Exploring the Mechanisms of Lian Hua Qing Wen Capsule against COVID-19 by Network Pharmacology and Molecular Docking Approach

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Research

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Abstract

Background The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19) disease has led to a wide-spread global pandemic. There is no specific antiviral drug proven effective for the treatment of patients with COVID-19 at present. Combination of western and traditional Chinese medicine (TCM) is recommended, and Lian Hua Qing Wen (LHQW) capsule is a basic prescription and widely used to treat COVID-19 in China. However, the mechanisms of LHQW capsule treating COVID-19 are not clear. The aim of the study is to explore the mechanisms of LHQW capsule treating COVID-19 based on network pharmacy and molecular docking approach.

Methods The active compounds and targets of LHQW capsule were obtained from traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP). COVID-19 related target genes were obtained from GeneCards database and OMIM database. Protein–protein interaction (PPI) networks of LHQW capsule targets and COVID-19-related genes were visualized and merged to identify the candidate targets for LHQW capsule treating COVID-19. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were also performed. The hub genes involved in the gene-related pathways were screened and their corresponding compounds were used for in vitro validation of molecular docking predictions.

Results A total of 185 active compounds of LHQW capsule were screened out, and 263 targets were predicted. Third hundred and fifty-two COVID-19 related target genes were obtained from GeneCards database and OMIM database. GO functional enrichment analysis showed that the biological processes of LHQW capsule treating COVID-19 were closely linked with the regulation of inflammation, immunity, cytokines production, vascular permeability, oxidative stress and apoptosis. KEGG enrichment analysis revealed that the pathways of LHQW capsule treating COVID-19 were significantly enriched in AGE–RAGE signaling pathway in diabetic complications, Kaposi sarcoma–associated herpesvirus infection, TNF, IL–17, and Toll–like receptor (TLR) signaling pathway. The hub targets genes in the gene-related pathways analysis of LHQW capsule treating COVID-19 included MAPK1, MAPK3, RELA, IL-6 and CASP8, which closely associated with inflammation, cytokines storm and apoptosis. Finally, molecular docking showed that top 5 compounds of LHQW capsule also had good binding activities to the important targets in COVID-19.

Conclusions The mechanisms of LHQW capsule treating COVID-19 may involve in inhibiting inflammatory response, cytokine storm and virus infection, and regulating immune reactions, apoptosis and endothelial barrier.

Background

The novel coronavirus 2019 (COVID-19), also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belongs to the genus β, with envelope, round or elliptic and often pleomorphic form, and 60–140 nm in diameter [1]. The ongoing pandemic of SARS-CoV-2 infections has led to more than 4 900...
647 cases and 320,107 deaths globally as of May 20, 2020. This pandemic is still ongoing and mortality is increasing, especially in North America and Europe. Therefore, it is very urgent to find new preventive and therapeutic agents as soon as possible. However, there are no specific antiviral drugs or vaccines against COVID-19 at present [2]. According to traditional Chinese medicine (TCM) science, COVID-19 was considered as “plague” and TCM plays important auxiliary roles in the treatment of COVID-19 [3, 4].

Lian Hua Qing Wen (LHQW) capsule was prescribed based on etiology and symptoms of COVID-19 and has been applied widely in China for treating COVID-19, which has shown satisfactory curative effects [5, 6]. Moreover, LHQW capsule has been listed in many countries for the prevention and treatment of COVID-19. LHQW capsule consists of 13 Chinese medicine extracts and has the effects of clearing away the plague and detoxify, promoting the dispersing function of the lung and discharging heat. The herbs in LHQW capsule include Forsythiae Fructus (FF), Lonicerae Japonicae Flos (LJF), Ephedra Herba (EH), Amygdalus Communis Vas (ACV), Gypsum Fibrosum (GF), Isatidis Radix (IR), Fortunes Bossfern Rhizome (FBR), Houttuyniae Herba (HH), Pogostemon Cablin (Blanco) Benth (PCB), Radix Rhei Et Rhizome (RRER), Rhodiola Rosea L (RRL), Menthae Herba (MH) and licorice (LI). However, the mechanisms of QFPDD treating COVID-19 are not clear. Network pharmacology and molecular docking approach are widely used to clarify the effects of compounds and potential mechanisms of compound-target-disease at the molecular level [7, 8].

In the present study, we performed bioinformatics investigation and molecular docking approach to elucidate an “ingredient-target-pathway” network of LHQW capsule treating COVID-19. The active compounds of LHQW capsule and their targets were firstly identified using the pharmacology analysis platform of the Chinese medicine system (TCMSP). Then, COVID-19 related target genes were obtained from GeneCards database and OMIM database. The mechanisms of LHQW capsule treating COVID-19 were explored by gene ontology (GO) and Kyoto Encyclopedia of gene and genomes (KEGG) pathway enrichment analysis. Molecular docking was used to further verify the mechanisms of herbs intervention in COVID-19. Based on TCM network pharmacology and molecular docking approaches, this study clarified the mechanisms of LHQW capsule treating COVID-19 at molecular and cellular levels.

**Methods**

The technical strategy of this research is shown in Fig. 1.

**Screening the bioactive ingredients**

The candidate ingredients of LHQW capsule were obtained from Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform [9] (TCMSP, http://tcmspw.com/tcmsp.php) and screened with the criteria of oral bioavailability (OB) ≥ 30% and drug-likeness ≥ 0.18 [10]. In total, 230 eligible compounds were obtained, 23 in FF, 23 in LJF, 22 in EH, 19 in ACV, 39 in IR, 28 in FBR, 7 in HH, 11 in PCB, 16 in RRER, 10 in MH, 91 in LI. Eventually, a total of 244 candidate compounds were obtained after removing the duplications.
Obtaining the Potential Targets of LHQW capsule

The potential targets of LHQW capsule were obtained from TCMSP (http://tcmspw.com/tcmsp.php) [9]. Four thousand targets were collected, 450 in FF, 403 in LJF, 406 in EH, 183 in ACV, 254 in IR, 104 in FBR, 204 in HH, 219 in PCB, 88 in RRER, 165 in MH, 1524 in LI. After deleting duplicates, there were 263 targets in total. The 244 candidate compounds were imported into the DrugBank database (https://www.drugbank.ca/) [11] and 185 compounds were obtained after removing 59 compounds which did not link to any targets.

Collecting COVID-19 related targets

The COVID-19 related targets genes were collected from GeneCards database (https://www.genecards.org) [12] and OMIM database (https://omim.org) [13]. The key word “novel coronavirus 19” was used to obtain COVID-19-related genes. There were altogether 352 COVID-19-related genes received.

PPI Network Construction

The compound-target networks were established to explore the complex interactions between the compounds of QFPDD and the targets of COVID-19 through using STRING and Cytoscape 3.7.2 (https://cytoscape.org/) [14]. In the network, nodes separately represented compounds or targets, and edges showed the interactions of the inter-node. The conditions of topological analysis included Betweenness Centrality (BC), Closeness Centrality (CC), Neighborhood Connectivity (NC), Number of Directed Edges (NDE), (Topological Coefficient (TC).

Bioinformatic Analysis

Database for Annotation, Visualization and Integrated Discovery (DAVID, https://david.ncifcrf.gov, v6.8) [15] was used to perform GO analysis including biological process, cellular component, and molecular functions. Functional categories were enriched within genes (FDR < 0.05) and the top 20 GO functional categories were selected. DAVID database was also used to carry out KEGG pathway analysis [15]. Pathways that had significant changes of FDR < 0.05 were identified for further analysis and the top 20 pathways were selected. The gene-pathway network was constructed to screen the key target genes of QFPDD treating COVID-19.

Molecular docking

PubChem and PDB were used to find the chemical and conformational information of the relevant proteins and small-molecule compounds [16, 17]. The AutoTools software was used to remove the
redundant protein chains, ligands and water molecules with hydrogenation before running docking experiments [18]. The AutoGrid software was used to calculate the energy lattice points with the grid box coordinates of 15 × 15 × 15 [18]. AutoDock Vina was used to simulate the docking condition between proteins and small molecules [18]. The Schrodinger software was used to analyse the preferential conformation and map the simulation.

Results

Compound-Target Network of LHQW capsule

Table 1 identified 185 candidate compounds in LHQW capsule. Figure 2 showed the compound-target network of LHQW capsule by using the screened compounds and their targets. The networks contained 448 nods (185 compounds and 263 targets in LHQW capsule and 4000 edges which indicated the compound-target interactions. One hundred and eighty-five candidate compounds had average degrees of 17.85, indicating that most compounds of LHQW capsule influenced multiple targets. Quercetin, kaempferol, luteolin, naringenin, and beta-sitosterol acted on 140, 55, 54, 34, 28 targets, respectively. And the OB of quercetin, kaempferol, luteolin, naringenin, and beta-sitosterol was 46.43, 41.88, 36.16, 59.29, 36.91%, respectively. Thus, these five top compounds may play important roles in LHQW capsule treating COVID-19.
Table 1
The final selected compounds in LHQW capsule for analysis.

| Molecule ID  | Molecule name                                                                                   | OB    | DL    | Source       |
|--------------|-------------------------------------------------------------------------------------------------|-------|-------|--------------|
| MOL001689    | acacetin                                                                                        | 34.97 | 0.24  | IR, MH       |
| MOL002322    | isovitexin                                                                                      | 31.29 | 0.72  | IR           |
| MOL001721    | Isaindigodione                                                                                  | 60.12 | 0.41  | IR           |
| MOL001722    | 2-O-beta-D-glucopyranosyl-2H-1,4-benzoxazin-3(4H)-one                                           | 43.62 | 0.31  | IR           |
| MOL001726    | pinoresinol-4-O-beta-D-apiosyl-beta-D-glucopyranoside                                           | 36.45 | 0.51  | IR           |
| MOL001728    | 3-[ 2' -(5'-hydroxymethyl)furyl ]-1 (2H) - isoquinolinone-7-O-BETA-D-glucoside_qt               | 51.74 | 0.18  | IR           |
| MOL001733    | EUPATORIN                                                                                       | 30.23 | 0.37  | IR           |
| MOL001734    | 3-[[2R,3R,5R,6S)-3,5-dihydroxy-6-(1H-indol-3-yloxy)-4-oxooxan-2-yl][methoxy]-3-oxoproanoic acid | 85.87 | 0.47  | IR           |
| MOL001735    | Dinatin                                                                                        | 30.97 | 0.27  | IR           |
| MOL001736    | (-)-taxifolin                                                                                   | 60.51 | 0.27  | IR           |
| MOL001749    | ZINC03860434                                                                                    | 43.59 | 0.35  | IR           |
| MOL001750    | glucobrassicin                                                                                  | 66.02 | 0.48  | IR           |
| MOL001755    | 24-Ethylcholest-4-en-3-one                                                                       | 36.08 | 0.76  | IR, EH       |
| MOL001756    | quindoline                                                                                      | 33.17 | 0.22  | IR           |

OB, oral bioavailability; DL, drug-likeness; IR, Isatidis Radix; MH, Menthae Herba; RRER, Radix Rhei Et Rhizome; LI, licorice; PCB, Pogostemon Cablin (Blanco) Benth; FBR, Fortunes Bossfern Rhizome; LJF, Lonicerae Japonicae Flos; ACV, Amygdalus Communis Vas; FF, Forsythiae Fructus; EH, Ephedra Herba; HH, Houttuyniae Herba.
| Molecule ID   | Molecule name                                                                 | OB     | DL  | Source |
|--------------|------------------------------------------------------------------------------|--------|-----|--------|
| MOL001767    | hydroxyindirubin                                                             | 63.37  | 0.30| IR     |
| MOL001769    | beta-sitosterol dodecanate                                                   | 34.57  | 0.57| IR     |
| MOL001771    | poriferast-5-en-3beta-ol                                                     | 36.91  | 0.75| IR, EH |
| MOL001774    | Ineketone                                                                    | 37.14  | 0.30| IR     |
| MOL001779    | Sinoacutine                                                                  | 49.11  | 0.46| IR     |
| MOL001781    | Indigo                                                                       | 38.20  | 0.26| IR     |
| MOL001782    | (2Z)-2-(2-oxoindolin-3-ylidene)indolin-3-one                                 | 48.40  | 0.26| IR     |
| MOL001783    | 2-(9-((3-methyl-2-oxopent-3-en-1-yloxy)-2-oxo-1,2,8,9-tetrahydrofuro[2,3-h]quinolin-8-yl)propan-2-yl acetate | 64.00  | 0.57| IR     |
| MOL001790    | Linarin                                                                      | 39.84  | 0.71| IR     |
| MOL001792    | DFV                                                                          | 32.76  | 0.18| IR     |
| MOL001793    | (E)-2-[(3-indole)cyanomet hylene]-3-indolinone                               | 54.59  | 0.32| IR     |
| MOL001798    | neohesperidin_qt                                                             | 71.17  | 0.27| IR     |
| MOL001800    | rosasterol                                                                   | 35.87  | 0.75| IR     |
| MOL001803    | Sinensetin                                                                   | 50.56  | 0.45| IR     |
| MOL001804    | Stigmasta-5,22-diene-3beta,7alpha-diol                                       | 43.04  | 0.82| IR     |
| MOL001806    | Stigmasta-5,22-diene-3beta,7beta-diol                                        | 42.56  | 0.83| IR     |

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| Molecule ID    | Molecule name                                                                 | OB    | DL  | Source                   |
|---------------|-------------------------------------------------------------------------------|-------|-----|--------------------------|
| MOL001810     | 6-(3-oxoindolin-2-ylidene)indolo[2,1-b]quinazolin-12-one                      | 45.28 | 0.89| IR                       |
| MOL001814     | (E)-3-(3,5-dimethoxy-4-hydroxybenzylidene)-2-indolinone                       | 57.18 | 0.25| IR                       |
| MOL001820     | (E)-3-(3,5-dimethoxy-4-hydroxybenzylidene)-2-indolinone                       | 65.17 | 0.25| IR                       |
| MOL001828     | 3-[(3,5-dimethoxy-4-oxo-1-cyclohexa-2,5-dienylidene)methyl]-2,4-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one | 51.84 | 0.56| IR                       |
| MOL001833     | Glucobrassicin-1-Sulfonate_qt                                                | 42.52 | 0.24| IR                       |
| MOL000358     | beta-sitosterol                                                               | 36.91 | 0.75| IR, EH, RRER, LJF, FF    |
| MOL000359     | sitosterol                                                                    | 36.91 | 0.75| IR, MH, LI, ACV          |
| MOL000449     | Stigmasterol                                                                  | 43.83 | 0.76| IR, LJF, ACV, EH         |
| MOL000953     | CLR                                                                           | 37.87 | 0.68| IR, ACV                  |
| MOL011616     | Fortunellin                                                                   | 35.65 | 0.74| MH                       |
| MOL001790     | Linarin                                                                       | 39.84 | 0.71| MH                       |
| MOL002881     | Diosmetin                                                                     | 31.14 | 0.27| MH, EH                   |
| MOL004328     | naringenin                                                                    | 59.29 | 0.21| MH, LI, EH               |
| MOL00471      | aloe-emodin                                                                   | 83.38 | 0.24| MH, RRER                 |
| MOL005190     | eriodictyol                                                                   | 71.79 | 0.24| MH, EH                   |
| MOL005573     | Genkwanin                                                                     | 37.13 | 0.24| MH, PCB, EH              |

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| Molecule ID | Molecule name | OB   | DL  | Source                      |
|------------|---------------|------|-----|-----------------------------|
| MOL000006  | luteolin      | 36.16| 0.25| MH, FF, LJF, EH             |
| MOL002235  | EUPATIN       | 50.80| 0.41| RRER                        |
| MOL002251  | Mutatochrome  | 48.64| 0.61| RRER                        |
| MOL002259  | Physciondigluco side | 41.65| 0.63| RRER                        |
| MOL002260  | Procyanidin B-5,3'-O-gallate | 31.99| 0.32| RRER                        |
| MOL002268  | rhein         | 47.07| 0.28| RRER                        |
| MOL002276  | Sennoside E_qt  | 50.69| 0.61| RRER                        |
| MOL002280  | Torachrysone-8-O-beta-D-(6'-oxayl)-glucoside | 43.02| 0.74| RRER                        |
| MOL002281  | Toralactone   | 46.46| 0.24| RRER                        |
| MOL002288  | Emodin-1-O-beta-D-glucopyranoside | 44.81| 0.80| RRER                        |
| MOL002293  | Sennoside D_qt | 61.06| 0.61| RRER                        |
| MOL002297  | Daucosterol_qt | 35.89| 0.70| RRER                        |
| MOL002303  | palmdin A     | 32.45| 0.65| RRER                        |
| MOL000554  | gallic acid-3-O-(6'-O-galloyl)-glucoside | 30.25| 0.67| RRER                        |
| MOL00096   | (-)-catechin  | 49.68| 0.24| RRER                        |
| MOL001484  | Inermine      | 75.18| 0.54| LI                          |
| MOL001792  | DFV           | 32.76| 0.18| LI                          |
| MOL000211  | Mairin        | 55.38| 0.78| LI, ACV, FF                 |
| MOL002311  | Glycyrol      | 90.78| 0.67| LI, ACV                     |
| MOL000239  | Jaranol       | 50.83| 0.29| LI                          |
| MOL002565  | Medicarpin    | 49.22| 0.34| LI                          |
| MOL000354  | isorhamnetin  | 49.60| 0.31| LI                          |

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| Molecule ID | Molecule name                                           | OB   | DL  | Source |
|------------|---------------------------------------------------------|------|-----|--------|
| MOL003656 | Lupiwighteone                                          | 51.64| 0.37| LI     |
| MOL003896 | 7-Methoxy-2-methyl isoflavone                          | 42.56| 0.20| LI     |
| MOL000392 | formononetin                                           | 69.67| 0.21| LI     |
| MOL000417 | Calycosin                                              | 47.75| 0.24| LI     |
| MOL000422 | kaempferol                                             | 41.88| 0.24| LI, LJF, FBR, FF, EH, HH |
| MOL004806 | euchrenone                                             | 30.29| 0.57| LI     |
| MOL004805 | (2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-di- | 31.79| 0.72| LI     |
|            | methyl-2,3-dihydropyrano[2,3-f]chromen-4-one           |      |     |        |
| MOL004808 | glyasperin B                                           | 65.22| 0.44| LI     |
| MOL004810 | glyasperin F                                           | 75.84| 0.54| LI     |
| MOL004811 | Glyasperin C                                           | 45.56| 0.40| LI     |
| MOL004814 | Isotrifoliol                                           | 31.94| 0.42| LI     |
| MOL004815 | (E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-y | 39.62| 0.35| LI     |
|            | l)prop-2-en-1-one                                      |      |     |        |
| MOL004820 | kanzonols W                                            | 50.48| 0.52| LI     |
| MOL004824 | (2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)- | 60.25| 0.63| LI     |
|            | 4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one         |      |     |        |
| MOL004827 | Semilicoisoflavone B                                   | 48.78| 0.55| LI     |

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| Molecule ID   | Molecule name                                      | OB   | DL  | Source |
|--------------|---------------------------------------------------|------|-----|--------|
| MOL004828    | Glepidotin A                                      | 44.72| 0.35| LI     |
| MOL004829    | Glepidotin B                                      | 64.46| 0.34| LI     |
| MOL004833    | Phaseolinisolavanan                              | 32.01| 0.45| LI     |
| MOL004835    | Gyalpalchalcone                                   | 61.60| 0.19| LI     |
| MOL004838    | 8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol | 58.44| 0.38| LI     |
| MOL004841    | Licochalcone B                                    | 76.76| 0.19| LI, ACV|
| MOL004848    | licochalcone G                                    | 49.25| 0.32| LI     |
| MOL004849    | 3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin | 59.62| 0.43| LI     |
| MOL004855    | Licoricone                                        | 63.58| 0.47| LI     |
| MOL004856    | Gancaonin A                                       | 51.08| 0.40| LI     |
| MOL004857    | Gancaonin B                                       | 48.79| 0.45| LI     |
| MOL004860    | licorice glycoside E                              | 32.89| 0.27| LI     |
| MOL004863    | 3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone | 66.37| 0.41| LI     |
| MOL004864    | 5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone | 30.49| 0.41| LI     |

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| Molecule ID   | Molecule name                                                                 | OB     | DL  | Source   |
|--------------|-------------------------------------------------------------------------------|--------|-----|----------|
| MOL004866    | 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone          | 44.15  | 0.41| LI       |
| MOL004879    | Glycyrin                                                                      | 52.61  | 0.47| LI       |
| MOL004882    | Licocoumarone                                                                 | 33.21  | 0.36| LI       |
| MOL004883    | Licoisoflavone                                                                | 41.61  | 0.42| LI       |
| MOL004884    | Licoisoflavone B                                                              | 38.93  | 0.55| LI       |
| MOL004885    | licoisoflavanone                                                              | 52.47  | 0.54| LI       |
| MOL004891    | shinpterocarpin                                                               | 80.30  | 0.73| LI       |
| MOL004898    | (E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)    | 46.27  | 0.31| LI       |
|              | prop-2-en-1-one                                                               |        |     |          |
| MOL004903    | liquiritin                                                                    | 65.69  | 0.74| LI, ACV  |
| MOL004904    | licopyranocoumarin                                                            | 80.36  | 0.65| LI       |
| MOL004905    | 3,22-Dihydroxy-11-oxo-delta(12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid| 34.32  | 0.55| LI       |
| MOL004907    | Glyzaglabrin                                                                  | 61.07  | 0.35| LI       |
| MOL004908    | Glabridin                                                                     | 53.25  | 0.47| LI, ACV  |
| MOL004910    | Glabranin                                                                     | 52.90  | 0.31| LI       |
| MOL004911    | Glabrene                                                                      | 46.27  | 0.44| LI       |
| MOL004912    | Glabrone                                                                       | 52.51  | 0.50| LI       |

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| Molecule ID  | Molecule name                                                                 | OB    | DL  | Source |
|-------------|-------------------------------------------------------------------------------|-------|-----|--------|
| MOL004913   | 1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone                      | 48.14 | 0.43| LI     |
| MOL004914   | 1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone                  | 62.90 | 0.53| LI     |
| MOL004915   | Eurycarpin A                                                                  | 43.28 | 0.37| LI     |
| MOL004917   | glycyroside                                                                   | 37.25 | 0.79| LI     |
| MOL004924   | (-)-Medicocarpin                                                             | 40.99 | 0.95| LI     |
| MOL004935   | Sigmoidin-B                                                                   | 34.88 | 0.41| LI     |
| MOL004941   | (2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one                              | 71.12 | 0.18| LI     |
| MOL004945   | (2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one       | 36.57 | 0.32| LI     |
| MOL004948   | Isoglycyrol                                                                   | 44.70 | 0.84| LI     |
| MOL004949   | Isolicoflavonol                                                               | 45.17 | 0.42| LI     |
| MOL004957   | HMO                                                                            | 38.37 | 0.21| LI     |
| MOL004959   | 1-Methoxyphaseollidin                                                        | 69.98 | 0.64| LI     |
| MOL004961   | Quercetin der.                                                                | 46.45 | 0.33| LI     |
| MOL004966   | 3'-Hydroxy-4’-O-Methylglabridin                                               | 43.71 | 0.57| LI     |
| MOL004974   | 3'-Methoxyglabridin                                                           | 46.16 | 0.57| LI     |

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| Molecule ID   | Molecule name                                                                 | OB    | DL   | Source |
|--------------|-------------------------------------------------------------------------------|-------|------|--------|
| MOL004978    | 2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol | 36.21 | 0.52 | LI     |
| MOL004980    | Inflacoumarin A                                                               | 39.71 | 0.33 | LI     |
| MOL004985    | icos-5-enoic acid                                                             | 30.70 | 0.20 | LI     |
| MOL004988    | Kanzonol F                                                                    | 32.47 | 0.89 | LI     |
| MOL004989    | 6-prenylated eriodictyol                                                      | 39.22 | 0.41 | LI     |
| MOL004990    | 7,2',4'-trihydroxy-5-methoxy-3-arylcoumararin                                 | 83.71 | 0.27 | LI     |
| MOL004991    | 7-Acetoxy-2-methylisoflavone                                                  | 38.92 | 0.26 | LI     |
| MOL004993    | 8-prenylated eriodictyol                                                      | 53.79 | 0.40 | LI     |
| MOL004996    | gadelaidic acid                                                               | 30.70 | 0.20 | LI     |
| MOL005000    | Vestitol                                                                      | 74.66 | 0.21 | LI     |
| MOL005000    | Gancaonin G                                                                   | 60.44 | 0.39 | LI     |
| MOL005001    | Gancaonin H                                                                   | 50.10 | 0.78 | LI     |
| MOL005003    | Licoagrocarpin                                                                | 58.81 | 0.58 | LI     |
| MOL005007    | Glyasperins M                                                                 | 72.67 | 0.59 | LI     |
| MOL005008    | Glycyrrhiza flavonol A                                                        | 41.28 | 0.60 | LI     |
| MOL005012    | Licoagroisoflavone                                                            | 57.28 | 0.49 | LI     |
| MOL005013    | 18α-hydroxyglycyrrhetic acid                                                  | 41.16 | 0.71 | LI     |
| MOL005016    | Odoratin                                                                      | 49.95 | 0.30 | LI     |
| MOL005017    | Phaseol                                                                       | 78.77 | 0.58 | LI, ACV|

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| Molecule ID   | Molecule name                  | OB   | DL   | Source                      |
|--------------|--------------------------------|------|------|-----------------------------|
| MOL005018    | Xambioona                      | 54.85| 0.87 | LI                          |
| MOL005020    | dehydroglyasperins C           | 53.82| 0.37 | LI                          |
| MOL000098    | quercetin                      | 46.43| 0.28 | LI, PCB, LJJ, FF, EH, HH    |
| MOL002879    | Diop                           | 43.59| 0.39 | PCB                         |
| MOL005884    | patchoulan 1,12-diol           | 38.17| 0.25 | PCB                         |
| MOL005890    | pachypodol                     | 75.06| 0.40 | PCB                         |
| MOL005911    | 5-Hydroxy-7,4'-dimethoxyflavanon | 51.54| 0.27 | PCB                         |
| MOL005916    | irsoidone                      | 37.78| 0.30 | PCB                         |
| MOL005918    | phenanthrone                   | 38.70| 0.33 | PCB                         |
| MOL005921    | quercetin 7-O-β-D-glucoside    | 49.57| 0.27 | PCB                         |
| MOL005922    | Acanthoside B                  | 43.35| 0.77 | PCB                         |
| MOL005923    | 3,23-dihydroxy-12-oleanen-28-oic acid | 30.86| 0.86 | PCB                         |
| MOL001040    | (2R)-5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one | 42.36| 0.21 | FBR                         |
| MOL002605    | 11-Hydroxyurnamantine         | 50.79| 0.71 | FBR                         |
| MOL002606    | Hopene                         | 6.82 | 0.77 | FBR                         |
| MOL002607    | Aspidinin                      | 2.13 | 0.37 | FBR                         |
| MOL002609    | Harmonyl                       | 43.80| 0.46 | FBR                         |
| MOL002610    | ZINC00035529                   | 58.39| 0.22 | FBR                         |
| MOL002612    | Filixic acid                   | 1.54 | 0.63 | FBR                         |

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| Molecule ID   | Molecule name                  | OB   | DL   | Source       |
|--------------|--------------------------------|------|------|--------------|
| MOL002613    | Flavaspidinin                  | 8.49 | 0.47 | FBR          |
| MOL002614    | Flavidin                       | 30.10| 0.26 | FBR          |
| MOL002615    | Neohop-13(18)ene solution      | 6.78 | 0.77 | FBR          |
| MOL013336    | Narirutin                      | 8.15 | 0.75 | FBR          |
| MOL002617    | Diplopterol                    | 11.25| 0.77 | FBR          |
| MOL002618    | ALBASPIDIN                     | 18.27| 0.51 | FBR          |
| MOL002619    | Albaspidin AA                  | 31.16| 0.36 | FBR          |
| MOL002620    | Dryocrassin                    | 3.01 | 0.36 | FBR          |
| MOL002621    | Aspidin                        | 2.40 | 0.52 | FBR          |
| MOL002622    | Filicin                        | 6.71 | 0.63 | FBR          |
| MOL002623    | Trisalbaspidin ABA             | 1.46 | 0.69 | FBR          |
| MOL002625    | Kaempfe-rol-3,7-dirhamnoside   | 3.75 | 0.79 | FBR          |
| MOL002626    | Adlantone                      | 12.57| 0.78 | FBR          |
| MOL002627    | Filicene                       | 6.81 | 0.76 | FBR          |
| MOL002628    | isopentenyaldenosine           | 29.78| 0.34 | FBR          |
| MOL002629    | 7-Fernene                      | 7.03 | 0.77 | FBR          |
| MOL002630    | 9-(11)-Fernene                 | 17.53| 0.77 | FBR          |
| MOL002631    | 9-(11)-Fernene                 | 6.67 | 0.78 | FBR          |
| MOL002632    | Adlantone                      | 13.91| 0.78 | FBR          |
| MOL002633    | Albaspidin AP                  | 24.44| 0.42 | FBR          |
| MOL001494    | Mandenol                       | 42.00| 0.19 | LJF, EH      |
| MOL001495    | Ethyl linolenate               | 46.10| 0.20 | LJF          |
| MOL002707    | phytouene                      | 43.18| 0.50 | LJF          |

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| Molecule ID   | Molecule name                                                                 | OB   | DL  | Source |
|--------------|------------------------------------------------------------------------------|------|-----|--------|
| MOL002914    | Eriodyctiol (flavanone)                                                      | 41.35| 0.24| LJF    |
| MOL003006    | (-)-(3R,8S,9R,9aS,10aS)-9-ethenyl-8-(beta-D-glucopyranosylxy)-2,3,9,9a,10a-hexahydro-5-oxo-5H,8H-pyranol[4,3-d]oxazolo[3,2-a]pyridine-3-carboxylic acid_qt | 87.47| 0.23| LJF    |
| MOL003014    | secologanic dibutylacetol_qt                                               | 53.65| 0.29| LJF    |
| MOL002773    | beta-carotene                                                               | 37.18| 0.58| LJF    |
| MOL003036    | ZINC03978781                                                                | 43.83| 0.76| LJF    |
| MOL003044    | Chryseriol                                                                   | 35.85| 0.27| LJF    |
| MOL003059    | kryptoxanthin                                                                | 47.25| 0.57| LJF    |
| MOL003062    | 4,5'-Retro-.beta.,.beta.-Carotene-3,3'-dione, 4',5'-didehydro-              | 31.22| 0.55| LJF    |
| MOL003095    | 5-hydroxy-7-methoxy-2(3,4,5-trimethoxyphenyl ) chromone                      | 51.96| 0.41| LJF    |
| MOL003101    | 7-epi-Vogeloside                                                            | 46.13| 0.58| LJF    |
| MOL003108    | Caeruloside C                                                                | 55.64| 0.73| LJF    |
| MOL003111    | Centauroside_qt                                                             | 55.79| 0.50| LJF    |
| MOL003117    | Ioniceracetalides B_qt                                                      | 61.19| 0.19| LJF    |
| MOL003124    | XYLOSTOSIDINE                                                                | 43.17| 0.64| LJF    |

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| Molecule ID   | Molecule name                                | OB   | DL  | Source |
|--------------|----------------------------------------------|------|-----|--------|
| MOL003128    | dinethylsecologanoside                       | 48.46| 0.48| LJF    |
| MOL010921    | estrone                                      | 53.56| 0.32| ACV    |
| MOL010922    | Diisoctyl succinate                          | 31.62| 0.23| ACV    |
| MOL002211    | 11,14-eicosadienoic acid                    | 39.99| 0.20| ACV    |
| MOL002372    | (6Z,10E,14E,18E)-2,6,10,15,19,23-hexamethyltetracosa-2,6,10,14,18,22-hexaene | 33.55| 0.42| ACV    |
| MOL005030    | gondoic acid                                 | 30.70| 0.20| ACV    |
| MOL000492    | (+)-catechin                                  | 54.83| 0.24| ACV, EH|
| MOL003410    | Ziziphin_qt                                   | 66.95| 0.62| ACV    |
| MOL004355    | Spinasterol                                   | 42.98| 0.76| ACV, HH|
| MOL007207    | Machiline                                     | 79.64| 0.24| ACV    |
| MOL012922    | l-SPD                                         | 87.35| 0.54| ACV    |
| MOL000173    | wogonin                                       | 30.68| 0.23| FF     |
| MOL003281    | 20(S)-dammar-24-ene-3β,20-diol-3-acetate     | 40.23| 0.82| FF     |
| MOL003283    | (2R,3R,4S)-4-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-2,3-dimethyltetralin-6-ol | 66.51| 0.39| FF     |
| MOL003290    | (3R,4R)-3,4-bis[(3,4-dimethoxyphenyl) methyl] oxolan-2-one | 52.30| 0.48| FF     |

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| Molecule ID   | Molecule name                                                                 | OB     | DL  | Source |
|--------------|-------------------------------------------------------------------------------|--------|-----|--------|
| MOL003295    | (+)-pinoresinol monomethyl ether                                               | 53.08  | 0.57| FF     |
| MOL003305    | PHILLYRIN                                                                     | 36.40  | 0.86| FF     |
| MOL003306    | ACon1_001697                                                                  | 85.12  | 0.57| FF     |
| MOL003308    | (+)-pinoresinol monomethyl ether-4-D-beta-glucoside_qt                       | 61.20  | 0.57| FF     |
| MOL003315    | 3beta-Acetyl-20,25-epoxydammarane-24alpha-ol                                  | 33.07  | 0.79| FF     |
| MOL003322    | FORSYTHINOL                                                                   | 81.25  | 0.57| FF     |
| MOL003330    | (-)-Phillygenin                                                               | 95.04  | 0.57| FF     |
| MOL003344    | β-amyrin acetate                                                              | 42.06  | 0.74| FF     |
| MOL003347    | hyperforin                                                                    | 44.03  | 0.60| FF     |
| MOL003348    | adhyperforin                                                                  | 44.03  | 0.61| FF     |
| MOL003365    | Lactucasterol                                                                 | 40.99  | 0.85| FF     |
| MOL003370    | Onjixanthone I                                                                | 79.16  | 0.30| FF     |
| MOL000522    | arctiin                                                                       | 34.45  | 0.84| FF     |
| MOL000791    | bicuculline                                                                    | 69.67  | 0.88| FF     |
| MOL010788    | leucopelargonidin                                                             | 57.97  | 0.24| EH     |
| MOL002823    | Herbacetin                                                                    | 36.07  | 0.27| EH     |
| MOL010489    | Resivit                                                                       | 30.84  | 0.27| EH     |
| MOL004798    | delphinidin                                                                   | 40.63  | 0.28| EH     |
| MOL001506    | Supraene                                                                      | 33.55  | 0.42| EH     |
| MOL004576    | taxifolin                                                                     | 57.84  | 0.27| EH     |
| MOL005043    | campest-5-en-3beta-ol                                                         | 37.58  | 0.71| EH     |

OB, oral bioavailability; DL, drug-likeness; IR, Isatidis Radix; MH, Menthae Herba; RRER, Radix Rhei Et Rhizome; LI, licorice; PCB, Pogostemon Cablin (Blanco) Benth; FBR, Fortunes Bossfern Rhizome; LJF, Lonicerae Japonicae Flos; ACV, Amygdalus Communis Vas; FF, Forsythiae Fructus; EH, Ephedra Herba; HH, Houttuyniae Herba.
| Molecule ID | Molecule name          | OB   | DL  | Source |
|------------|------------------------|------|-----|--------|
| MOL005842  | Pectolinarigenin       | 41.17| 0.30| EH     |
| MOL007214  | (+)-Leucocyanidin      | 37.61| 0.27| EH     |
| MOL011319  | Truflex OBP            | 43.74| 0.24| EH     |
| MOL003851  | Isoramanone            | 39.97| 0.51| HH     |
| MOL004345  | 1-methyl-2-nonacosyl-4-quinolone | 31.54| 0.50| HH     |
| MOL004350  | Ruvoside_qt            | 36.12| 0.76| HH     |
| MOL004351  | C09747                 | 37.28| 0.25| HH     |

OB, oral bioavailability; DL, drug-likeness; IR, Isatidis Radix; MH, Menthae Herba; RRER, Radix Rhei Et Rhizome; LI, licorice; PCB, Pogostemon Cablin (Blanco) Benth; FBR, Fortunes Bossfern Rhizome; LJF, Lonicerae Japonicae Flos; ACV, Amygdalus Communis Vas; FF, Forsythiae Fructus; EH, Ephedra Herba; HH, Houttuyniae Herba.

**PPI Networks Analysis of LHQW capsule and COVID-19**

To reveal the mechanisms of LHQW capsule against COVID-19, 50 shared target genes were added to STRING and Cytoscape to construct a PPI network for exploring the interaction relationships with each other (Fig. 3). Network Analyzer in cytoscape was used to analyse the degree of each target for further identifying the more important targets in the network. The results and parameters from the PPI topological analysis are listed in Table 2. MAPK3, MAPK8, CASP3, MAPK1, IL6 and RELA were the top 6 genes based on degree.
Table 2
Topological analysis of the PPI network of the 50 genes. Data were ranked by degree.

| Gene Symbol | Degree | \(^1\text{BC}\) | \(^2\text{CC}\) | \(^3\text{NC}\) | \(^4\text{NDE}\) | \(^5\text{TC}\) |
|-------------|--------|----------------|----------------|----------------|----------------|----------------|
| MAPK3       | 37     | 0.053          | 0.911          | 22.162         | 37             | 0.541          |
| MAPK8       | 36     | 0.045          | 0.891          | 22.778         | 36             | 0.556          |
| CASP3       | 35     | 0.041          | 0.872          | 22.743         | 35             | 0.555          |
| MAPK1       | 35     | 0.041          | 0.872          | 22.686         | 35             | 0.553          |
| IL6         | 34     | 0.035          | 0.854          | 23.647         | 34             | 0.577          |
| RELA        | 31     | 0.027          | 0.804          | 23.968         | 31             | 0.585          |
| CASP8       | 30     | 0.025          | 0.788          | 23.900         | 30             | 0.583          |
| FOS         | 30     | 0.028          | 0.788          | 23.800         | 30             | 0.580          |
| MAPK14      | 30     | 0.018          | 0.788          | 24.700         | 30             | 0.602          |
| EGFR        | 29     | 0.024          | 0.774          | 23.759         | 29             | 0.579          |
| BCL2L1      | 28     | 0.017          | 0.759          | 24.679         | 28             | 0.602          |
| IL1B        | 28     | 0.010          | 0.759          | 25.893         | 28             | 0.632          |
| CCL2        | 28     | 0.010          | 0.759          | 25.893         | 28             | 0.632          |
| IL2         | 28     | 0.018          | 0.759          | 25.500         | 28             | 0.622          |
| PTGS2       | 28     | 0.009          | 0.759          | 26.214         | 28             | 0.639          |
| ICAM1       | 28     | 0.013          | 0.759          | 25.607         | 28             | 0.625          |
| IL4         | 27     | 0.009          | 0.745          | 26.111         | 27             | 0.637          |
| STAT1       | 27     | 0.015          | 0.745          | 25.889         | 27             | 0.631          |
| HMOX1       | 24     | 0.008          | 0.707          | 26.125         | 24             | 0.637          |
| NOS2        | 23     | 0.008          | 0.695          | 25.565         | 23             | 0.624          |
| CXCL10      | 22     | 0.004          | 0.683          | 26.273         | 22             | 0.641          |
| MCL1        | 21     | 0.009          | 0.672          | 25.333         | 21             | 0.618          |
| CD40LG      | 20     | 0.003          | 0.661          | 28.100         | 20             | 0.685          |
| NOS3        | 19     | 0.003          | 0.651          | 27.000         | 19             | 0.659          |

\(^1\text{BC}\) (Betweenness Centrality); \(^2\text{CC}\) (Closeness Centrality); \(^3\text{NC}\) (Neighborhood Connectivity); \(^4\text{NDE}\) (Number of Directed Edges); \(^5\text{TC}\) (Topological Coefficient).
| Gene Symbol | Degree | ¹BC | ²CC | ³NC | ⁴NDE | ⁵TC |
|------------|--------|-----|-----|-----|------|-----|
| IRF1       | 18     | 0.002 | 0.641 | 26.278 | 18 | 0.641 |
| CXCL2      | 17     | 0.001 | 0.631 | 26.588 | 17 | 0.648 |
| SOD1       | 17     | 0.003 | 0.631 | 26.882 | 17 | 0.656 |
| SERPINE1   | 17     | 0.002 | 0.631 | 27.941 | 17 | 0.681 |
| IL1A       | 15     | 0.001 | 0.586 | 24.733 | 15 | 0.651 |
| PARP1      | 15     | 0.002 | 0.612 | 27.933 | 15 | 0.681 |
| HSPA5      | 15     | 0.002 | 0.612 | 27.467 | 15 | 0.670 |
| HSPB1      | 14     | 0.000 | 0.603 | 28.500 | 14 | 0.695 |
| BCL2       | 13     | 0.003 | 0.577 | 24.231 | 13 | 0.621 |
| CXCL11     | 12     | 0.000 | 0.554 | 24.333 | 12 | 0.658 |
| BAX        | 11     | 0.002 | 0.562 | 23.545 | 11 | 0.604 |
| PRKCB      | 11     | 0.001 | 0.577 | 26.455 | 11 | 0.645 |
| RB1        | 10     | 0.001 | 0.562 | 28.300 | 10 | 0.708 |
| CDK4       | 10     | 0.001 | 0.569 | 26.100 | 10 | 0.637 |
| BAD        | 10     | 0.001 | 0.554 | 25.600 | 10 | 0.656 |
| PRKCA      | 10     | 0.002 | 0.569 | 26.500 | 10 | 0.646 |
| PRKCE      | 10     | 0.003 | 0.569 | 23.400 | 10 | 0.571 |
| CALM1      | 9      | 0.000 | 0.562 | 29.111 | 9  | 0.710 |

¹ BC (Betweenness Centrality); ² CC (Closeness Centrality); ³ NC (Neighborhood Connectivity); ⁴ NDE (Number of Directed Edges); ⁵ TC (Topological Coefficient).

GO and KEGG Pathway Enrichment analysis

Performing GO and KEGG pathway enrichment analysis to expound the biological functions of the 50 core targets in the networks of LHQW capsule and COVID-19. The top 20 significantly enriched terms with a greater number of involved targets in biological process (BP), cellular component (CC), and molecular function (MF) categories are shown in Fig. 4A-C, which indicated that LHQW capsule may regulate virus infection, oxidative stress, endothelial barrier and cytokine storm via response to molecule of bacterial origin, response to oxidative stress, membrane raft, membrane microdomain, cytokine receptor binding and cytokine activity to exert its therapeutic effects against COVID-19. The data of GO analysis were provided in supplementary table 1.
Figure 4D indicated the top 20 significantly enriched pathways according to the analysis of KEGG signaling pathway data. Among these potential pathways, AGE–RAGE signaling pathway in diabetic complications was the most prominently enriched pathway. Others important pathways involved in Kaposi sarcoma–associated herpesvirus infection, TNF, IL–17, and Toll–like receptor signaling pathway, which were categorized for inflammation, virus infection and immune response. The data of KEGG pathway analysis were provided in supplementary table 2.

**Gene-pathway network analysis**

As genes cannot directly exhibit their biological and pharmacological activities independently, a gene-pathway network was established to further elucidate the molecular mechanisms of LHQW capsule treating COVID. According to the degree of the pathways, the study selected the top 30 pathways and 42 genes to perform topological analysis with BC. Figure 5 identified MAPK3, MAPK1, RELA, IL-6 and CASP8 as relatively high-relevant target genes in virus infection, inflammation, and apoptosis. Moreover, these top five target genes were considered as the key markers for LHQW capsule treating COVID-19.

**Molecular docking analysis**

Discovery Studio software [18] was used to validate network pharmacology by molecular docking, including the respective top 5 targets in PPI network and the top 5 compounds in LHQW capsule. The LibDock score represented the degree of docking coincidence of molecules. If the score was higher, the binding of ligands to receptor proteins was better. Molecular docking results found that quercetin had good affinity to bind MAPK3, which was the key target protein molecules in COVID-19. Besides, these results also showed that other important compounds (such as, kaempferol, luteolin, naringenin, and beta-sitosterol) in LHQW capsule had regulatory effects of other targets in COVID-19, indicating that the molecular docking results were consistent with the network pharmacology screening results. The partial docking results were showed in Fig. 6 and other results were provided in supplementary table 3.

**Discussion**

COVID-19 has brought a tremendous threat to public health, especially the elderly over 60 years old being more likely to die after infection [1]. The clinical symptoms of COVID-19 have been reportedly ranged from mild to severe, ultimately leading to death. The mild symptoms included fever, cough, shortness of breath and pneumonia after viral infection, while the severe cases would rapidly developed to acute respiratory distress syndrome, septic shock, metabolic acidosis, coagulation dysfunction and multiple organ failure that eventually brought about mortality [19, 20]. There has been no effective antiviral drug to treat COVID-19 until now, even though significant efforts are used to develop therapeutic interventions against coronavirus infection [2]. Fortunately, the application of TCM in the auxiliary treatment of COVID-19 has achieve satisfactory therapeutic effects in China [21, 22]. LHQW capsule has been recommended for the treatment of patients with mild symptoms in 7th edition of COVID-19 treatment guidelines and
widely used in the clinical treatment of COVID-19 in China [23]. LHQW capsule has been demonstrated to have anti-infection or antiviral effects in vitro or in vivo [24–26]. In the present study, network pharmacological and molecular docking approaches were used to explore the mechanisms of LHQW capsule treating COVID-19.

According to the GO analysis, the LHQW capsule treating COVID-19 is widely involved in regulating inflammation, virus infection, endothelial barrier and cytokine storm via mediating these processes such as response to molecule of bacterial origin, response to oxidative stress, membrane raft, membrane microdomain, cytokine receptor binding and cytokine activity, which were significantly enriched in the GO analysis. Molecule of bacterial origin is involved in Toll-Like Receptor Signaling, which represents a largely evolutionarily conserved pathogen recognition machinery responsible for recognition of bacterial, fungal, protozoan, and viral pathogen associated microbial patterns and initiation of inflammatory response [27]. Oxidative stress is an imbalance between oxidants and antioxidants when the organism exposures to adverse stimuli, playing important roles in virus infection [28]. Membrane raft and membrane microdomain are not only closely associated with inter-endothelial junctions and adhesion of endothelium, but also involved in immune cell adhesion and migration across endothelium [29]. Cytokine storm, emerged from prolonged cytokine/chemokine responses during COVID-19, causes ARDS or multiple-organ dysfunction, ultimately leading to physiological deterioration and death [30]. Quercetin, a typical flavonoid, is one of the major compounds of FF, LIF, EH, HH, PCB, and LI in LHQW capsule and has been reported to have the effects of anti-inflammation, antiviral, strengthening the endothelial barrier integrity and inhibiting the expression of cytokines [31–34]. Kaempferol is flavonoid found in FF, LIF, EH, FBR, HH, and LI of LHQW capsule, and can protect against inflammation, virus infection, endothelial barrier dysfunction, and cytokines release [35–38]. Another important compounds, such as luteolin, naringenin, and beta-sitosterol, in LHQW capsule also have these protective effects [39–42]. Thus, the results of GO analysis indicated that the mechanisms of LHQW capsule treating COVID-19 might be related with suppressing inflammation, virus infection, endothelial barrier dysfunction and cytokine storm.

The internal regulation of the body involves a complex regulatory network rather than a single signaling pathway. Therefore, the therapeutic effects of drugs against diseases involve in many pathways. KEGG enrichment analysis showed that LHQW capsule treating COVID-19 included AGE − RAGE signaling pathway in diabetic complications, Kaposi sarcoma − associated herpesvirus infection (KSHV), TNF, IL − 17, and Toll − like receptor (TLR) signaling pathway, which were associated with inflammation, virus infection and immune response. Taking IL − 17 and TLR signaling pathways as examples to explore the mechanisms of LHQW capsule treating COVID-19. IL − 17 is a key T helper cell population and founding member of a novel family of inflammatory cytokines [43]. IL-17 signaling can not only activate downstream pathways that include NF-κB, MAPKs and C/EBPs to induce the expression of anti-microbial peptides, cytokines and chemokines, but also is critical for protection against a variety of fungal and bacterial infections [44, 45]. TLRs are a well-known family of pattern recognition receptors that play important roles in host immune system and inflammation [46]. TLR signaling activation can result in the production of cytokines, chemokines and interferons and transcription factor NF-κB [47, 48], thus
inducing inflammatory and immune response. Previous studies have demonstrated that quercetin not only exerted the effect of anti-inflammation by regulating IL-17 signaling [49, 50], but also effectively promoted the immunoregulatory effect by activating the TLR-3 pathway and inhibiting downstream cytokines production [51, 52]. Similarly to quercetin, another important compound also have these effects. As a result, LHQW capsule treating COVID-19 may directly interfere with IL-17 and TLR signaling, and further regulate the downstream signaling pathways, such as the NF-κB signaling pathway, leading to the inhibition of cytokines production, including TNF-α, IL-1β, IL-8.

Based on gene-pathway network analysis, MAPK3, MAPK1, RELA, IL-6, and CASP8 are the more important genes in LHQW capsule treating COVID-19. Clinical and laboratory data of COVID-19 showed evidence of inflammatory and immune injury, confirming that cytokine storms could be a crucial factor linked to the severity and mortality of COVID-19. MAPK3 and MAPK1, belong to serine/threonine protein kinase family, and the activation of MAPK promotes virus infection and inflammatory response [53–55]. REL/NF-κB family of transcription factors plays a central role in initiation and resolution of inflammatory responses [56, 57]. IL-6, promptly and transiently produced in response to infections and tissue injuries, contributes to host defense through the stimulation of acute phase responses, hematopoiesis, inflammatory and immune reactions [58, 59]. Caspase-8 is the initiator caspase of extrinsic apoptosis and required for the activation of NF-κB and secretion of cytokines in response to activated antigen receptors [60]. Quercetin, kaempferol, luteolin and naringenin, all can inhibit the activation of MAPK and RELA, decrease the expression of IL-6 and CASP8 [61–65]. Moreover, the most critical targets had good binding activities to main compounds, which indicated that pharmacodynamic mechanisms of LHQW capsule had sufficient material basis through preliminary analysis.

**Conclusion**

This study investigated the effective active ingredients and molecular mechanisms of LHQW capsule in the treatment of COVID-19 from the perspective of network pharmacology and molecular docking. The therapeutic effects potentially involved in inhibiting inflammatory response, cytokine storm and virus infection, and regulating immune reactions, apoptosis and endothelial barrier.

**Abbreviations**

COVID-19: novel coronavirus 2019; LHQW: Lian Hua Qing Wen; TCM: traditional Chinese medicine; OB: oral bioavailability; DL: drug-likeness; IR: Isatidis Radix; MH: Menthae Herba; RRER: Radix Rhei Et Rhizome; LI: licorice; PCB: Pogostemon Cablin (Blanco) Benth; FBR: Fortunes Bossfern Rhizome; LJF: Lonicerae Japonicae Flos; ACV: Amygdalus Communis Vas; FF: Forsythiae Fructus; EH: Ephedra Herba; HH: Houttuyniae Herba.

**Declarations**

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Not applicable.

Authors’ contributions

CL contributed to analysis and manuscript preparation, was a major contributor in writing the manuscript; QH contributed to the conception of the study and reviewed the manuscript; TY and WHT helped perform the data analyses; SDZ modified the manuscript and provided funding support; All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interests.

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Figure 1

The technical strategy of this research based on network pharmacology and molecular docking to explore the mechanisms of Lian Hua Qing Wen Capsule against COVID-19.
Figure 2

Compound-Target Network of LHQW capsule. The green prismatic represents targets; the red, light green, yellow, orange, blue, green, grey, violet, dark blue, deep purple and pink represent IR, RRER, LI, PCB, FBR, LJF, ACV, FF, EH, HH, and multiple targets, respectively.
Figure 3

Visualization of the PPI of the target genes using STRING and Cytoscape.
Figure 4

Gene ontology and KEGG pathway enrichment of candidate targets of LHQW capsule against COVID-19. The top 20 GO functional categories with $P < 0.05$ were selected. (A) biological process, (B) cellular component, (C) molecular function, (D) pathways that had significant changes of $P < 0.05$ were identified. Size of the spot represents number of genes and color represents FDR value.
Figure 5

Gene-Pathway Network of LHQW capsule against COVID-19. The topological analysis of 30 pathways and 42 genes was carried out with betweenness centrality (BC). The green prismatic represent target genes and the orange hexagon represent pathways. Big size represents the larger BC.
Figure 6

Molecular docking between compounds and targets. (A) quercetin bound to the active pocket of MAPK3, (B) kaempferol bound to the active pocket of MAPK3, (C) quercetin bound to the active pocket of MAPK1, (D) kaempferol bound to the active pocket of MAPK1.