useful to design competitive 13 immune targets antagonists which will pave the unparalleled way to combat COVID-19. Overall, this holistic study will stand as the platform to improve our understanding of the immunobiology of SARS-CoV2 and the acquired essential knowledge could be helpful in implementing an accurate intervention strategy in mere future. The ethical implications of drugs that enhancing immunity and inhibiting the human COVID-19 pathogenic processes are significant but it should be appropriately alleviated with ethical, legal and social considerations as field researchers enter the advanced world of drug development and provide valid targets for pivotal therapy against COVID-19.

Ethics

No animal or human subjects were used in this study.

Declaration of Competing Interest

The authors declare no competing interests.

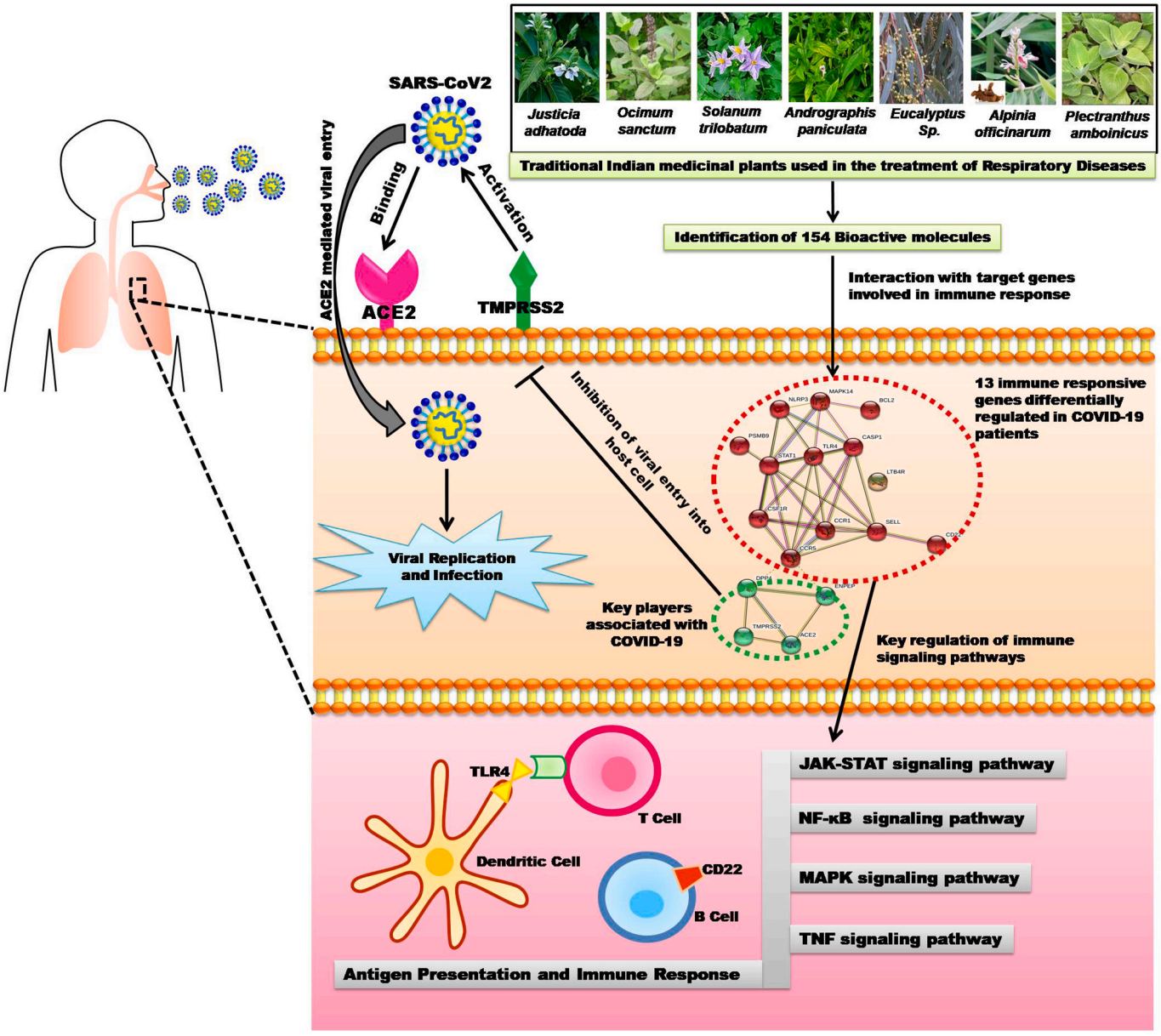

Fig. 10. Schematic representation of the current study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygeno.2020.08.003.

References

[1] V.M. Corman, J. Lienau, M. Witzenrath, Coronaviruses as the cause of respiratory infections, Internist (Berl). 60 (2019) 1136–1145, https://doi.org/10.1007/s00108-019-00671-5.

[2] C.I. Paules, H.D. Marston, A.S. Fauci, Coronavirus infections-more than just the common cold, JAMA. (2020), https://doi.org/10.1001/jama.2020.0757.

[3] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet (London, England). 395 (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

[4] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G.F. Gao, W. Tan, A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (2020) 727–733, https://doi.org/10.1056/NEJMoa2001017.

[5] A.E. Gorbalenya, S.C. Baker, R.S. Baric, R.J. de Groot, C. Drosten, A.A. Gulyaeva, B.L. Haagmans, C. Lauber, A.M. Leontovich, B.W. Neuman, D. Penzar, S. Perlman, L.L.M. Poon, D. Samborskiy, I.A. Sidorov, I. Sola, J. Ziebuhr, Severe acute respiratory syndrome-related coronavirus–the species and its viruses, a statement of the coronavirus study group, BioRxiv. (2020), https://doi.org/10.1101/2020.02.07.937862 2020.02.07.937862.

[6] C. Sohrabi, Z. Alsafi, N. O'Neill, M. Khan, A. Kerwan, A. Al-Jabir, C. Iosifidis, R. Agha, World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19), Int. J. Surg. 76 (2020) 71–76, https://doi.org/10.1016/j.ijsu.2020.02.034.

[7] W.J. McKibbin, R. Fernando, The global macroeconomic impacts of COVID-19: seven scenarios, SSRN Electron. J. (2020), https://doi.org/10.2139/ssrn.3547729.

[8] W. Li, M.J. Moore, N. Vasilieva, J. Sui, S.K. Wong, M.A. Berne, M. Somasundaran, J.L. Sullivan, K. Luzuriaga, T.C. Greenough, H. Choe, M. Farzan, Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus, Nature. 426 (2003) 450–454, https://doi.org/10.1038/nature02145.
[9] M. Hussain, N. Jabeen, F. Raza, S. Shabbir, A.A. Baig, A. Amanullah, B. Aziz, Structural variations in human ACE2 may influence its binding with SARS-CoV-2 spike protein, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.25832.
[10] D. Wrapp, N. Wang, K.S. Corbett, J.A. Goldsmith, C.-L. Hsieh, O. Abiona, B.S. Graham, J.S. McLellan, Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, Science. 367 (2020) 1260–1263, https://doi.org/10.1126/science.abb2507.
[11] S. Belouzard, V.C. Chu, G.R. Whittaker, Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites, Proc. Natl. Acad. Sci. U.S.A. 106 (2009) 5871–5876, https://doi.org/10.1073/pnas.0809524106.
[12] M. Hoffmann, H. Hofmann-Winkler, S. Pöhlmann, Priming Time: How Cellular Proteases Arm Coronavirus Spike Proteins, Act. Viruses by Host Proteases, (2018), pp. 71–98, https://doi.org/10.1007/978-3-319-75474-1_4.
[13] I. Davidson-Hunt, Ecological Ethnobotany: stumbling toward new practices and paradigms, MASA J. 16 (2000) 1–13.
[14] A. Elaissi, Z. Rouis, N.A. Ben Salem, S. Mabrouk, Y. ben Salem, K.B.H. Salah, M. Aouni, F. Farhat, R. Chemli, F. Harzallah-Skhiri, M.L. Khouja, Chemical composition of 8 eucalyptus species' essential oils and the evaluation of their antibacterial, antifungal and antiviral activities, BMC Complement. Altern. Med. 12 (2012) 81, , https://doi.org/10.1186/1472-6882-12-81.
[15] V. Prasanth, S. Palakeerti, *In Silico* studies of *Justicia adhatoda*, *Ocimum sanctum* plant compounds as *Mycobacterium tuberculosis* Ftsz inhibitors, Int. J. Bio. 01 (2012) 22–25 http://www.ebioscholar.com/ijb/index.php/ijb/article/view/9.
[16] K.J. Naquvi, S.L. Dohare, M. Shuaib, M.I. Ahmad, CHEMICAL composition of volatile oil of *Ocimum sanctum* Linn, Int. J. Biomed. Adv. Res. 3 (2012) 129–131, https://doi.org/10.7439/ijbar.v3i2.290.
[17] M.S. Hossain, Z. Urbi, A. Sule, K.M. Hafizur Rahman, *Andrographis paniculata* (Burm. F.) wall. Ex Nees: a review of ethnobotany, phytochemistry, and pharmacology, Sci. Wor. J. 2014 (2014) 274905, , https://doi.org/10.1155/2014/274905.
[18] K. Sebei, F. Sakouhi, W. Herchi, M.L. Khouja, S. Boukhchina, Chemical composition and antibacterial activities of seven Eucalyptus species essential oils leaves, Biol. Res. 48 (2015) 7, https://doi.org/10.1186/0717-6287-48-7.
[19] P. Balakrishnan, T. Ansari, M. Gani, S. Subrahmanyam, Review article a perspective on bioactive compounds from *Solanum trilobatum*, Res. J. Chem. Pharm. 7 (2015) 507–512.
[20] G. Arumugam, M.K. Swamy, U.R. Sinniah, *Plectranthus amboinicus* (lour.) Spreng: botanical, phytochemical, pharmacological and nutritional significance, Molecules. 21 (2016) 369, https://doi.org/10.3390/molecules21040369.
[21] S. Shukla, S. Hegde, A. Kumar, G. Chaudhary, S.K. Tewari, D.K. Upreti, M. Pal, Chemical composition and antibacterial activity of essential oil from leaves of *Justicia adhatoda* against methicillian resistant and sensitive strain along with their clinical isolates, J. Essent. Oil Bear. Plants. 20 (2017) 116–122, https://doi.org/10.1080/0972060X.2016.1260061.
[22] A.M. Basri, H. Taha, N. Ahmad, A review on the pharmacological activities and phytochemicals of *Alpinia officinarum* (galangal) extracts derived from bioassay-guided fractionation and isolation, Pharmacogn. Rev. 11 (2017) 43–56, https://doi.org/10.4103/phrev.phrev_55_16.
[23] G. Zhou, O. Soufan, J. Ewald, R.E.W. Hancock, N. Basu, J. Xia, NetworkAnalyst 3.0: a visual analytics platform for comprehensive gene expression profiling and meta-analysis, Nucleic Acids Res. 47 (2019) W234–W241, https://doi.org/10.1093/nar/gkz240.
[24] E.E. Bolton, Y. Wang, P.A. Thiessen, S.H. Bryant, B.V (Ed.), Chapter 12 PubChem: Integrated Platform of Small Molecules and Biological Activities, Elsevier, 2008, , https://doi.org/10.1016/S1574-1400(08)00012-1.
[25] R. Petryszak, M. Keays, Y.A. Tang, N.A. Fonseca, E. Barrera, T. Burdett, A. Füllgrabe, A.M.-P. Fuentes, S. Jupp, S. Koskinen, O. Mannion, L. Huerta, K. Megy, C. Snow, E. Williams, M. Barzine, E. Hastings, H. Weisser, J. Wright, P. Jaiswal, W. Huber, J. Choudhary, H.E. Parkinson, A. Brazma, Expression atlas update–an integrated database of gene and protein expression in humans, animals and plants, Nucleic Acids Res. 44 (2016) D746–D752, https://doi.org/10.1093/nar/gkv1045.
[26] M.E. Smoot, K. Ono, J. Ruscheinski, P.-L. Wang, T. Ideker, Cytoscape 2.8: new features for data integration and network visualization, Bioinformatics. 27 (2011) 431–432, https://doi.org/10.1093/bioinformatics/btq675.
[27] C.S. Sharma, S.S. Mishra, H.P. Singh, N. Kumar, *In silico* adme and toxicity study of some selected antineoplastic drugs, Int. J. Pharm. Sci. Drug Res. 8 (2016) 65–67, https://doi.org/10.25004/IJPSDR.2016.080110.
[28] M. Pomaznoy, B. Ha, B. Peters, GOnet: a tool for interactive gene ontology analysis, BMC Bioinformatics. 19 (2018) 470, https://doi.org/10.1186/s12859-018-2533-3.
[29] A.M. Alsamman, H. Zayed, The transcriptomic profiling of COVID-19 compared to SARS, MERS, Ebola, and H1N1, BioRxiv. (2020) 2020.05.06.080960, , https://doi.org/10.1101/2020.05.06.080960.
[30] D. Szklarczyk, J.H. Morris, H. Cook, M. Kuhn, S. Wyder, M. Simonovic, A. Santos, N.T. Doncheva, A. Roth, P. Bork, L.J. Jensen, C. von Mering, The STRING database in 2017: quality-controlled protein-protein association networks, made broadly accessible, Nucleic Acids Res. 45 (2017) D362–D368, https://doi.org/10.1093/nar/gkw937.
[31] R. Jeyasri, P. Muthuramalingam, V. Suba, M. Ramesh, J.-T. Chen, *Bacopa monnieri* and their bioactive compounds inferred multi-target treatment strategy for neurological diseases: a cheminformatics and system pharmacology approach, Biomolecules. 10 (2020), https://doi.org/10.3390/biom10040536.
[32] L.-T. Lin, W.-C. Hsu, C.-C. Lin, Antiviral natural products and herbal medicines, J. Tradit. Complement. Med. 4 (2014) 24–35, https://doi.org/10.4103/2225-4110.124335.
[33] M. Akram, I.M. Tahir, S.M.A. Shah, Z. Mahmood, A. Altaf, K. Ahmad, N. Munir, M. Daniyal, S. Nasir, H. Mehboob, Antiviral potential of medicinal plants against HIV, HSV, influenza, hepatitis, and coxsackievirus: a systematic review, Phytother. Res. 32 (2018) 811–822, https://doi.org/10.1002/ptr.6024.
[34] A. Choudhury, S. Mukherjee, *In silico* studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs, J. Med. Virol. n/a (2020), https://doi.org/10.1002/jmv.25987.
[35] K. Prasad, F. Khatoon, S. Rashid, N. Ali, A.F. AlAsmari, M.Z. Ahmed, A.S. Alqahtani, M.S. Alqahtani, V. Kumar, Targeting hub genes and pathways of innate immune response in COVID-19: a network biology perspective, Int. J. Biol. Macromol. 163 (2020) 1–8, https://doi.org/10.1016/j.ijbiomac.2020.06.228.
[36] A. Shah, Novel coronavirus-induced NLRP3 Inflammasomeactivation: a potential drug target in the treatment of COVID-19, Front. Immunol. 11 (2020) 1021, https://doi.org/10.3389/fimmu.2020.01021.
[37] E.G. Favalli, F. Ingegnoli, O. De Lucia, G. Cincinelli, R. Cimaz, R. Caporali, COVID-19 infection and rheumatoid arthritis: faraway, so close!, Autoimmun. Rev. 19 (2020) 102523, , https://doi.org/10.1016/j.autrev.2020.102523.
[38] J. Gao, Z. Tian, X. Yang, Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies, Biosci. Trends. 14 (2020) 72–73, https://doi.org/10.5582/bst.2020.01047.
[39] G. Herbein, W.A. O'Brien, Tumor necrosis factor (TNF)-alpha and TNF receptors in viral pathogenesis, Proc. Soc. Exp. Biol. Med. Soc. Exp. Biol. Med. (New York, N.Y.). 223 (2000) 241–257, https://doi.org/10.1046/j.1525-1373.2000.22335.x.
[40] R. Zhang, X. Wang, L. Ni, X. Di, B. Ma, S. Niu, C. Liu, R.J. Reiter, COVID-19: melatonin as a potential adjuvant treatment, Life Sci. 250 (2020) 117583, , https://doi.org/10.1016/j.lfs.2020.117583.