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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Systems pharmacology-based drug discovery and active mechanism of natural products for coronavirus pneumonia (COVID-19): An example using flavonoids

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ABSTRACT

Background: Recently, the value of natural products has been extensively considered because these resources can potentially be applied to prevent and treat coronavirus pneumonia 2019 (COVID-19). However, the discovery of nature drugs is problematic because of their complex composition and active mechanisms.

Methods: This comprehensive study was performed on flavonoids, which are compounds with anti-inflammatory and antiviral effects, to show drug discovery and active mechanism from natural products in the treatment of COVID-19 via a systems pharmacological model. First, a chemical library of 255 potential flavonoids was constructed. Second, the pharmacodynamic basis and mechanism of action between flavonoids and COVID-19 were explored by constructing a compound–target and target–disease network, targets protein-protein interaction (PPI), MCODE analysis, gene ontology (GO), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment.

Results: In total, 105 active flavonoid components were identified, of which 6 were major candidate compounds (quercetin, epigallocatechin-3-gallate (EGCG), luteolin, fisetin, wogonin, and licochalcone A). 152 associated targets were yielded based on network construction, and 7 family proteins (PTGS, GSK3β, ABC, NOS, EGFR, and IL) were included as central hub targets. Moreover, 528 GO items and 178 KEGG pathways were selected through enrichment of target functions. Lastly, molecular docking demonstrated good stability of the combination of selected flavonoids with 3CL Pro and ACEII.

Conclusion: Natural flavonoids could enable resistance against COVID-19 by regulating inflammatory, antiviral, and immune responses, and repairing tissue injury. This study has scientific significance for the selective utilization of natural products, medicinal value enhancement of flavonoids, and drug screening for the treatment of COVID-19 induced by SARS-COV-2.

1. Background

The infectivity and fatality rate of coronavirus pneumonia 2019 (COVID-19) induced by SARS-COV-2 is significantly higher than that of other viral pneumonias. As of January 14, 2022, COVID-19, the third large-scale epidemic after severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), has infected 318 million people and caused 5.5 million deaths globally [1,2]. At present, the development and efficacy verification of specific therapeutics or vaccines still require balance speed with rigor. Moreover, elimination of pulmonary inflammation and repair of injury in patients with coronavirus infection are also important tasks [3]. Thus, it is essential to explore effective drugs with stable access and low economic costs.

Natural products (such as flavonoids, alkaloids, artemisinins, and peptides) with polypharmacological properties have shown great promise as novel therapeutics for various complex diseases [4]. The biological activities of these functional molecules against COVID-19 have been successfully explored. In the notice on issuing the diagnosis

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and treatment protocol for novel coronavirus pneumonia trial *version 1–8* and other treatment guidelines in China, more than 250 prescriptions and patent medicines, including natural products (with Western medicine), were added to the recommended drugs for the prevention and treatment of COVID-19 [5]. By analyzing the frequency, compatibility principle, and action mechanism of recommended drugs, scientists have used natural products, especially flavonoids, as key compounds to reduce the incidence of severe or critical events, improve clinical recovery, and help alleviate symptoms such as cough or fever.

Flavonoids, which are typical compounds found in natural products, are widely distributed in nature and have a long history of medicinal and edible homology [6]. They not only exist in medicinal plants but also account for a large proportion of people's daily food and their adaptability to organisms has reached a certain level [7]. For the treatment of COVID-19, flavonoids can serve as an important resource based on their numerous pharmacological properties, such as antioxidant and anti-inflammatory effects, which have been verified by summary of comprehensive information and updated evidence for patients with various symptoms [8,9]. In addition, a series of specific in silico and in vitro experimental studies confirmed the mechanism of flavonoids in preventing and treating COVID-19 [10]. For example, baicalin and baicalein have been reported to inhibit coronavirus in infected Vero E6 cells, as determined by CCK-8 combined with qRT-PCR [11]. As some flavonoids have been used in practical applications to alleviate SARS-CoV-2 infection, a rapid and effective method is necessary to explore more active molecules in natural flavonoids and study their mechanisms of action.

Systems pharmacology is a holistic and systematic research method that uses a variety of group technologies, including systems biology, integration of computer virtual computing, high-throughput genomic analysis, and network databases [12,13]. In recent years, systems pharmacology has become an effective tool for revealing the regulatory network effect of biological targets and chemical entities of drugs in the body because of its emphasis on the comprehensiveness of drug interactions, which is consistent with the multi-target and multi-pathway characteristics of natural products [14,15]. In addition, as a research method combining physical and chemical principles with scientific calculation algorithms, molecular docking technology can predict the binding effect of natural flavonoids with COVID-19-related proteins and calculate the parameters of the binding mode, binding energy, and stability by computer simulation [16].

In this study, based on essential theory and clinical experience, a method of network pharmacology combined with molecular docking was adopted to demonstrate the advantages of effective substances in flavonoids against COVID-19 with the comprehensive regulation of multiple targets and pathways. By establishing a complete program with multi-disciplinary and multi-technology as shown in Fig. 1, this study could manage natural product resources with high throughput and enhance the efficiency of screening compounds to enrich the drug library systematically. This exploration of the scientific value and mechanism of action of potential natural products can provide a novel approach for the development of new drugs and bioproducts for the prevention and treatment of COVID-19.

2. Materials and methods

2.1. Compounds collection and screening

Natural flavonoids with pharmacological activity were retrieved from five TCM pharmacology databases including TCMSP (http://tcmspw.com/tcmsp.php), TCMID (http://www.megabionet.org/tcmid), TCMIP (http://www.tcmip.cn/TCMIP), BATMAN-TCM (http://bionet.ncpsb.org.cn/batman-tcm/), and YaTCM (http://cadd.pharmacy.nankai.edu.cn/yatcm) [17–21]. The structures of compounds were then compared with the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and PubChem CID was obtained [22]. According to ADME pharmacokinetic properties (absorption, distribution, metabolism, and exclusion) in TCMSP database, the chemical compounds satisfying oral bioavailability (OB) ≥30% and drug-likeness property (DL) ≥0.18 were selected as candidate active components [23–25]. Meanwhile, some compounds with low OB or DL were also selected because of their excellent pharmacological activities or high contents, such as puerarin, isoflavone, and others [26–28].

2.2. Potential target prediction and validation

The structure of candidate flavonoids was uniformly stored in SDF format using ChemBioDraw *version 19.0* and the SMILES format was imported into the SwissTargetPrediction database (http://www.swisstargetprediction.ch), searching for similarities between targets to find the top 100 targets for each compound [29,30]. The attribute was set to "homo sapiens". The specific parameter probability of each target was calculated during data processing. Protein targets with parameter probability ≥0 were standardized as UniProt ID in the UniProt protein database (https://www.uniprot.org) [31]. With "novel coronavirus pneumonia", "novel coronavirus", and other diseases related to COVID-19 as keywords, the potential targets were explored in the GeneCards database (https://www. genecards.org) [32]. A high score indicated that the target was closely related to the disease. In addition, the targets of four Western medicines (which have been used clinically

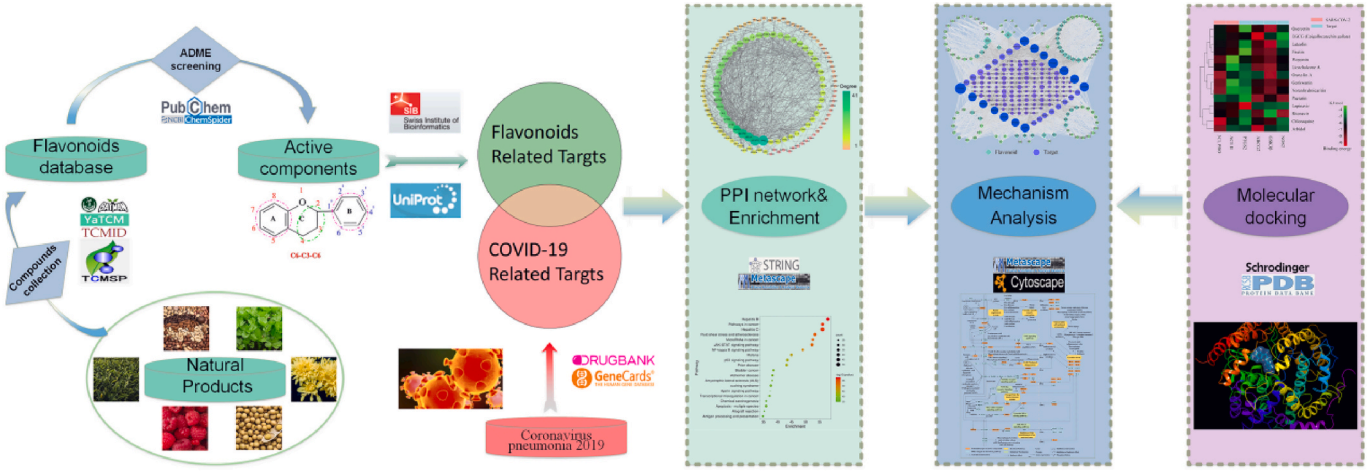

Fig. 1. Whole technical route of present research based on network pharmacology and molecular docking for revealing flavonoids against COVID-19 in multiple targets and pathways.

for COVID-19 treatment), namely, lopinavir, ritonavir, chloroquine (no longer recommended), and arbidol were searched in the DrugBank database (https://www.drugbank.ca) for supplementation [33]. By comparing and removing the repeat targets in two databases, the COVID-19-related targets were obtained and standardized as UniProt ID. A Venn diagram was established to clarify the relationship between the two sets of potential target information using Venny *version 2.1* (https://bioinfogp.cnb.csic.es/tools/venny). The intersection targets were selected as targets of natural flavonoids for the prevention and treatment of COVID-19.

2.3. PPI network and MCODE modules analysis

The intersection target was submitted to the STRING *version 11.0* database (https://string-db.org) to construct protein-protein interaction (PPI) network mode [34,35]. The biological species was set to "*Homo sapiens*" and the minimum interaction threshold was set to "highest confidence (>0.9)". Cytoscape *version 3.8.0* was used to map relevant target information, thereby constructing the analysis network, removing isolated nodes, and retaining the largest connected subgraph [36]. High-correlation targets were obtained in terms of network degree-value and betweenness centrality. Furthermore, the Metascape platform (http://metascape.org) was used to explore biological process of interaction between potential targets [37]. The P-value was set to "<0.01", the smallest count was set to "3", and the enrichment factor was set to ">1.5". According to the P-value after enrichment analysis, the top three functional modules were selected using the molecular complex detection (MCODE) plug-in [38].

2.4. GO function and KEGG pathways enrichment

In organisms, genes cannot perform their functions independently. Gene ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were used to provide a more systematic and comprehensive understanding of the mechanisms of action [39,40]. The associated targets of the candidate flavonoids and COVID-19 were recorded on the Metascape. The input/analysis as species was set to "*H.sapiens*", the P-value was set to "<0.01". The main biological processes were corrected using the Bonferroni method and the correlation was estimated using the enrichment score (-log10 (P-value)). On the basis of the multi-system pathological changes in patients and the wide availability of natural flavonoids in this survey, the traditional single method of analyzing pathway correlation by P-value is prone to bias. Therefore, using the hierarchical clustering results of Metascape, cluster analysis for KEGG pathways was carried out in combination with the ClueGO plug-in to reduce the research deviation in network proximity analysis [41].

2.5. Network construction and analysis

The CytoHubba tool was applied to calculate three network topology parameters (degree-value of connection, betweenness, and closeness) of compounds and targets, thereby identifying key nodes. The green diamond nodes, blue circular nodes, and red hexagonal nodes represent active flavonoids, protein targets, and disease categories, respectively. The size and color depth of the nodes were correlated with three network topology parameters, namely, the degree-value of connection, betweenness, and closeness. The straight lines represent interaction while the degree-value and betweenness centrality reflect the betweenness of regulatory effects.

2.6. Molecular docking verification

The top four correlation targets and top ten correlation flavonoids in the network were used as the receptors and ligands respectively. 3CL Pro (PDBID: 6m2n) and ACEII (PDBID: 1r4l) were used as COVID-19-related receptors because 3CL Pro is the main protease involved in virus replication and ACEII is a cell receptor of SARS-COV-2 invading the human body [42–46]. Western medicine for COVID-19 was used as a positive control for ligands. The crystal structures of protein targets and compounds were obtained from the PDB protein database (http://www.rcsb.org/), and the scientific name of the source organism was set to "*Homo sapiens*" [47]. Schrodinger *version 2018* software was used to conduct molecular docking between the ligand and the receptor [48]. After the standardized operation of dehydrogenation and water addition of the compound, the possibility and stability of docking were evaluated based on the space site and binding ability. A binding energy of less than −5 kJ/mol represents a good binding effect. The smaller the docking score, the higher binding rate between the receptor and ligand. The docking results verified the scientific nature of the study based on network pharmacology.

3. Result

3.1. Active compounds screening

A chemical substance library containing 255 representative flavonoids was constructed and the active compounds were matched to specific pharmacokinetic parameters. The potential flavonoid category distributions are shown in Fig. 2. Their parent nuclei were classified into 12 types depending on their flavonoid substitution sites and substituent types. The y-axis in Fig. 2 represents the number of candidate compounds in each category. The compounds with the highest proportions were flavones, flavonols, and chalcones. A total of 105 active compounds were obtained through OB ≥ 30% and DL ≥ 0.18 threshold screening or literature supplement. They were numbered according to their categories and their characteristic information is presented in Table 1.

3.2. Target prediction and validation

A total of 829 protein targets with parameter probability >0, which were related to 105 active compounds, were screened. 792 COVID-19

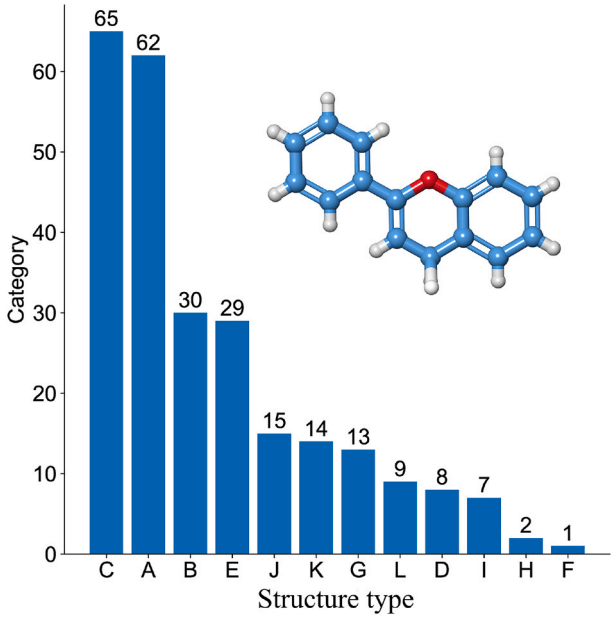

Fig. 2. Distribution of structure type for 255 candidate flavonoids. The y-axis represented the number of candidate compounds in each category. A—Flavone; B—Flavanone; C—Flavonol; D—Flavanonl; E—Isoflavone; F—Isoflavanone; G— Chalcone; H—Dihydrochalcone; I—Anthocyanidin; J—Flavanol; K—Biflavonoid; L—Miscellaneous Flavonoid.

Table 1
ADME characteristic information of 105 active flavonoids.

Label	Compound	PubChem CID	OB/%	DL	Label	Compound	PubChem CID	OB/%	DL
A1	Panicolin	5320399	76.26	0.29	C7	Erianthin	5320351	49.55	0.48
A2	Norartocarpetin	72344	61.67	0.52	C8	Rhamnazin	5320945	47.14	0.34
A3	Norartocarpetin	5481970	54.93	0.24	C9	Quercetin	5280343	46.43	0.28
A4	Corymbosin	10970376	51.96	0.41	C10	Morin	5281670	46.23	0.27
A5	IsoSinensetin	632135	51.15	0.44	C11	Eupalitin	5748611	46.11	0.33
A6	Sinensetin	145659	50.56	0.45	C12	Galangin	5281616	45.55	0.21
A7	Salvigenin	161271	49.07	0.33	C13	Icaritin	5318980	45.41	0.44
A8	6-Hydroxyluteolin	5281642	46.93	0.28	C14	Quercetagetin	5281680	45.01	0.31
A9	Cirsiliol	160237	43.46	0.34	C15	Axillarin	5281603	42.60	0.37
A10	Oroxylin A	5320315	41.37	0.23	C16	Eupatolitin	5317291	42.55	0.37
A11	Pectolinarigenin	5320438	41.17	0.30	C17	Kaempferol	5280863	41.88	0.24
A12	Negletein	471719	41.16	0.23	C18	Noranhydroicaritin	5318624	38.04	0.53
A13	Baicalin	64982	40.12	0.75	C19	Syringetin	5281953	36.82	0.37
A14	Linarin	5317025	39.84	0.71	C20	Herbacetin	5280544	36.07	0.27
A15	Norwogonin	5281674	39.40	0.21	C21	Gossypetin	5280647	35.00	0.31
A16	Andrographin	5318506	37.57	0.33	D1	Garbanzol	442410	83.67	0.21
A17	Genkwanin	5281617	37.13	0.24	D2	Taxifolin	439533	57.84	0.27
A18	Luteolin	5280445	36.16	0.25	D3	(±)-Fustin	5317435	50.91	0.24
A19	Chrysoeriol	5280666	35.85	0.27	D4	Astilbin	119258	36.46	0.74
A20	Fortunellin	5317385	35.65	0.74	D5	Engeletin	6453452	36.27	0.70
A21	Acacetin	5280442	34.97	0.24	E1	Formononetin	5280378	69.67	0.21
A22	Pedalitin	31161	34.02	0.31	E2	Licoricone	5319013	63.58	0.47
A23	Baicalein	5281605	33.52	0.21	E3	3′-O-Methylorobol	5319744	57.41	0.27
A24	Hypolaetin	5281648	33.24	0.28	E4	Odoratin	13965473	49.95	0.30
A25	IsoVitexin	162350	31.29	0.72	E5	Isoflavone	72304	49.03	0.13
A26	Diosmetin	5281612	31.14	0.27	E6	4′-7-Dihydroxy-3′-Methoxyisoflavone	5319422	48.57	0.24
A27	Hispidulin	5281628	30.97	0.27	E7	Calycosin	5280448	47.75	0.24
A28	Wogonin	5281703	30.68	0.23	E8	Irilone	5281779	46.87	0.36
A29	Skrofulein	188323	30.35	0.30	E9	Pratensein	5281803	39.06	0.28
A30	Eupatorin	97214	30.23	0.37	E10	Isoformononetin	3764	38.37	0.21
B1	Hesperetin	72281	70.31	0.27	E11	Irisolidone	5281781	37.78	0.30
B2	Dihydrooroxylin	25721350	66.06	0.23	E12	Puerarin	5281807	24.03	0.69
B3	Butin	92775	65.94	0.21	F1	Violanone	44446884	80.24	0.30
B4	Liquiritin	503737	65.69	0.74	G1	Licochalcone A	5318998	40.79	0.29
B5	Naringenin	439246	59.29	0.21	G2	Okanin	5281294	98.81	0.20
B6	Isoxanthohumol	513197	56.81	0.39	G3	Licochalcone B	5318999	76.76	0.19
B7	Alpinetin	821279	55.23	0.20	I1	Delphinidin	128853	40.63	0.28
B8	Norkurarinol	44563159	51.28	0.64	I2	Pelargonidin	440832	37.99	0.21
B9	Pinocembrin	68081	64.72	0.18	I3	Petunidin	441774	30.05	0.31
B10	Farrerol	91144	42.65	0.26	J1	Proanthocyanidin B1	11250133	67.87	0.66
B11	Pinostrobin	6950539	41.92	0.20	J2	LeucoPelargonidin	3286789	57.97	0.24
B12	Neoponcirin	16760075	41.24	0.72	J3	Epigallocatechin-3-Gallate (EGCG)	65064	55.09	0.77
B13	Carthamidin	188308	41.15	0.24	J4	Catechin	9064	54.83	0.24
B14	Poriol	301798	38.45	0.24	J5	(+)-Epicatechin gallate	5276454	53.57	0.75
B15	IsoBavachin	193679	36.57	0.32	J6	LeucoCyanidin	440833	30.84	0.27
B16	Poncirin	45359875	36.55	0.74	J7	LeucoDelphinidin	44563331	30.02	0.31
B17	Liquiritigenin	114829	32.76	0.18	L1	Aureusidin	5281220	53.42	0.24
C1	Azaleatin	5281604	54.28	0.30	L2	Sumatrol	442824	70.92	0.91
C2	Patuletin	5281678	53.11	0.34	L3	Silydianin	11982272	59.65	0.76
C3	Fisetin	5281614	52.6	0.24	L4	Phaseollidin	119268	52.04	0.53
C4	Kumatakenin	5318869	50.83	0.29	L5	Cyclomulberrochromene	5481969	36.79	0.87
C5	Eupatin	5317287	50.8	0.41	L6	Karanjin	100633	69.56	0.34
C6	Isorhamnetin	5281654	49.6	0.31					

A—Flavone; B—Flavanone; C—Flavonol; D—Flavanonl; E—Isoflavone; F—Isoflavanone; G—Chalcone; H—Dihydrochalcone; I—Anthocyanidin; J—Flavanol; K—Biflavonoid; L—Miscellancous Flavonoid.

targets and 44 Western medicine targets were retrieved. After removing duplicates, a total of 831 COVID-19 disease-related targets were identified. After Venn mapping (Fig. 3), 152 intersection targets were obtained for all the 105 active flavonoids as shown in Table 2. Their characteristics are presented in Table S1. The targets covered a variety of categories with enzymes, kinases, and signaling pathways accounting for a high proportion.

3.3. PPI network and MCODE module analysis

The number of edges and the average node degree-values in the PPI network were 643 and 8.46, respectively. Additionally, 52 protein targets were greater than the average degree-value. Furthermore, topological parameters were calculated using the CytoHubba tool, as shown in Fig. 4A. On the basis of degree-value of the close constituent

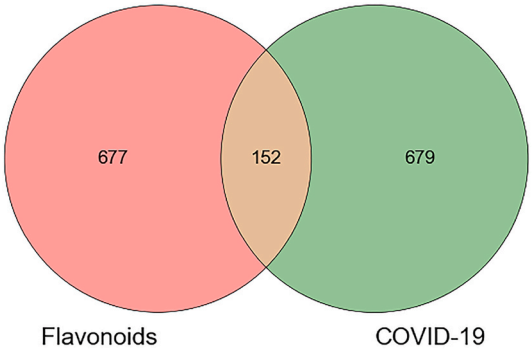

Fig. 3. Venn diagram of flavonoids and COVID-19-related targets.

Table 2
152 potential targets of natural flavonoids against COVID-19.

NO.	Gene Symbol	Uniprot ID	NO.	Gene Symbol	Uniprot ID	NO.	Gene Symbol	Uniprot ID
1	ABCB1	P08183	52	EIF2AK3	Q9NZJ5	103	MAPT	P10636
2	ABCC1	P33527	53	ENPP1	P22413	104	MCL1	Q07820
3	ABCG2	Q9UNQ0	54	EP300	Q09472	105	NAE1	Q13564
4	ACEII	Q9BYF1	55	ERN1	O75460	106	NFKB1	P19838
5	ADAM17	P78536	56	EZR	P15311	107	NOS2	P35228
6	ADAMTS1	Q9UHI8	57	F10	P00742	108	NOS3	P29474
7	ANPEP	P15144	58	F2	P00734	109	NPEPPS	P55786
8	APOD	P05090	59	FCER2	P06734	110	NR1I2	O75469
9	BAD	Q92934	60	FGF2	P09038	111	PARP1	P09874
10	BAK1	Q16611	61	FGFR2	P21802	112	PI4KB	Q9UBF8
11	BAX	Q07812	62	FGFR3	P22607	113	PIK3CA	P42336
12	BCL2	P10415	63	FKBP1A	P62942	114	PIK3CB	P42338
13	BCL2A1	Q16548	64	FOS	P01100	115	PIK3CD	O00329
14	BCL2L1	Q07817	65	G6PD	P11413	116	PIK3CG	P48736
15	BCL2L2	Q92843	66	GAPDH	P04406	117	PIK3R1	P27986
16	BRD4	O60885	67	GOT1	P17174	118	PITRM1	Q5JRX3
17	CASP3	P42574	68	GPT	P24298	119	PLA2G4A	P47712
18	CASP6	P55212	69	GSK3A	P49840	120	PLAT	P00750
19	CASP8	Q14790	70	GSK3B	P49841	121	POR	P16435
20	CAT	P04040	71	GSTM1	P09488	122	PPARG	P37231
21	CCL2	P13500	72	GUSB	P08236	123	PRKACA	P17612
22	CCNA2	P20248	73	HDAC2	Q92769	124	PRKCA	P17252
23	CCND1	P24385	74	HMOX1	P09601	125	PRKCB	P05771
24	CCND3	P30281	75	HPGDS	O60760	126	PRKCE	Q02156
25	CCNE1	P24864	76	HSP90B1	P14625	127	PTGS1	P23219
26	CD4	P01730	77	HSPA5	P11021	128	PTGS2	P35354
27	CD40LG	P29965	78	HSPB1	P04792	129	RB1	P06400
28	CDK2	P24941	79	ICAM1	P05362	130	RELA	Q04206
29	CDK4	P11802	80	IFNB1	P01574	131	SERPINE1	P05121
30	CDKN1B	P46527	81	IFNG	P01579	132	SIGMAR1	Q99720
31	CHEK2	O96017	82	IKBKB	O14920	133	SIRT1	Q96EB6
32	COMT	P21964	83	IL1A	P01583	134	SLC6A4	P31645
33	COQ8B	Q96D53	84	IL1β	P01584	135	SLC28A3	Q9HAS3
34	CREB1	P16220	85	IL2	P60568	136	SLC29A1	Q99808
35	CRP	P02741	86	IL4	P05112	137	SOD1	P00441
36	CTSB	P07858	87	IL6	P05231	138	STAT1	P42224
37	CTSL	P07711	88	IL10	P22301	139	STAT3	P40763
38	CXCL2	P19875	89	IMPDH1	P20839	140	STAT6	P42226
39	CXCL8	P10145	90	IMPDH2	P12268	141	SUMO1	P63165
40	CXCL10	P02778	91	IRF1	P10914	142	TBK1	Q9UHD2
41	CXCL11	O14625	92	IRF3	Q14653	143	TGFB1	P01137
42	CYP1A1	P04798	93	ITGAL	P20701	144	TLR9	Q9NR96
43	CYP1A2	P05177	94	JAK1	P23458	145	TNF	P01375
44	CYP2C9	P11712	95	LCK	P06239	146	TP53	P04637
45	CYP2C19	P33261	96	LDHA	P00338	147	TTR	P02766
46	CYP3A4	P08684	97	LGALS3	P17931	148	TUBB3	Q13509
47	CYP3A7	P24462	98	MAPK1	P28482	149	TXN	P10599
48	DNMT1	P26358	99	MAPK3	P27361	150	VCP	P55072
49	DPP4	P27487	100	MAPK8	P45983	151	VEGFA	P15692
50	EGFR	P00533	101	MAPK14	Q16539	152	VIM	P08670
51	EGR1	P18146	102	MAPKAPK2	P49137			

relationship, the top three functional modules with abundant biological processes were obtained after enrichment analysis. The results showed that the same family of targets (MAPK, IL, and PTGS) commonly gathered into a functional module in Fig. 4B–D. Meanwhile, different genes coordinate with each other to complete a series of biochemical reactions. The MCODE in our research performs highly correlated biological functions, such as viral carcinogenesis, apoptosis, and regulation of cytokine production.

3.4. GO function and KEGG pathways enrichment

A total of 515 GO items were obtained, including 360 biological processes (BP) items, 76 cellular components (CC) items, and 92 molecular functions (MF). The top ten correlation terms for each category are shown in Fig. 5A. Furthermore, Fig. 5B shows the distribution of the three types of GO item clusters. The position of target gene products in cells were mainly distributed in membrane rafts, membrane microdomains, transferring enzyme complexes, and sticking to a variety of cell membranes. Biological processes were mainly involved in cellular responses to inorganic substances, molecules of bacterial origin, toxic substances, and lipopolysaccharide (LPS). Molecular function mainly involved cytokines receptors, protein phosphatase binding, and protein kinase activity. The enrichment score of the three highly correlated items, which comprised apoptosis signaling pathways, leukocyte differentiation, and regulation of cytokine production, also exceeded 33 (Fig. 5A). In addition, 178 KEGG pathways were identified through annotation analysis and the top 20 pathways are shown in Fig. 5C. The color and size of the circle represent the P-value and target counts, respectively. The KEGG pathways with high correlation were hepatitis B, pathways in cancer, hepatitis C, fluid shear stress and atherosclerosis, microRNAs in cancer, JAK-STAT signaling pathway, and NF-kappaβ signaling pathway. KEGG pathway clusters analysis (Fig. 5D) showed that 44.74% of the pathways were involved in the hepatitis B cluster, while other high-correlation clusters included microRNAs in cancer, chronic myeloid leukemia, tuberculosis, and VEGF signaling pathway.

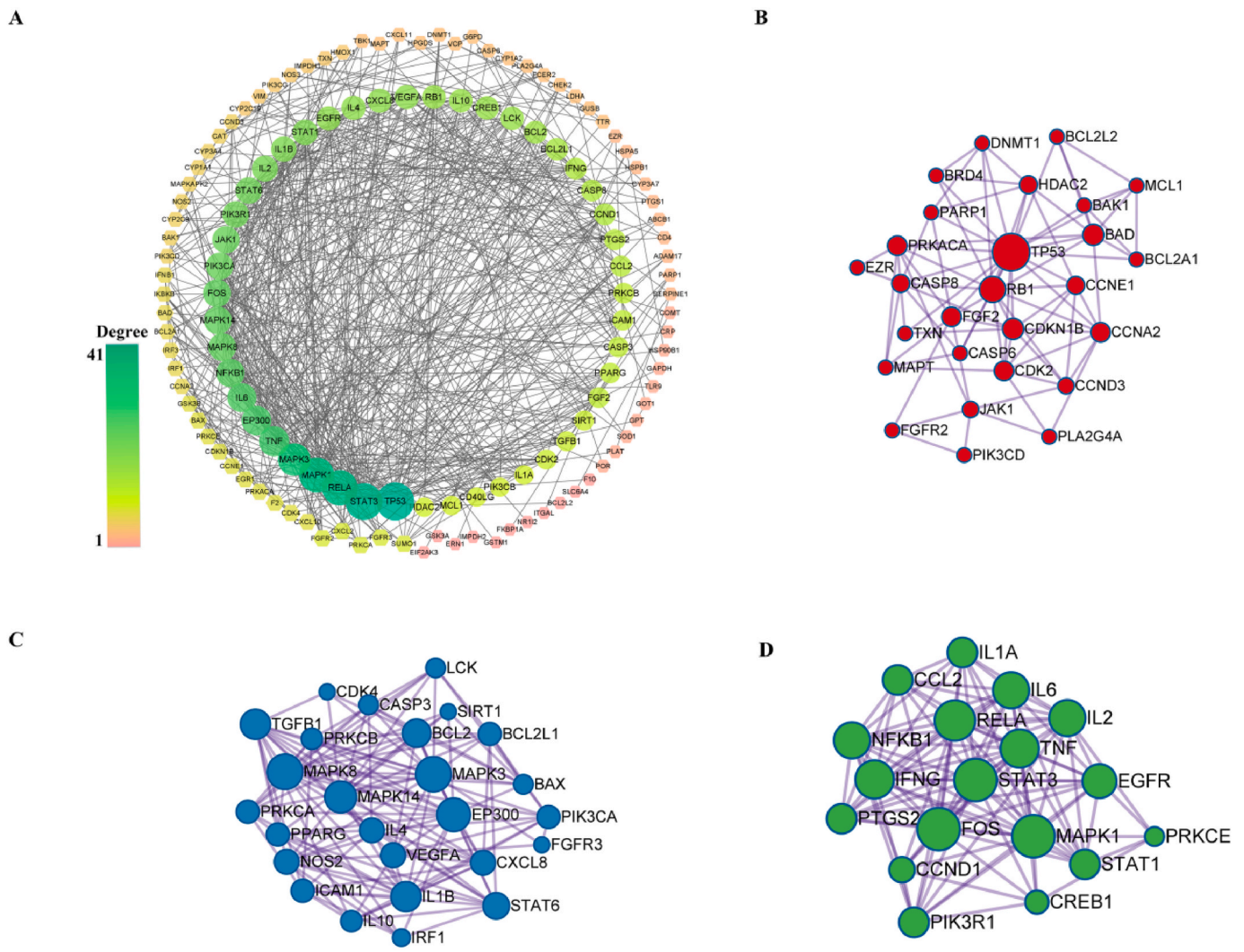

Fig. 4. PPI network and MCODE modules of intersection targets. (A) An overall view of the whole PPI network. (B–D) Three high correlation MCODE in PPI network. The size and color depth of node were correlated with three network topology parameters (degree-value of connection, betweenness, and closeness).

3.5. Network construction and analysis

Candidate flavonoids and potential targets were imported into Cytoscape to build a compound–target (C–T) network as shown in Fig. 6. Quercetin (C9) and epigallocatechin-3-gallate (EGCG, J3), which are also two of the most abundant polyphenols in edible plants, connected 57 and 51 proteins in the C–T network, respectively. Luteolin (A18), fisetin (C3), wogonin (A28), licochalcone A (G1), oroxylin A (A10), genkwanin (A17), puerarin (E12), and noranhydroicaritin (C18) also showed strong pharmacological activities. In the network, the degree-value of 30 active components were greater than the median, and their structures are shown in Fig. S1. The targets with significant correlation were PTGS2, PTGS1, ABCG2, GSK3β, ABCB1, ABCC1, NOS2, EGFR, CDK2, PIK3CG, and PPARG. In addition, a target–disease (T–D) network was built with the summarized targets and corresponding disease information. Disease categories in Fig. 7 closely related to potential targets were concentrated in neuronal, blood, cancer, immune, and infectious diseases, which were highly consistent with the pathological characteristics of patients. Network displayed targets had a significant influence on the respiratory tract, cardiovascular system, gastrointestinal organ, and skin.

3.6. Molecular docking verification

The crystal structures of the top four correlation protein targets were obtained in PDB to serve as receptors, which included PTGS2 (PDBID: 5f19), ABCG2 (PDBID: 5omy), GSK3β (PDBID: 6y9r), and NOS2 (PDBID: 5xn3). The docking results showed that the flavonoids, as a typical example of natural products, with 3CL Pro and ACEII generally reflected the combination of good stability capacity, some even better than clinical medicine. Specific binding energy is shown in Fig. 8, and the change in color from green to red indicates a change in combination effect from low to high. The binding energy values (kJ/mol) of molecular docking between the ligands and receptors are shown in Table S2. A recent study on surface plasmon resonance (SPR) and fluorescence resonance energy transfer (FRET) binding showed that compounds with good binding ability to 3CL Pro included EGCG (J3) and other flavonoids, such as quercetin (C9), kaempferol (C17), luteolin (A18), isorhamnetin (C6), and wogonin (A28), which also verified the rationality of the docking results [49].

The active site of the protein was centered on the active site of the original ligand in the crystal structure. Given the high homology of the conformation of flavonoids, the binding effects (binding sites and forces) between flavonoids and COVID-19-related proteins were predominantly similar. As an example (Fig. 9A), for the 3CL Pro combined with genkwanin (A17), the hydroxyl groups formed hydrogen bonds with

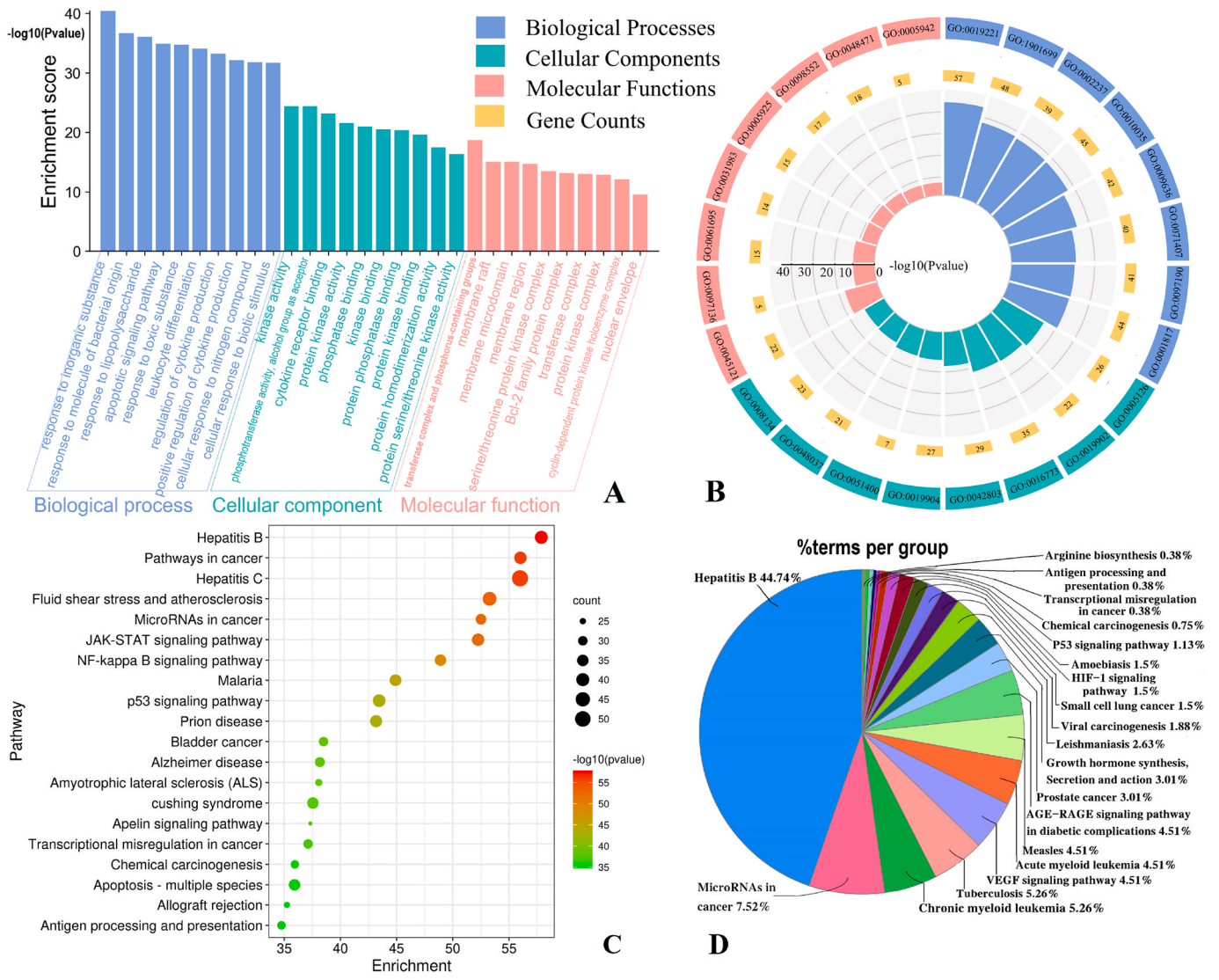

Fig. 5. GO function and KEGG pathway enrichment of intersection targets. (A) Enrichment diagram of BP, CC, and MF terms. The vertical axis represents the enrichment score. (B) The cluster analysis of high correlation GO terms. (C) The bubble diagram of KEGG Pathway. The smaller the P-value (the redder the color), the higher the enrichment score. (D) The cluster analysis of KEGG pathway. The size of the region represents the proportion of pathways.

residues of ASP187, and CYS44 at the active site of 3CL hydrolase, while carbonyl and methyl also interacted with GLU166 and GLY143. When ACEII was combined with quercetin (C9) in Fig. 9B, Pi-Pi stacking between the benzene ring, TRP349 and TYR510 was the key relationship. The hydrogen bonds between hydroxyl groups, TYR515, and GLU375 were indispensable. These interactions promoted the stable binding of small flavonoid molecules to their active sites, thereby inhibiting protein activity [50–52]. Such active flavonoids could be used as potential inhibitors to block 3CL Pro and ACEII combined with related targets at the molecular level, which could inhibit SARS-CoV-2 replication.

4. Discussion

A total of 105 active compounds in the C-T network were widely distributed among natural flavonoids and most of them were closely related to multiple targets. PTGS (PTGS2, PTGS1), GSK3β, ABC (ABCG2, ABCB1, ABCC1), NOS (NOS2, NOS1), EGFR, IL (IL6, IL1β), blood coagulation factor (F2, F10), and other family targets were located at the center of the network, which gathered into the biological module. Association rules and compatibility network analysis indicated that distinct flavonoids could act together with the same target whereas multiple targets could be easily controlled by the same compound. This material base indicated that multiple flavonoid components could regulate multiple symptoms by applying to multiple targets in different pathways. Consistent with autopsy reports of patients, the network also showed that COVID-19 is involved in infection, inflammation, immune response, blood coagulation, tissue injury, and genetic polymorphism [53]. Fig. 10 shows the expression and regulatory interaction of flavonoid-related targets in pathways. The mechanisms of action were divided into inflammatory, antiviral, immune regulation, and tissue injury repair.

4.1. Inflammatory

With the deepening of viral infections, cytokine storms have occurred in patients. Such events cause the uncontrolled release of excessive inflammatory factors by immune cells, which attack immune organs, and affect blood and circulatory systems [54]. Clinical investigations showed that 82.1% and 36.2% of the patients had lymphopenia and thrombocytopenia, respectively. Pneumonia was observed in 79.1% of the patients and ground-glass opacity (50%) was the most frequent chest computed tomography finding. These results

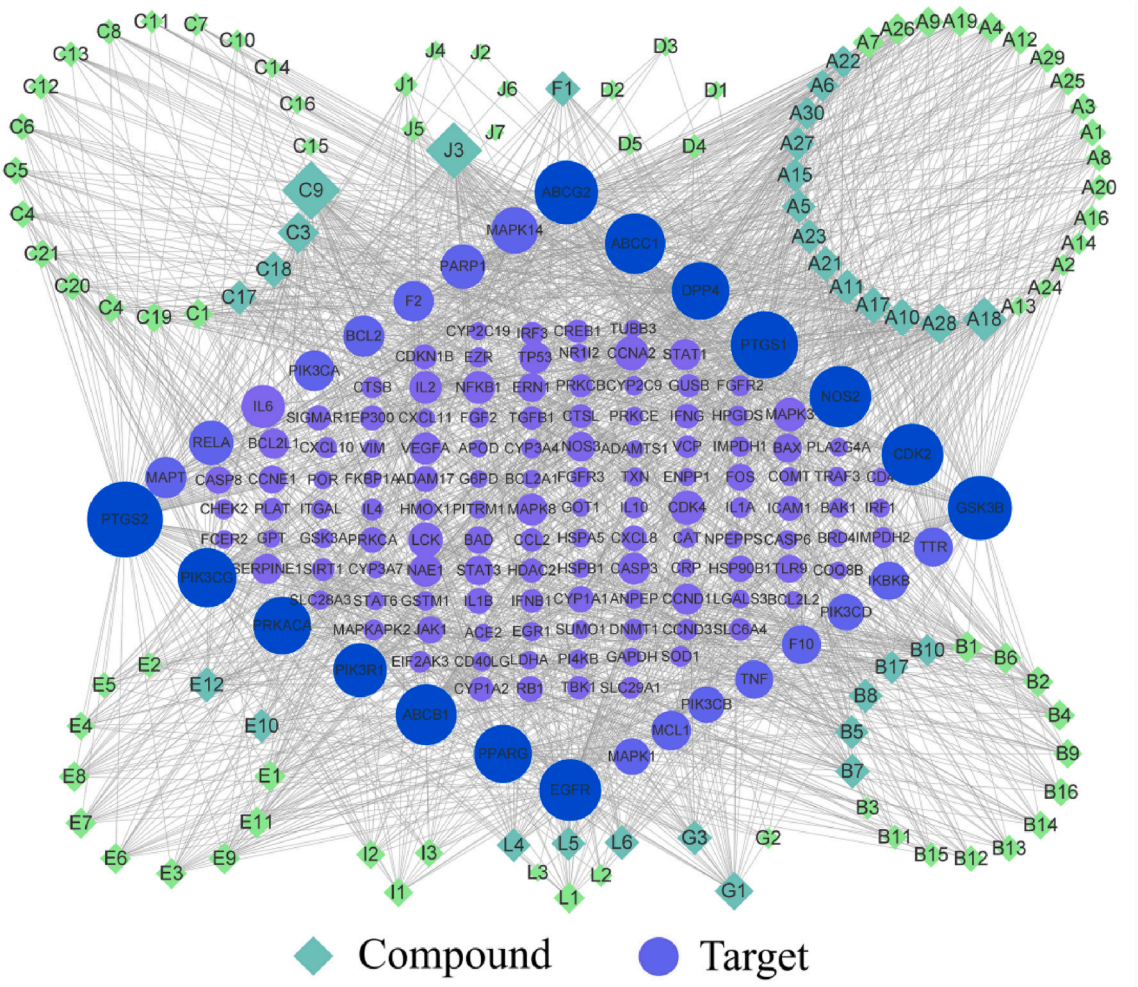

Fig. 6. C-T network of active flavonoids and associated targets. The size and color depth of node were correlated with three network topology parameters (degree-value of connection, betweenness, and closeness).

suggested that inflammatory storms and subsequent tissue damage were the most critical factors [55]. Therefore, as a key cytokine that triggers inflammatory storms, IL6 was used as an early warning indicator for severe cases in notice of issuing the diagnosis and treatment protocol for novel coronavirus pneumonia trial (trial *version 8*). TNF, CCL2, IL2, CXCL10, IL1β, and other important inflammatory mediators are closely related to many biological processes [56]. Typically, the aggravation of inflammatory reactions generates mucus production and collagen deposition in the respiratory tract and even causes death through acute respiratory distress syndrome (ARDS). Thus, inflammation-associated proteins were at the center of the network and inflammation-related KEGG pathways accounted for a large proportion. First, flavonoids reduce the expression of inflammatory genes in cells at the translational and transcriptional levels. For instance, wogonin (A28) interfered with the nuclear localization sequence and amplicon of NF-κβ, thereby affecting the mRNA transcription of inflammatory factors in macrophages [57]. In addition, bioactive immunomodulatory compounds such as fisetin (C3) decrease the number of infiltrating neutrophils and affect the self-renewal, division, proliferation, and survival of immune cells (such as monocyte and dendritic cells) [58]. Furthermore, the enrichment scores of the Toll-like receptor and TNF signaling pathways in Fig. 5C were 31.8 and 35.2, respectively, which indicated that flavonoids were beneficial for regulating the two pathways as shown in Fig. 10. Flavonoids not only affect inflammasome activation but also interfere with the synthesis of protein complexes such as MAPK and NF-κβ. The expression intensity of inflammatory storms can be suppressed by flavonoids to achieve an anti-inflammatory effect in three ways.

4.2. Antiviral

The main active mechanism is conventional therapy with symptomatic support. The use of antiviral drugs to control outbreaks of infectious diseases is not a long-term strategy [59]. For instance, studies have shown that chloroquine potentially increases the frequency of cardiac side effects in patients [60]. Flavonoids have demonstrated antiviral activity against various viruses in animal models of varying diseases. First, active ingredients are beneficial for resisting the invasion and secretion of viruses, thereby inhibiting their infection in cells [61,62]. Furthermore, flavonoids interfere with the replication, transcription, and translation of the coronavirus RNA genome [10]. They mainly affect the function of intracellular organelles (endoplasmic reticulum, endosome, and others) or the secretion of protein factors (kinases, enzymes, and others) [63]. This process blocks the synthesis of viral proteins and the assembly of virus particles. Moreover, flavonoids are helpful in directional regulation to induce apoptosis and pyroptosis in infected host cells [64]. Flavonoids assist the activation of complements to secret membrane attack complex (MAC), forming hydrophilic membrane-penetrating channels that alter intracellular osmotic pressure, and contribute to cell disintegration [65,66]. These lesions affect FcγR-mediated phagocytosis or form neutrophil extracellular traps (NETs), ultimately eliminating the virus. For instance, kaempferol (C17)

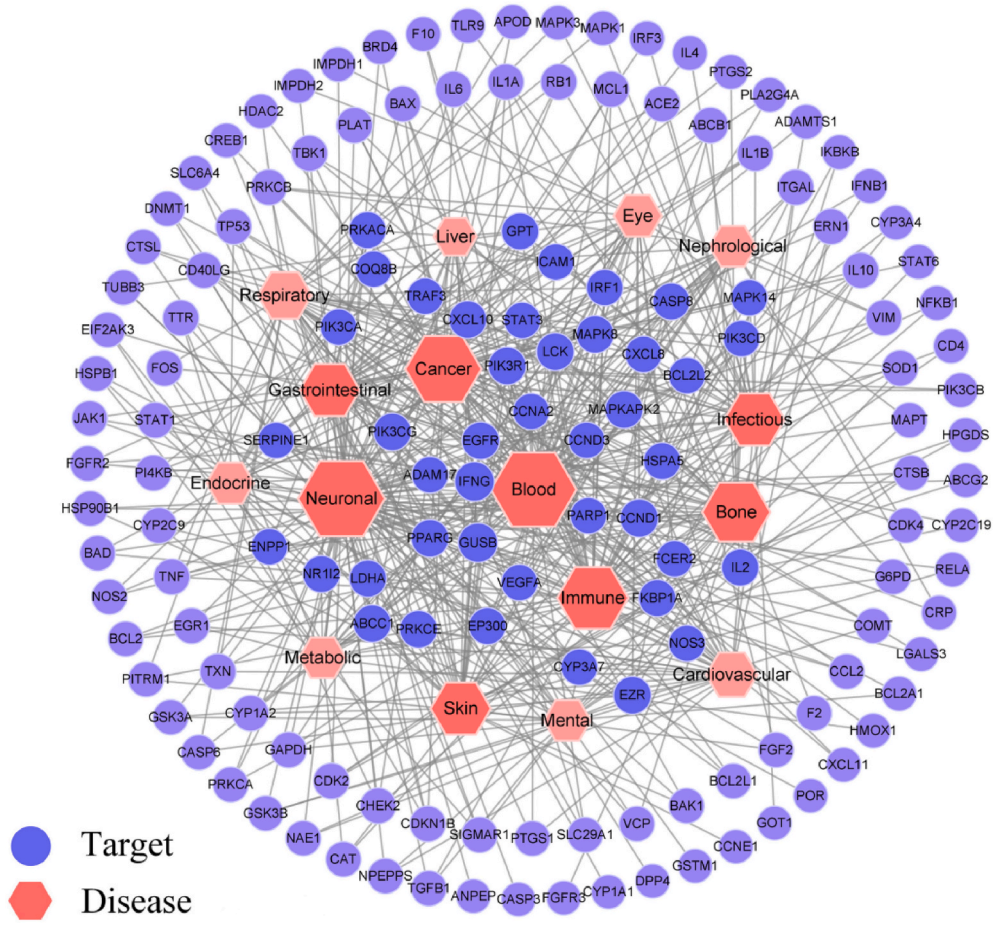

Fig. 7. T-D network of associated targets and significant disease categories. The size and color depth of node were correlated with three network topology parameters (degree-value of connection, betweenness, and closeness).

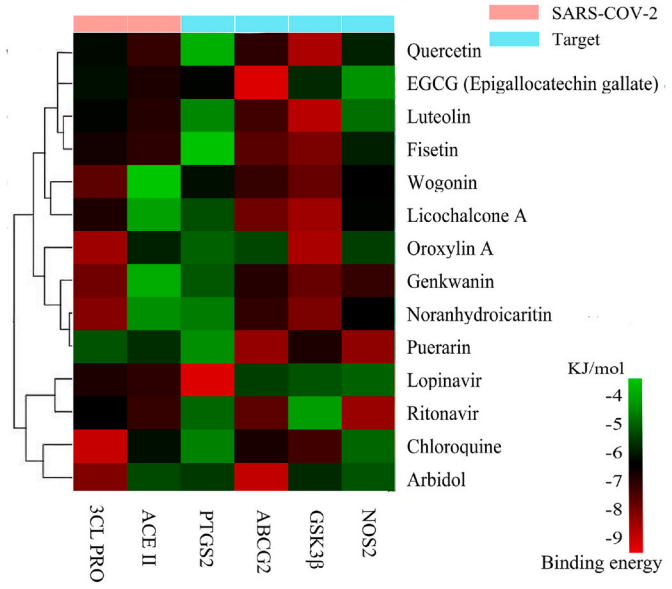

Fig. 8. Molecular docking of flavonoids binding with targets and their binding energy.

and its derivatives inhibit the 3A ion channel of SARS-CoV, thereby reducing viral release [67]. Quercetin (C9) and wogonin (A28) affect plaque formation in different influenza virus strains [68,69]. Similarly, numerous compounds targeting proteins (PTGS, DPP4, and CASP) can inhibit coronavirus replication both before and after viral infection [70]. The regulation of GSK3β and TNF by these compounds affects the phosphorylation of various proteins and the transformation of apoptotic factors, respectively [71,72]. In enrichment analyses, cytosolic DNA-sensing pathway, JAK-AKT signaling pathway, and RIG-I-like receptor signaling pathway showed statistically significant differences compared with the others. These results indicated that flavonoids tended to establish antiviral states through these pathways which recognize SARS-COV-2 and generate immune responses [64,73]. In summary, the broad-spectrum antiviral effect of flavonoids is based on their multi-target synergistic characteristics.

4.3. Immune regulation

Rapid increases in viral factor levels following SARS-CoV-2-infected mammals, resulting in immune dysfunction contained pathogen-associated molecular pattern (PAMP) and damage-associated molecular pattern (DAMP). Overexpression of natural killer cell-mediated cytotoxicity causes fever, diarrhea, and even serious complications such as macrophage activation syndrome (MAS) and multiple organ dysfunction syndrome (MODS). Moreover, 76% of the surveyed patients in Jinyintan Hospital still had symptoms and the antibody level decreased generally after six months of discharge [74]. Therefore, three tasks of restoring the immune response include inhibiting the destruction of the innate immune system, maintaining homeostasis to alleviate abnormal symptoms, and regulating energy metabolism to promote nutrition absorption. Flavonoids have unique and significant advantages for these processes. By regulating the expression of PTGS family targets

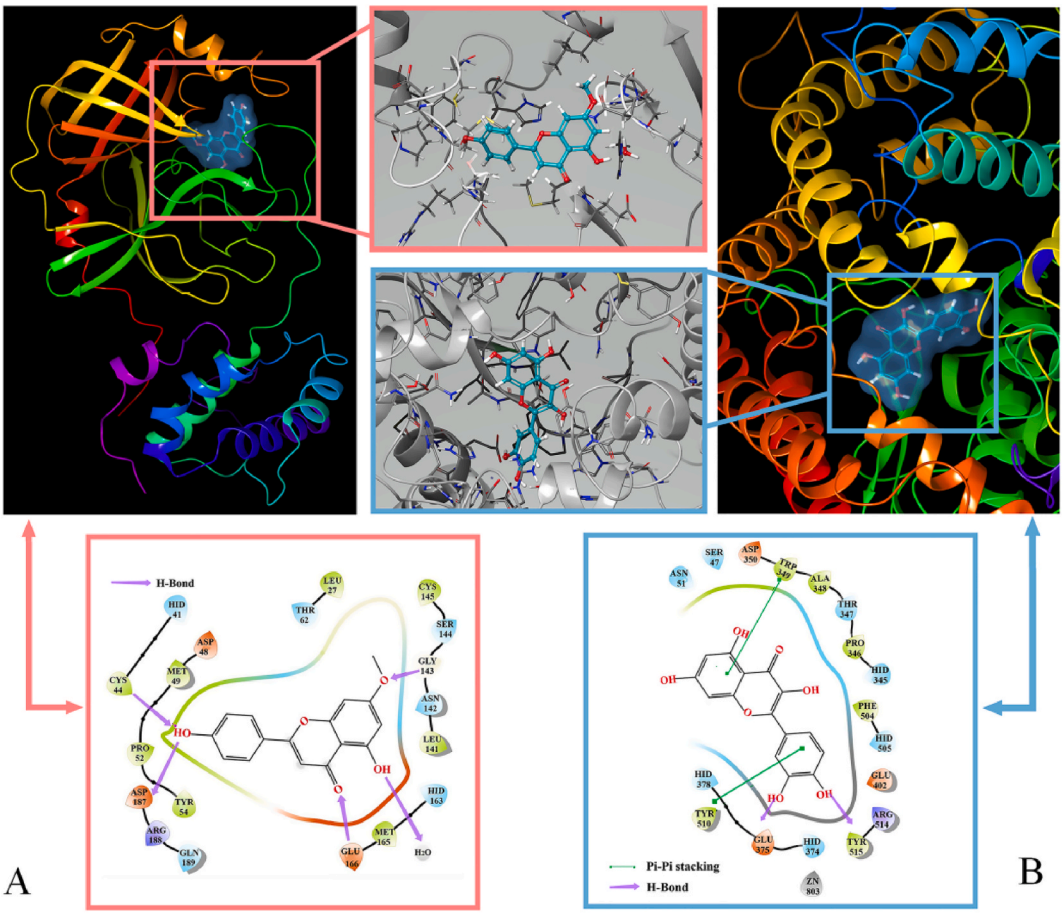

Fig. 9. Combination effects between flavonoids and COVID-19-related proteins. (A) Combination effect between genkwanin with 3CL Pro. (B) Combination effect between quercetin with ACEII.

in the C–T network center, these ingredients affect the biosynthesis of prostaglandins and mediate a series of cellular activities [75,76]. Flavonoids also regulate cell receptors through target genes (DPP4, FOS, MAPK, and others), assisting the normal stress, differentiation and transformation of lymphocytes (monocytes, macrophages, and dendritic cells). For instance, licochalcone A (LCA, G1), a natural chalcone isolated from the root of licorice, plays a pro-apoptotic and anti-proliferative roles in various cancer cell lines [77]. Furthermore, flavonoids are beneficial for stabilizing a number of functional cofactors such as glucosidase, convertase, and NADPH-oxidase, which gradually achieve adaptive immunity [78]. For example, fisetin (C3) triggers the activation of caspase-3 and caspase-8 and the lysis of polymerase (ADP-ribose), contributing to the induction of apoptosis [79]. Noranhydroicaritin (C18) is a typical tyrosinase inhibitor that regulates autophagy [80]. Moreover, flavonoids can remarkably contribute to the field of secretion and transportation of cellular substances. For instance, oroxylin A (A10) and other compounds can interact with solute carrier transporters and ATP-binding cassette transporters (ABC) [81]. Notably, overexpression of ABC family targets results in increased effusion and decreased intracellular accumulation of natural products such as anticancer drugs and other drugs, leading to the failure of anticancer and antibacterial chemotherapy [82]. Therefore, the high frequency of targeting ABC with flavonoids in the C–T network is expected to be a breakthrough in the development of stable therapy for COVID-19. In addition, flavonoids possessed positive feedback for membrane fusion, actin polymerization, and endocytosis to eliminate the adverse effects of metabolic syndrome.

4.4. Repairing tissue injury

Among the multi-directional injuries resulting from SARS-COV-2, the most significant is the respiratory system. Viruses invade the respiratory mucosa through veins, thereby infecting alveolar epithelial cells (AEC) and other non-immune cells. Subsequently, an imbalance between oxidation and antioxidation is an important pathological mechanism of pulmonary fibrosis. Excessive cytokines production by inflammatory storms triggers acute lung injury (ALI). In addition to inhibiting the release of inflammatory cytokines, many flavonoids affect the biological and physical properties of the cell membrane, thereby directly reducing oxidative stress injury in the lung [83]. More compounds indirectly ameliorate pathological changes by regulating targets and signaling pathways. For instance, components treat hypertonic pulmonary edema through the VEGF signaling pathway and inhibit “epithelial–interstitial transformation” to alleviate pulmonary fibrosis through NOS family targets [84]. Furthermore, the combination of the S protein of SARS-COV-2 spike and ACEII receptor on the cell surface promote the secretion of angiotensin (I) and angiotensin (II). This phenomenon concurrently inhibits the secretion of angiotensin (1–7). These pathological changes dysregulate the coagulation cascade, produce thrombosis, compromise blood supply, and damage the blood vessels and myocardial system [85]. Flavonoids, which have good binding energy with ACEII and have a major impact on the renin–angiotensin system, can down-regulate the binding degree between viruses and cells at the molecular level. They also participate in angiogenesis and maintain the integrity of vascular development. For instance, quercetin (C9) significantly inhibited intercellular communication between gap junctions, thereby achieving myocardial protection [86]. Naringenin (B5) inhibits

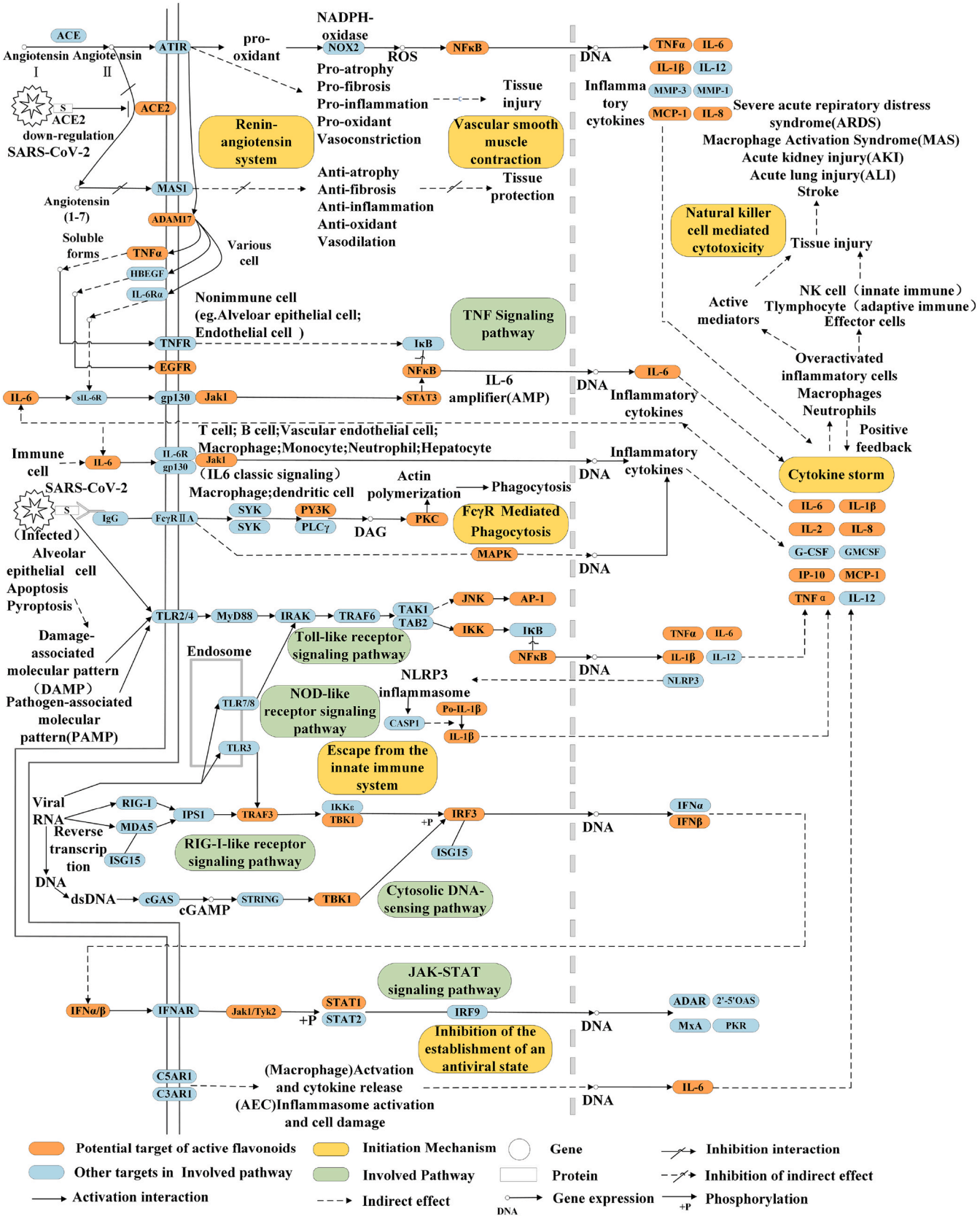

Fig. 10. Underlying mechanisms of flavonoids in the treatment of COVID-19. Ingredients from flavonoids attenuate the symptoms by acting on inflammatory, antiviral, and immune regulation and repairing tissue injury.

VGEF-induced angiogenesis by inhibiting the activity of the double-pore channel [87]. Coagulation assays of many compounds show a prolonged activation time of partial fibrinogen thrombin, and blood coagulation factor, which is also widely reflected in the network, thereby maintaining blood homeostasis and wound healing [88]. As EGCG has neuroprotective effects against nerve injury [89,90], flavonoids are effective options for repairing different histopathological damages in the T–D network, such as stroke and acute kidney injury (AKI).

The physiological activity and structure–activity relationship of flavonoids warrant further investigation. As a result of the difficulty of central ring connection, the lack of carbon double bonds, and other unstable factors, flavones (with the carbon ring double bond), flavonols (with hydroxyl), isoflavones (special benzene ring connection position), and chalcone have a high proportion of active compounds. In addition, on the basis of central epoxidation and the presence of specific hydroxyl groups, a slight change in the structure may affect the molecular dynamics and pharmacokinetics even if the molecular weights are similar. For instance, quercetin (C9), galangin (C12), and kaempferol (C17) have distinct efficacies with different numbers of -OH groups on a ring. Most of the 105 active compounds in our study were hydrophobic flavonoids, and the connected aglycones had planar structures. Common substitutions are hydroxyl, methyl, carbonyl, and glycoside. However, a few of them, such as norkurarinol (B8) and puerarin (E12), have a more complex structures. The glycoside linkage location is relatively fixed and the main linkage types are O-glycoside and C-glycoside. Pharmacokinetic properties of glycosides are associated with their structure. The latter usually has low solubility and difficult hydrolysis due to its stable C-glycoside. Flavonoid glycosides usually contain one or two glycoside residues, most of which are derivatives of the known glycogen structures. This finding indicated that the chemical structure of flavonoids exhibited a certain regularity. After calculating the binding energy value (kJ/mol) and analyzing the docking effect of 64 groups in Table S2, different flavonoids showed conservative or similar binding conformations across the active site of the same receptor, indicating that similar physiological activities of flavonoids were closely related to their highly homologous structures [91,92]. For instance, co-treatment with luteolin (A18) and kaempferol (C17) enhances the inhibitory effect on the expression of drug-metabolizing enzymes [93]. This unique material foundation can reasonably strengthen the compatibility effect.

With the improvement in natural product extraction and separation detection methods, the acquisition and analysis of high-purity functional monomers have become simple and inexpensive. The comprehensive utilization of natural resources such as flavonoids and the promotion of their medicinal value have important scientific and economic significance. Among the 30 active ingredients with degree-value greater than the median, a few compounds in relevant studies have been shown to participate in the prevention and treatment of COVID-19. Studies and applications on the remaining active compounds are limited, indicating that flavonoids have great potential for mining space in drug development. This study confirmed that the protein targets had a significant effect on the regulation of expression and organization distribution, while the active function of targets and the expression of pathways were highly dependent on the flavonoid structure and the pathological mechanism of COVID-19. These results indicated that flavonoids, as an alternative therapeutic or preventive option, could enhance the clinical treatment of infectious diseases. Considering the diversity of flavonoid aglycones and glycosyls, the influence of synergistic pharmacological activities caused by these connection positions and connection methods will be the focus of further research.

5. Conclusion

This study systematically revealed the overall efficacy and intervention characteristics of 105 natural flavonoids and 152 COVID-19 related targets, which integrated compound screening, target prediction, PPI network and MCODE analysis, C–T and T–D network construction, GO function, KEGG pathway enrichment, and molecular docking. The unique synergistic effects of compounds such as flavones and flavonols were also highlighted by their homologous structures and functional groups. Combined with the clinicopathological features, the mechanisms of flavonoids in treating COVID-19 by regulating inflammation, antiviral, immunity, and tissue injury repair were further summarized. Our study provides a new strategy for exploring the unique antiviral activity, biological safety, and multitarget characteristics of natural flavonoids in vivo and in vitro. Thus, this study is beneficial for developing effective and economical innovative drugs or health products for the prevention and treatment of COVID-19.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.compbiomed.2022.105241.

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