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Case Study

Quercetin for COVID-19 and DENGUE co-infection: a potential therapeutic strategy of targeting critical host signal pathways triggered by SARS-CoV-2 and DENV

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Abstract

Background: The clinical consequences of SARS-CoV-2 and DENGUE virus co-infection are not promising. However, their treatment options are currently unavailable. Current studies have shown that quercetin is both resistant to COVID-19 and DENGUE; this study aimed to evaluate the possible functional roles and underlying mechanisms of action of quercetin as a potential molecular candidate against COVID-19 and DENGUE co-infection.
Methods: We used a series of bioinformatics analyses to understand and characterize the biological functions, pharmacological targets and therapeutic mechanisms of quercetin in COVID-19 and DENGUE co-infection.
Results: We revealed the clinical characteristics of COVID-19 and DENGUE, including pathological mechanisms, key inflammatory pathways and possible methods of intervention, 60 overlapping targets related to the co-infection and the drug were identified, the protein–protein interaction (PPI) was constructed and TNFα, CCL-2 and CXCL8 could become potential drug targets. Furthermore, we disclosed the signaling pathways, biological functions and upstream pathway activity of quercetin in COVID-19 and DENGUE. The analysis indicated that quercetin could inhibit cytokines release, alleviate excessive immune responses and eliminate inflammation, through NF-κB, IL-17 and Toll-like receptor signaling pathway.
Conclusions: This study is the first to reveal quercetin as a pharmacological drug for COVID-19 and DENGUE co-infection. COVID-19 and DENGUE co-infection remain a potential threat to the world's public health system. Therefore, we need innovative thinking to provide admissible evidence for quercetin as a potential molecule drug for the treatment of COVID-19 and DENGUE, but the findings have not been verified in actual patients, so further clinical drug trials are needed.

Key words: quercetin; COVID-19; DENGUE; co-infection; computational biology

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Introduction

COVID-19 (Corona Virus Disease-2019), which continues to be endemic worldwide, is on the basis of a novel virus coronavirus strain, SARS-CoV-2, an enveloped, positive-sense, single-stranded RNA, β-coronavirus of the family Coronaviridae [1]; the overproduction of cytokines caused by excessive and uncontrolled inflammation can dramatically contribute to the development of it [2]. In March 2020, the World Health Organization (WHO) publicly avowed COVID-19 a pandemic. Globally, as of 21 December 2020, there have been 75 479 471 confirmed cases of COVID-19, including 1 686 267 deaths, reported to WHO (https://covid19.who.int/). Before the vaccine became widely available in clinical practice, COVID-19 has a serious impact on the world of human medical research, health care and disease prevention and control [3]. Nonetheless, many areas worldwide suffer from endemics that are not of less danger than the current pandemic; for instance, at the same time as the global COVID-19 pandemic, DENGUE, a mosquito-borne, dengue virus infected, which occurs mainly in tropical and subtropical climates, has risen dramatically due to the influence of a combination of factors, such as a growing population, uncontrolled urbanization, mosquito-borne transmission and the spread of the virus with the rapid movement of the global population [4].

Additionally, a growing number of cases have reported bring to notice the alarming probability of two co-epidemics happening simultaneously, with even describes the relationship of them as a 'deadly combination of two' [5]. Unfortunately, in South America and South-East Asian countries such as Brazil, Paraguay, Colombia, Argentina, Mexico, Bolivia, Malaysia, Philippines, Vietnam, Singapore, India, Indonesia, Pakistan, Thailand and Bangladesh, has already been reported the cases of COVID-19 and DENGUE co-infection, almost all these countries both of them are occurring simultaneously [6].

In fact, the clinical consequences of SARS-CoV-2 and DENGUE virus co-infection are not promising. In order to alleviate mortality and address the prospects of epidemic co-infection that may overwhelm health-care systems across multiple countries, it is urgently to conduct more intensive medical research of SARS-CoV-2 and dengue virus (DENV) to elucidate potential drug targets. Some findings have demonstrated a strong association of decreased white blood cells, neutrophils and lymphocytes, with SARS-CoV-2 and DENV co-infection [7]. Therefore, we put forward a new hypothesis from the perspective of host immunity, that is whether we can maintain immune balance by regulating the human immune response and regulating excessive inflammatory response, to explore the key components of the nodal host signaling paths that can be triggered by SARS-CoV-2 and DENGUE at the same time, seeking potential treatment strategies. Excitingly, quercetin has been shown to be a common and major active ingredient in COVID-19 and DENGUE [8–10]. These ingredients could inhibit cytokines release, alleviate excessive immune responses and eliminate inflammation. Not only that, quercetin dose-dependent inhibition of ICAM-1, IL-6, IL-8 and MCP-1 are considered to have anti-inflammatory effects [11],which can be regulated by inhibiting inflammatory factors acting on both COVID-19 and DENGUE infections. In our study, we compared quercetin with DENV and SARS-COV-2 by bioinformatics and obtained 60 common core targets and common critical pathways through WIKI and KEGG enrichment; quercetin is expected to be a potential molecular candidate against COVID-19 and DENGUE.

Materials and methods

Quercetin-related targets

We collected potential targets of quercetin in various databases containing information on drug–gene interactions and the druggable genome or allow us estimated the most probable macromolecular targets of a small molecule, including DrugBank (https://go.drugbank.com/), Comparative Toxicogenomics Database (CTD, http://ctdbase.org/), Drug Gene Interaction Database (DGIdb, https://www.dgidb.org/), SwissTargetPrediction (http://www.swisstargetprediction.ch/) and Pharm Mapper (http://www.lilab-ecust.cn/pharmmapper/). In order to improve the accuracy of analysis, for each database, we choose the top 50 genes as candidate targets.

Identification of COVID-19/DENGUE-associated genes

COVID-19-related targets were gathered from DEGs by analyzing available transcriptomic RNA-seq COVID-19 data (GSE147507 [12], GSE155249 [13] and GSE157103 [14], available at: https://www.ncbi.nlm.nih.gov/geo).We downloaded the attachment information in these three published articles and obtained the DEGs, screening criteria for DEGs were Benjamini–Hochberg adjusted P-values (False discovery rate, FDR) $<1\times10^{-6}$ and $|\log2FC|\geq1$, and genes that meet the inclusion criteria will be used in further analysis (downloaded on 10 March 2021).

In addition, we also screened COVID-19-related human target genes through PubChem (https://pubchem.ncbi.nlm.nih.gov/), CTD (http://ctdbase.org/), COVID-19 DisGeNET data collection (https://www.disgenet.org/covid/diseases/summary/), COVID-19 Host genes database (https://baillielab.net/) and KEGG DISEASE (https://www.genome.jp/kegg/disease/). The dataset of COVID-19 DisGeNET data collection (Version 5) contains 1843 human target genes over 49 410 publications. We finally chose the top 500 genes from the above three online resources as candidate targets (downloaded on 17 March 2021).

Regarding DENGUE-related genes, we acquired DEGs from GSE38246, GSE51808 and GSE84331 datasets (https://www.ncbi.nlm.nih.gov/geo), which were analyzed by GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/); screening criteria for DEGs were FDR $<1\times10^{-6}$ and $|\log2FC|\geq1$. Besides, we selected genes related to DENGUE by searching CTD (http://ctdbase.org/), DisGeNET (https://www.disgenet.org) and GeneCards (https://www.genecards.org/).

The common gene identification between quercetin and COVID-19/DENGUE-related targets was obtained using the Venn diagram tool (http://bioinformatics.psb.ugent.be/webtools/Venn/). The volcano plots of DEGs were performed by ggplot2 in R (version 3.6.1, https://www.r-project.org/).

Protein–protein interaction analysis and network construction

Common genes are inserted in STRING (version 11.0, https://string-db.org/) [15] for generating a PPI network. The PPI results were analyzed and visualized through Cytoscape (version: 3.8.1, https://cytoscape.org/) [16]. The cytoHubba software (http://apps.cytoscape.org/apps/cytohubba) [17] was used to performed network topology analysis.

Gene ontology and pathway enrichment analysis

Gene ontology (GO) terms (version 2018) and all the pathways enrichment (version 2019) were obtained through the web-based

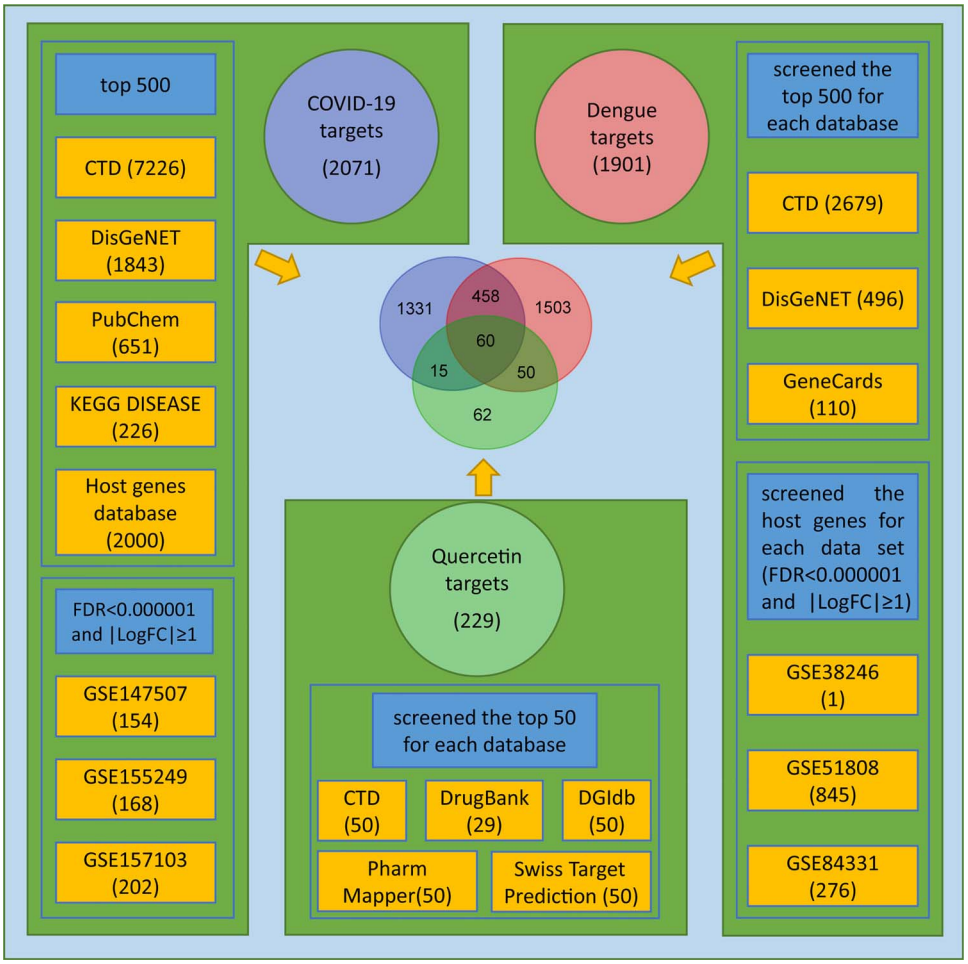

Figure 1. The screening process of obtaining common targets between COVID-19 and dengue. False discovery rate (FDR) using a Benjamini-Hochberg approach (FDR $< 1 \times 10^{-6}$) and $|\log 2FC| \geq 1$. Venn diagram tool (http://bioinformatics.psb.ugent.be/webtools/Venn/). CTD: Comparative Toxicogenomics Database (http://ctdbase.org/) DisGeNET: a platform containing genes associated to human diseases (https://www.disgenet.org/) DGIdb: the Drug Gene Interaction Database (https://www.dgidb.org/) DrugBank: a pharmaceutical knowledge base (https://go.drugbank.com/) PubChem: a collection of accessible chemical information (https://pubchem.ncbi.nlm.nih.gov/) KEGG DISEASE: indicates association of genes to diseases (https://www.genome.jp/kegg/disease/) Host genes database: genes implicated in SARS-CoV2 infection (https://baillielab.net/) GeneCards: The Human Gene Database (https://www.genecards.org/) GEO: Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/).

platform Enrichr (https://maayanlab.cloud/Enrichr/) [18] for the common genes between quercetin and COVID-19/DENGUE.

Inferring upstream pathway activity

Extracting the activity of signal transduction pathways from transcriptome data is important for inferring the mechanism origin of abnormal transcriptome regulation. Therefore, we used SPEED2 (https://speed2.sys-bio.net/) [19] to infer upstream pathway activity from common genes between quercetin and COVID-19/DENGUE. When providing a list of genes, the Web server allows inferences about signaling pathways that may cause these genes to be dysregulated.

Results

Target identification of quercetin, COVID-19 and DENGUE

The screening process of obtaining common targets between COVID-19, DENGUE and quercetin was shown in Figure 1. We obtained 229 targets of quercetin, there are 50, 50, 29, 50, 50 and 50 targets were selected from CTD, DGIdb, DrugBank, Pharm Mapper and Swiss, respectively, after removing duplication, and we finally obtained 187 unique targets.

We finally obtained 2071 unique genes related to COVID-19 after the removal of duplications: 154 (identified from GSE147507), 168 (GSE155249), 202 (GSE157103), 500/7226 (CTD), 500/1843 (DisGeNET), 500/651 (PubChem), 226/226 (KEGG DISEASE) and 500/2000 (COVID-19 Host genes database). In particular, GSE147507 contained several data sets, including four samples of COVID19 patients and uninfected human lung biopsies, and the lung samples were processed in technical replicates (GSM4462413, GSM4462414, GSM4462415 and GSM4462416); moreover, we also selected six samples of human bronchial epithelial cells (NHBE) in our study (GSM4432378, GSM4432379, GSM4432380, GSM4432381, GSM4432382 and GSM4432383). Volcano plots of DEGs were shown in Figure 2A–C, which displayed the dysregulated condition of those genes.

After the removal of duplications, there were 1901 unique genes scratched together related to DENGUE: 1 (GSE38246), 276 (identified from GSE84331), 845 (GSE51808), 500/2679 (CTD), 496 (DisGeNET) and 110 targets (GeneCards). Volcano plots of DEGs between samples of DENV infected patients and control samples were shown in Figure 2D–F.

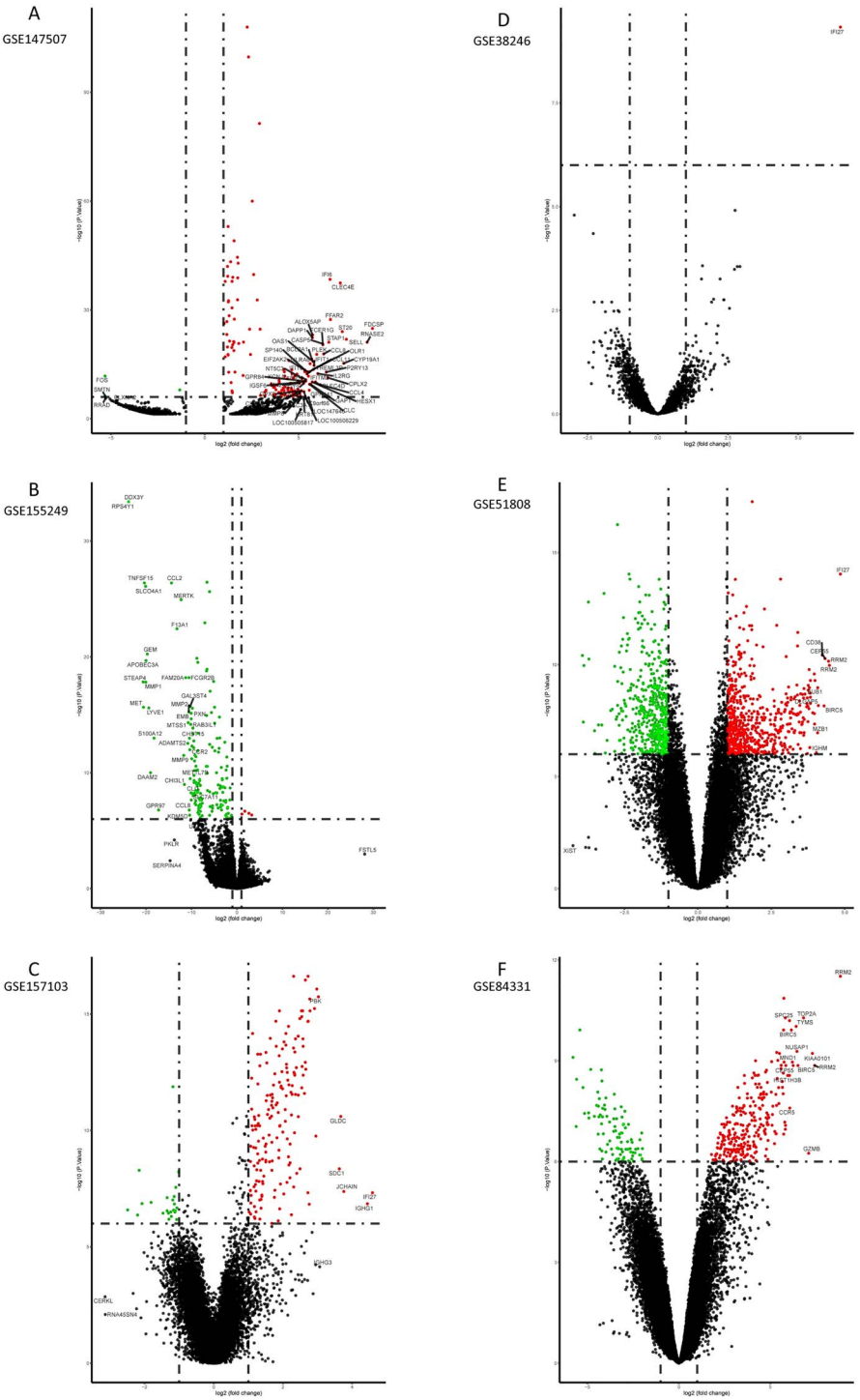

Figure 2. The red dots represent up-regulated genes, green represent down-regulated (FDR, Benjamini-Hochberg adjusted p-values < 0.000001). (**A**) Volcano plots of differentially expressed genes (DEGs) from GSE147507 and PMID32416070. (**B**) DEGs from GSE155249 and PMID33429418, which contained bronchoalveolar lavage fluid samples collected from patients with COVID-19. (**C**) DEGs from GSE157103 and PMID33096026, which contained blood samples from COVID-19 patients. (**D**) 105 peripheral blood mononuclear cell (PBMC) samples collected from 41 children hospitalized with dengue virus (DENV) infection in Nicaragua, and from 8 healthy controls. (**E**) Whole blood samples from 28 dengue patients and 9 healthy control. (**F**) PBMC samples from 7 dengue patients and 5 healthy control.

Finally, we obtained 518 shared targets of COVID-19 and DENGUE, 60 common genes between quercetin and co-infection, which were shown with the online Venn diagram tool. These 60 genes will be used in further host factor interaction network analyses.

Pathway enrichment analysis of COVID-19 and DENGUE

To further studied the biological functions of the common pathways between COVID-19 and DENGUE, KEGG and WIKI were used to perform enrichment analysis. The length of the bar

represents the significance of that specific gene-set or term. In addition, the brighter the color, the more significant that term is. The top 10 were shown in Figure 3A, involving Measles, Toll-like receptor signaling pathway, Influenza A, Hepatitis B signaling pathway (Supplementary Table S1, see Supplementary Data available online at http://bib.oxfordjournals.org/).

Wiki pathway enrichment analysis showed that those targets were meaningfully enriched in multiple pathways, including Type II interferon, NF-kB, IL-6 and IL-10 signaling pathway. The most important 10 pathways were obtained, including Toll-like Receptor, Regulation of toll-like receptor signaling pathways, Allograft Rejection, etc. (Figure 3B and Supplementary Table S2, see Supplementary Data available online at http://bib.oxfordjournals.org/).

Protein–protein interaction and network analysis

We identified 60 shared targets of quercetin related to COVID-19 and DENGUE. The shared targets were loaded in STRING and the documents generated by the analysis were re-introduced into Cytoscape for further network topology analysis and visual representation (Figure 3C and Supplementary Table S3, see Supplementary Data available online at http://bib.oxfordjournals.org/). The PPI network contained 904 edges and with an average node degree of 30.1, its clustering coefficient was 0.758 (PPI enrichment P-value $<$ 1.0e–16). Among those common targets, TP53, AKT1, EGFR, VEGFA, MAPK1, CASP3, MAPK3, JUN, IL6, TNF, TLR4, PTGS2, CXCL8, IL1β, CCL2 and NF-κB had higher degree value.

Gene annotation of common targets

To study the function of 60 shared targets between COVID-19, DENGUE and quercetin, reveal the potential mechanism behind the drug, the Enrichr tool was used to perform the analysis of gene set enrichment including GO terms and signal pathways. With the GO enrichment analysis, we studied the biological process and molecular functions of the common targets and ranked the top 10 GO terms, respectively; the longer the bar, the higher the ranking, the more vital the role (Figure 3D and E and Supplementary Tables S4 and S5, see Supplementary Data available online at http://bib.oxfordjournals.org/). Through the ranking of GO BP, it was shown that regulation of calcidiol 1-monooxygenase activity, positive regulation of fever generation, positive regulation of oxidative stress-induced cell death, and cell response to cadmium ion were significant. And with the analysis of GO MF, 1-phosphatidylinositol-4-phosphate 3-kinase activity, RNA polymerase II basal transcription factor binding and histone threonine kinase activity took an important role in the interaction.

The pathway enrichment study was performed with KEGG and WikiPathways, and the rankings of pathway terms were obtained (Figure 3F and G and Supplementary Tables S6 and S7, see Supplementary Data available online at http://bib.oxfordjournals.org/). From the result of KEGG, the top 10 important pathways were shown, including IL-17, AGR-RAGE signaling pathway in diabetic complications, Hepatitis B and TNF signaling pathway. For WikiPathways, resistin as a regulator of inflammation, photodynamic therapy-induced AP-1 survival signaling, NF-kB survival signaling and aryl hydrocarbon receptor were vital.

Upstream pathway activity

SPEED2 offers an easy method to score signaling activity for sets of dysregulated genes gained from transcriptome analysis. To infer the upstream pathway activity from common targets, we scored the genes. The colors implied adjusted P-value, and the ranked lists about activity were determined by the absolute P-value; the brighter the color, the higher the ranking, which shown IL-1 played a vital role. Moreover, we evaluated the consistently up- and down-regulated genes after pathway perturbation, when the adjusted P-value $>$0, the corresponding genes were up-regulated, thus, IL-1, TNF-α and TLR signaling pathways were up-regulated and the Wnt, Hypoxia signaling pathways were down-regulated (Figure 3H).

Discussion

COVID-19 and DENGUE affect human health and social development adversely. In our study, we investigated whether quercetin has a potentially protective effect on the DENV and SARS-COV-2 co-infection; to clarify the question, we compared quercetin with DENV and SARS-COV-2 by integrated bioinformatics, so we obtained 60 common core targets and common pathways through WIKI and KEGG pathways, which implied that taking advantage of quercetin would be a potential therapeutic strategy.

Performing the analysis from the perspective of host factors

To find the appropriate treatment, relevant studies are developing from antivirus and host. Direct-acting antiviral agents (DAAs) have several inherent limitations, including a narrow antiviral spectrum and susceptibility to drug resistance; the antiviral drugs on the market are rarely used to treat emerging viruses. Besides, the other limitation is the genetic barrier to DAAs resistance, making the virus refractory to the treatment of DAAs. In comparison, host targeting antivirals have non-negligible advantages, which are demonstrated to manifest broad-spectrum antiviral activities and less prone to therapy resistance [20, 21]. Therefore, in this study, we studied the potential mechanisms of quercetin in the treatment of co-infection from the perspective of the host.

The function of the common DEGs between the co-infection and quercetin

In our study, it was indicated that the common targets about the SARS-COV-2, the DENV and the quercetin were TP53, AKT1, EGFR, VEGFA, MAPK1, CASP3, MAPK3, JUN, IL6, TNF, TLR4, PTGS2, CXCL8, IL1β, CCL2 NF-κB and so on. Combing with previous studies, the following targets were likely vital for the mechanism of treatment: TNF, NF-κB, IL1β, IL6, CCL-2 and CXCL8.

Quercetin has the function of scavenging free radicals and anti-allergy, stimulating the immune system, antiviral, inhibiting histamine release and reducing proinflammatory cytokines [22]. Quercetin can inhibit the secretion of TNFα, which avoid trigger different pathways, for example NF-κB [23]; subsequently, the disruption affects the production of IL1β, TNFα and IL6 [24]. In addition, quercetin significantly reduces the expression of CCL-2, which is a critical chemokine that regulates the monocytes and macrophages in migration and infiltration during the process of inflammation [25–27]. Quercetin inhibits CXCL8 inducing the neutrophils chemoattraction in a concentration-dependent manner [28] and also decreases the activity and recruitment of RELA [29, 30]. All mechanisms mentioned contribute to the anti-inflammatory and immunomodulating properties of quercetin, and the targets mentioned above are important for the infection of SARS-COV-2 and DENV.

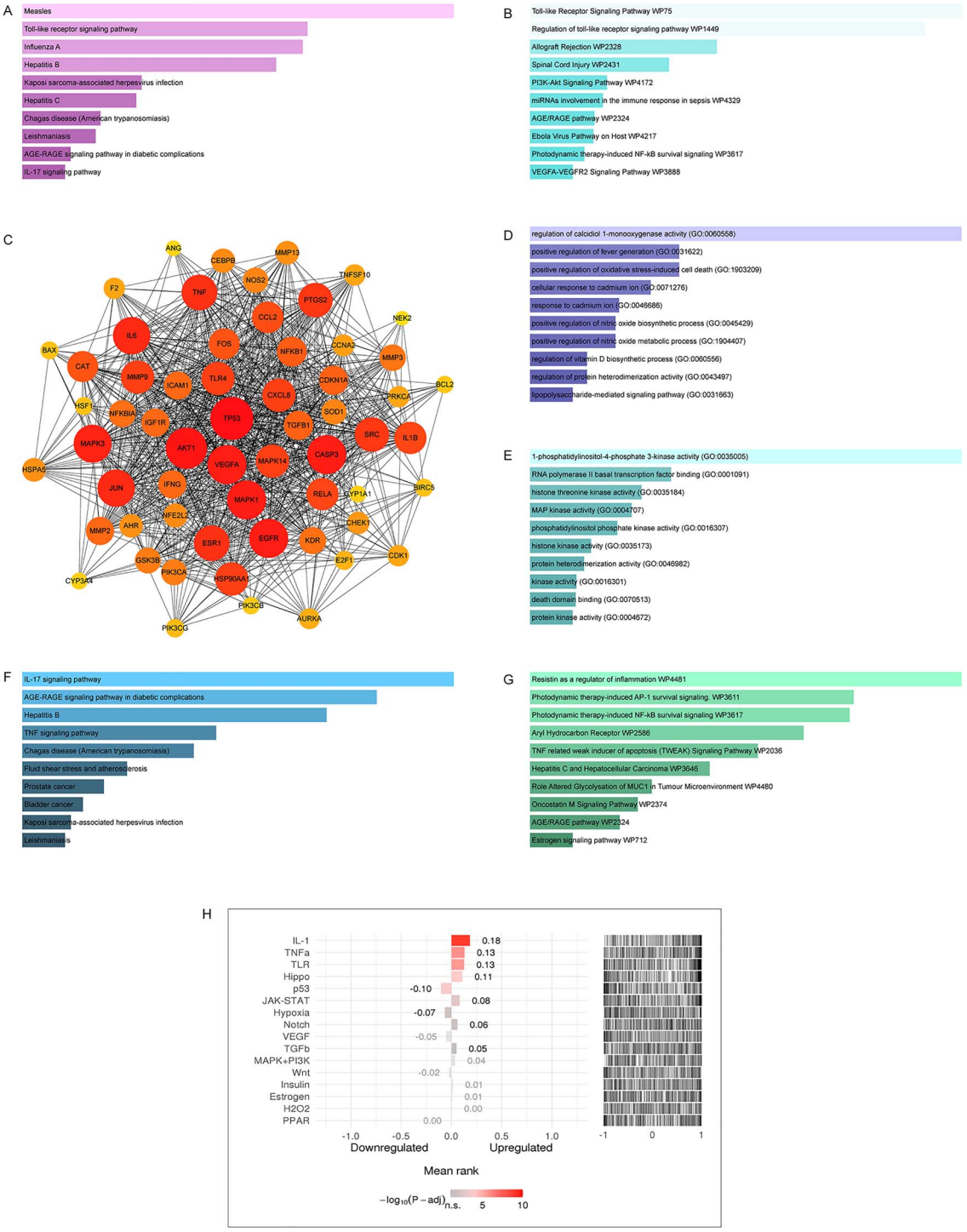

Figure 3. (**A**) Pathway analysis of COVID-19 and DENGUE identification through KEGG. The results of the pathway terms were sorted by the combined score. (**B**) Pathway analysis of COVID-19 and DENGUE identification through WIKI. The results of the pathway terms were sorted by the combined score. (**C**) Protein-protein interactions (PPIs) network for identified common differentially expressed genes that are shared by two diseases (COVID-19 and DENGUE) and quercetin. Nodes in orange color indicate common host factor genes and edges specify the interconnection in the middle of two genes. The analyzed network held 60 nodes and 904 edges. (**D**) Biological process-related GO terms identification result according to combined score. The higher the enrichment score, the higher number of genes are involved in a certain ontology. (**E**) Molecular function-related GO terms identification result according to combined score. The higher the enrichment score, the higher number of genes are involved in a certain ontology. (**F**) Pathway analysis result of quercetin and COVID-19/DENGUE identification through KEGG. The results of the pathway terms were sorted by the combined score. (**G**) Pathway analysis result of quercetin and COVID-19/DENGUE identification through WIKI. The results of the pathway terms were sorted by the combined score. (**H**) Pathway activity ranking (adjusted p-value < 0.05). The colors implied adjusted P-value, and the brighter the color, the higher the ranking.

Table 1. Side effects of Quercetin

No.	Quercetin's side effects	references
1	Quercetin was considered genetically toxic in early research in the 1970s.	MHarwood [66]
2	Quercetin shows mutagenicity *in vitro* experiments.	
3	There are slight negative effects on fetal growth, such as growth retardation, developmental defects and decreased vitality.	Batiha, G. E. [67]
4	Quercetin is banned from use with fluoroquinolone antibiotics because of its competitive binding to bacterial DNA gyrase.	
5	Quercetin resulted in a small increase in the prevalence of malignant tumors to the young offspring of mice lacking DNA repair *in vitro* experiments.	Vanhees K [68]
6	High-dose IV quercetin in patients with compromised health can lead to Nephrotoxicity.	Bischoff S.C [69]
7	Co-administration of high quercetin doses with digoxin will produce toxic effects.	Wang Y.H [70]
8	Quercetin is thought to increase serum concentration of drugs metabolized by CYP3A4 (e.g. diltiazem).	Choi J.S [71]

Patients infected with SARS-COV-2 had high amounts of pro-inflammatory cytokines [31]. Among them, IL-1β plays a vital role in the inflammatory response of early infections; IL-8 is related to overall inflammation [32]. And NF-kB is the nuclear effector of many pathways, such as those emanated by the TNF and TLR [33]. RELA, as a member of the NF-kB family, is a widely expressed powerfully transcriptional activator that activates the expression of several inflammatory and immune-response genes [33, 34]. In addition, TNF can increase neutrophil chemotaxis and the expression of CXCL8, especially for severe patients [35, 36]. The other chemokines and pro-inflammatory cytokines, for example CCL2, all contribute to cytokine storms [37], which will destroy the immune system and eventually cause fatal damage.

After the DENV infection, the level of IL-1β, TNF, CCL2, CXCL8 and IL-6 would be upregulated, which develop the pro-inflammatory activities and recruit other immune cells to the infected site, further enhance inflammation [38–40]. For example, TNF-α can be released into the plasma after the activation of platelet by DENV; meanwhile, the activated platelets interacting with monocytes can induce monocytes to secrete CXCL8, IL-10 and IL-6 [41, 42]. DENV induces platelet synthesizing IL-1β [43], increasing vascular permeability, especially when it binds to TNFα [44]; besides, the permeability can be affected by CCL2 which is able to disrupt the tight connections of endothelial cells in blood vessels [45]; eventually, the exaggerated vascular permeability will induce the occurrence of DENGUE hemorrhagic fever [23].

Those important targets can trigger the correlation pathways resulting in the development of the disease. Interestingly, both targets and pathways of SARS-COV-2 and DENV can be regulated by quercetin.

Enrichment analysis of the collective pathways in the interaction

Through the WIKI and KEGG pathways analysis, combing with relevant literature and research, we found that the major signaling pathways were Toll-like receptor signaling pathway, NF-kB signaling pathway, TNF signaling pathway and IL-17 signaling pathway.

In the COVID-19 lungs, TLR, the upstream protein of NF-κB pathways, is upregulated [46], which can detect the viral RNAs, after the viral spike protein binding to the host cells by the entry receptor ACE2 [47]. Similarly, the viral components of DENV can be recognized by TLR as well [48]. And quercetin can significantly reduce serum levels of TNF-α and suppress the HMGB1-TLRs-NF-κB signaling pathway [49].

Thus, the detecting pathways of the infection can be suppressed; moreover, quercetin has several biological properties, among them, the anti-inflammatory function is significant, which can regulate the immunological response by affecting the relevant pathways.

Specifically, up-regulated genes in patients with severe or critical COVID-19 belong to the NF-κB pathway, promoting the production of pro-inflammatory cytokines and chemokines, for example TNF [50]. The binding and shedding of the entry receptor for the SARS-COV-19, ACE2, is accompanied by the production of TNF-α and TNF-α-converting enzyme [51]; TNF-α not only is associated with the severity of COVID-19 [52] but also induces the production of XAF1, which was reported to promote DENGUE virus-induced apoptosis [53, 54].

When it comes to DENGUE, the NF-κB pathway is important as well. And the secretion of TNF can activate the NF-κB pathway in a paracrine fashion [55], so that inducts the interferon signaling, inducing antiviral response [56]. Furthermore, through a DENGUE hemorrhage mouse model, it was reported that TNF-α caused the death of the endothelial cell and induced hemorrhage [57].

IL-17 signaling pathway also plays a significant role in COVID-19, and it can lead to the induction of chemokine via activates some pathways, finally causes lung damage [58]; in addition, it not only can reduce infected cells' apoptosis, leading to the persistence of the virus, but seem to increase the virus' virulence to increase their replication [59, 60]. For patients with severe or non-severe DENGUE, the increased level of IL-17 in serum could be detected; the cytokine has the ability to regulate the inflammatory and anti-inflammatory molecules that are indispensable for the pathogenesis of the DENGUE [61].

Some relevant studies have shown that quercetin has good anti-inflammatory effects, immunomodulatory activities, antioxidant, vasodilatory and other biological properties [62]. For the co-infection of SARS-COV-2 and DENV, firstly, quercetin has a wide range of antiviral properties and can interfere with the virulence of pathogens with multiple steps [63]. Secondly, quercetin, an anti-inflammatory component, is able to decrease the inflammatory response via dose-dependently inhibiting the NF-κB signaling pathway and effectively reduces the level of inflammatory factors TNF-α, IL-6 and IL-17 [62, 64, 65].

In summary, both SARS-COV-2 and DENV infection can damage lung tissue and even cause death by inducing overactive inflammatory responses. We used the bioinformatics method in

this work to identify the 60 core targets and several critical pathways of the DENV, SARS-COV-2 and quercetin. Combining it with the results of previous studies, we inferred that quercetin may treat the co-infection mainly by regulating the targets in the IL-17, TNF, NF-κB and TLR signaling pathways, subsequently regulating immunological response. Our study implied that quercetin is worthy of attention in treating the co-infection, but there are some limitations, which must be tested further; in other words, further *in vitro* and *in vivo* experimental validation is needed to support our research.

Quercetin's side effects

Our study shows that quercetin can be one of the potential candidates for COVID-19 and dengue co-infection, but we must point out the insuperable fact that quercetin has certain side effects and drug interactions [66–71] (Table 1). When it is used as a treatment, some of the negative effects of quercetin must be treated with caution.

Limitations

There are some limitations to this study. First, the experiment involved plenty of data, and the formats of different datasets were not completely consistent, so massive pre-processing and standardization were required. But different studies use different methods to measure genomic data, so there is no complete unity. Secondly, the selection of datasets is subjective to some extent, and the imbalance of class distribution in datasets is unavoidable. Even so, the researchers have chosen the most closely related data sets for the disease as the basis for the experiments, based on clinical reality. Finally, this study focuses on the feasibility of quercetin in the treatment of COVID-19 and DENGUE co-infection, but the metabolic absorption mechanism of quercetin in the human body has not been clarified.

Conclusion

Taken together, the bioinformatics and computational findings highlight immunity modulation, anti-inflammation and antivirus as key pathways of quercetin treatment in COVID-19 and DENGUE co-infection. In this study, the potential host factors of Quercetin against COVID-19 and DENGUE were identified; the therapeutic mechanisms were preliminarily revealed, which may be validated in a preclinical study. Although there were limitations, the findings provided a possible approach for the treatment of the co-infection, paving the way for further clinical trials.

Key Points

- Co-infection of SARS-CoV-2 and DENV is a potential public health event around the world, but there is a lack of effective treatment drugs.
- Quercetin has a wide range of anti-inflammatory and antiviral pharmacological effects; it is becoming a common and major active ingredient in the treatment of COVID-19 and DENGUE.
- Our analysis indicated that quercetin has 60 gene targets that overlap with COVID-19 and DENGUE, so it may become a potential therapeutic drug for SARS-CoV-2 and DENV co-infections by regulating the key signaling pathways of host inflammation and immunity.

Supplementary data

Supplementary data are available online at https://academic.oup.com/bib.

Authors' contributions

W.J.Z. conceived and designed the study, plotted the figures based on network pharmacology, using online databases. H.W. conducted data analysis and performed literature searches. T.W. carried out literature searches and studies of the background of the disease. S.F.Z. and X.H.L. reviewed and revised the manuscript.

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Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request. Supplementary data are available online at https://academic.oup.com/bib.

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