Network Pharmacology and Molecular Docking of Shiwei Qingwen Decoction Reveal TNF as a Potential Target for Alleviating Mild COVID-19 Symptoms

Chen-xiong Yang1*, Shang-zhi Ma2*, Qian Zhang3, Shu-yun Guo3, Xiao-di Hu2, Yan-ju Liu2, Li Wen2* and Zhong-shi Zhou2

Abstract

Objective: Shiwei Qingwen decoction (SWQWD) is effective in preventing COVID-19. This study examined the active components of SWQWD and its potential targets for preventing COVID-19. The study used network pharmacology and molecular docking technology to verify the role of SWQWD targets through animal experiments and explored the mechanisms that enhance immunity to alleviate mild COVID-19 symptoms. Methods: First, SWQWD- and COVID-19-related targets were retrieved from TCMSP, GeneCards, and OMIM databases. Second, protein–protein interaction networks were established using the String database. The drug active ingredient target network was constructed in Cytoscape to identify the core target proteins. Third, Gene Ontology (GO) Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed to predict the SWQWD mechanism of action. Finally, the targets were validated by molecular docking in an acute lung injury (ALI) rat model. Results: The SWQWD compound target network contained 79 compounds and 277 targets, coinciding with the 73 targets of COVID-19. The most important gene in the core subnetwork was a tumor necrosis factor (TNF). The 3 most potent compounds, quercetin, kaempferol, and luteolin, can enter the active pockets of TNF and have potential therapeutic roles in COVID-19. Conclusion: Quercetin, kaempferol, and luteolin in SWQWD may enhance immunity by regulating multiple TNF signal pathways. After administering SWQWD, the content of tumor necrosis factor-α was significantly reduced in the bronchoalveolar lavage fluid (BALF) of ALI rats in comparison to the model group. We believe SWQWD is able to prevent and control COVID-19 through the target of TNF.

Keywords
Shiwei Qingwen decoction, COVID-19, network pharmacology, molecular docking, TNF, ALI

Received: June 12th, 2022; Accepted: August 23rd, 2022.

Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by a novel genus β coronavirus. The disease is highly infectious and may exist with other human respiratory transmitted diseases. The clinical symptoms include fever, cough, upper respiratory tract congestion, fatigue, and dyspnea. Critically ill patients can show acute respiratory distress syndrome, respiratory failure, multiple organ failure, and even death. In addition, COVID-19 patients have reduced counts of white blood cells and lymphocytes, and, thus, low immunity. Prevention of COVID-19 is crucial because there is no specific drug for treatment, yet new variants are constantly emerging worldwide. Traditional Chinese Medicine (TCM) has been demonstrated to improve the immune systems and health conditions of patients against COVID-19.

Thus, an expert group from the Jingmen Hospital of TCM considered the characteristics of COVID-19 and how it regulated human immunity and designed Shiwei Qingwen decoction (SWQWD) for preventing and alleviating mild COVID-19 symptoms. Early in 2020, > 1000 medical staff of the Jingmen Hospital of TCM hospital received SWQWD as a...
preventive strategy. There is no infection report among the SWQWD-treated front-line medical staff to date. Therefore, SWQWD has been promoted in the whole city, and the drug has achieved an excellent preventive effect. This formula can improve the patient’s immune and gastrointestinal functions, and is not only for the inflammation of the lungs. However, the mechanism of SWQWD in preventing COVID-19 is still unclear.

Following the characteristics of the multi-regulation of signaling pathways, multicomponent points, and multiple targets of Chinese herbal medicine, network pharmacology may be a new, well-documented method for finding meaningful information on SWQWD. SWQWD consists of 10 TCMs with complex components and many targets, which aligns with the characteristics and advantages of network pharmacology. Thus, molecular docking was used to identify further the potential SWQWD substances that can bind to the 3 key targets of COVID-19.

Based on the current understanding of COVID-19, the novel coronavirus infection is associated with acute lung injury (ALI), which has massively increased with the COVID-19 pandemic. ALI has common pathological responses with many lung source diseases. For instance, the epithelial cells in ALI patients show alveolar damage with several inflammatory cells such as neutrophils in the lung tissue. In addition, ALI is characterized by excessive release of inflammatory factors, and an imbalance between the inflammatory anti-inflammatory system, and oxidation antioxidant system. Eventually, ALI induces an inflammatory “waterfall”-like cascade, lung injury aggravation, microvascular permeability, pulmonary edema, and lung dysfunction, which is very similar to the “cytokine storm” phenomenon in COVID-19 patients.

Especially, there is a significant increase in pro-inflammatory cytokine serum and local expression, particularly tumor necrosis factor-α (TNF-α).

Here, we used network pharmacology and molecular docking technologies to analyze SWQWD and explore the potential mechanism and targets of COVID-19 prevention. In addition, we constructed an ALI rat model using a tracheal infusion of LPS to simulate the lung lesions in COVID-19 patients. ELISA was used to detect the content of the core infusion of LPS to simulate the lung lesions in COVID-19 patients.

GO and KEGG Enrichment Analysis

The active components of the drug and the potential action targets (in section “Acquisition of SWQWD Compounds Specific to COVID-19 Targets and Screening of Active Components and Targets of SWQWD”) were analyzed using the Network Analyzer function of Cytoscape3.6.0 software. Thus, the “TCM-component-target-disease” network was constructed, and the core nodes were screened following the network topological characteristics. Therefore, the top 10 key compounds with topological parameters were extracted.

Components Target Molecular Docking

The key target proteins were downloaded and analyzed by their core subnetwork 3D structures.
Figure 1. The flowchart of this study.
Table 1. Basic Information on the Main Active Compounds of the Various Herbs in Shiwei Qingwen Decoction.

| Mol ID      | Chemical component                      | OB (%) | DL  | Herb                                    |
|------------|------------------------------------------|--------|-----|-----------------------------------------|
| MOL000049  | β-acetoxyatractylone                     | 54.07  | 0.22| *Atractylodes macrocephala* Koidz       |
| MOL000072  | 8β-ethoxy atracylenolideII               | 35.95  | 0.21| *Atractylodes macrocephala* Koidz       |
| MOL000173  | Wogonin                                  | 30.68  | 0.23| *Atractylodes Lancea* (Thunb.)Dc         |
| MOL000188  | β-acetoxyatractylone                     | 40.57  | 0.22| *Atractylodes Lancea* (Thunb.)Dc         |
| MOL004328  | Naringenin                               | 59.29  | 0.21| *Citrus Reticulata*                     |
| MOL005828  | Nobiletin                                | 61.67  | 0.52| *Citrus Reticulata*                     |
| MOL001454  | Berberine                                | 36.86  | 0.78| *Jujubae Fructus*                       |
| MOL000358  | Beta-sitosterol                           | 36.91  | 0.75| *Jujubae Fructus*                       |
| MOL011753  | 5-O-Methylvisamminol                     | 37.99  | 0.25| *Saposhnikoviae Radix*                  |
| MOL000011  | (2R,3R)-3-(4-hydroxy-3-methoxy-phenyl)-5-methoxy-2-methylol-2,3-dihydropyrano[5,6-h][1,4]benzodioxin-9-one | 68.83  | 0.66| *Saposhnikoviae Radix*                  |
| MOL00422   | Kaempferol                               | 41.88  | 0.24| *Fortunes Bossfern Rhizome*              |
| MOL002610  | ZINC00035529                             | 58.39  | 0.22| *Fortunes Bossfern Rhizome*              |
| MOL000392  | Formononetin                             | 69.67  | 0.21| *Hedyasarum Multijugum Maxim*            |
| MOL000417  | Calycosin                                | 47.75  | 0.24| *Hedyasarum Multijugum Maxim*            |
| MOL000354  | Isorhamnetin                             | 49.6   | 0.31| *Hedyasarum Multijugum Maxim*            |
| MOL000378  | 7-O-methylisomucronulatol                | 74.69  | 0.3 | *Hedyasarum Multijugum Maxim*            |
| MOL005059  | Kryptoxanthin                            | 47.25  | 0.57| *Lonicera japonicae Flos*                |
| MOL002773  | Beta-carotene                            | 37.18  | 0.58| *Lonicera japonicae Flos*                |
| MOL003044  | Chrysoriol                               | 35.85  | 0.27| *Lonicera japonicae Flos*                |
| MOL000449  | Stigmasterol                             | 43.83  | 0.76| *Phragmitis Rhizoma*                     |
| MOL000006  | Luteolin                                 | 36.16  | 0.25| *Eupatorium Fortunei Turcz*              |

Figure 2. (A) Venn diagram showing the common targets between COVID-19 and Shiwei Qingwen decoction (SWQWD). (B) A herbal compound target disease network consisting of 162 nodes and 693 edges. The blue diamond-shaped nodes on the outer periphery represent potential genes. The octagonal nodes with different colors on the inner circumference represent the effective compounds of different herbal medicines, respectively. The square nodes represent the 10 herbs of the Ten Flavors Clear Distemper Soup. The node size is positively correlated with the degree value; the larger the node, the larger the degree value.

“Constructing the PPI and Core Subnetwork of Key Target Proteins”) from PDB files of the RSCB PDB database (https://www.rcsb.org/). Using the AutoDock Tools version 1.5.6, the key target proteins were used as receptors and the active ingredient candidates as ligands. Discovery Studio software determined the active pocket of the receptor, and Autodock Vina determined the docking. The docking results were visualized in PyMol software. We also use
Table 2. Specific Topological Parameters of the Top 10 Chemical Components.

| Mol ID   | Compound         | CAS    | BC      | CC      | DC   |
|----------|------------------|--------|---------|---------|------|
| MOL000098| Quercetin        | 117-39-5 | $3.31 \times 10^{-1}$ | $5.18 \times 10^{-1}$ | 155  |
| MOL000422| Kaempferol       | 520-18-3 | $5.94 \times 10^{-2}$ | $4.25 \times 10^{-1}$ | 60   |
| MOL000006| Luteolin         | 491-70-3 | $1.21 \times 10^{-1}$ | $4.36 \times 10^{-1}$ | 58   |
| MOL000173| Wogonin          | 632-85-9 | $6.27 \times 10^{-2}$ | $4.20 \times 10^{-1}$ | 40   |
| MOL000358| Beta-sitosterol  | 474-58-8 | $3.44 \times 10^{-2}$ | $4.12 \times 10^{-1}$ | 32   |
| MOL005828| Nobiletin        | 480-41-1 | $4.23 \times 10^{-2}$ | $4.04 \times 10^{-1}$ | 16   |
| MOL000392| Formononetin     | 485-72-3 | $2.82 \times 10^{-2}$ | $4.04 \times 10^{-1}$ | 15   |
| MOL000354| Naringenin       | 480-41-1 | $6.75 \times 10^{-2}$ | $3.98 \times 10^{-1}$ | 15   |
| MOL000378| Isorhamnetin     | 480-19-3 | $1.44 \times 10^{-2}$ | $4.04 \times 10^{-1}$ | 14   |
| MOL000358| 7-O-methylisoucronulatol | 90-19-7 | $1.30 \times 10^{-2}$ | $4.04 \times 10^{-1}$ | 13   |

Figure 3. GO and KEGG enrichment analysis of the top 20 SWQWD targets. (A) GO-BP enrichment analysis; (B) GO-CC enrichment analysis; (C) GO-MF enrichment analysis; (D) KEGG enrichment analysis. The more red the color, the smaller the P-value, the larger the point, the greater the number of genes enriched into the pathway. Abbreviations: SWQWD, Shiwei Qingwen decoction; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.
Protein Ligand Interaction Profiler (PLIP) to check the formed interactions between the protein and the ligand.\textsuperscript{20}

**Animal Models and Decoction Preparation**

Sixty SPF SD male rats were randomly divided into 6 groups: control, model, SWQWD high dose (36.8 g/kg), SWQWD medium dose (18.4 g/kg), SWQWD low dose (9.2 g/kg), and positive drug groups (dexamethasone 0.001 g/kg), respectively. Treatment administration started 3 d after adaptive feeding with 1 mL/100 g for 7 d. One hour after the last administration, rats were anesthetized with a 3% pentobarbital 40 mg/kg solution. In contrast, control rats were intratracheally instilled with sterile PBS 100 \( \mu \)L, and the rats in the other groups were intratracheally instilled with 1 mg/mL LPS 100 \( \mu \)L. The rats were killed after 6 h of anesthesia, and BALF was collected from each animal. TNF-\( \alpha \) was detected in BALF samples using an ELISA detection kit (Bioss, lot: BA06185133) (Bioss Antibodies, MA, USA), following the manufacturer’s protocol. The Hubei Experimental Animal Center provided the animals under the experimental animal quality certificate: no. 42000600043471. The rats were maintained in cages at ambient temperature (20 °C-25 °C and 50%-60% relative humidity). Animal bedding was replaced weekly, and used beddings was washed and disinfected accordingly. The caged rats were illuminated for 10 to 14 h a day, fed, and provided drinking water every morning. The animal experiments were conducted in strict compliance with the ethical requirements of animal experimentation, ethical batch number: HUCMS202109001.

SWQWD was prepared from a mixture of 10 kg *Saposhnikoviae* Radix, 16.3 kg *Astragali* Radix, 2.2 kg *Phragmitis* Rhizoma, 10 kg *Lonicerae japonicae*, 10 kg *Eupatori Herba*, 6.6 kg *Woodwardiae* Rhizoma, 6.6 kg *Atractylodi* Rhizoma, 6.6 kg *Citri reticulatae* Pericarpium, 2.2 kg *Jujubae* Fructus, and 10 kg *Atractylodes macrocephala* Koidz. The mixture (80.5 kg) was put in an extraction tank and soaked in...
Figure 5. Identification of the key subnetwork using Cytoscape. (A) The protein–protein interaction (PPI) network and the first filtration by CytoNca. The yellow nodes were screened using a score higher than the median. (B) The subnetwork was constructed by a second filtration via CytoNca. The yellow nodes were screened using a score higher than the median. (C) The core sub-networks filtered using the CytoNca plugin. (D) Core sub-networks analyzed using the CytoHubba plugin; the darker the color, the higher the ranking.
805 L of water (10 \times \text{the total weight}) for 1 h. The second decoction was in 644 L (8 \times \text{times the total weight}), and this was cooked twice at a constant temperature of 100 °C, first for 30 min, followed by 20 min. Afterward, the supernatant of the secondary decoction was collected by filtration and combined with the first decoction. The filtrate was vapor distilled, and the volatile liquid was incorporated into the concentration tank to make vacuum concentrations (temperature 60 °C-80 °C) of approximately 1.1 to 1.3. The vacuum concentrate was dried in a Galanz microwave oven (P7021TP-6) (Galanz, Shandong, China) to obtain the infusion extracts weighing 28.6 kg (yield 35.5%). Next, the infusion extracts were vacuum-sealed in aluminum packaging plastic bags for later use.

**Statistical Analysis**

The experimental data were statistically analyzed using Graphpad Prism software, and pairwise comparisons between groups were performed using the LSD t-test with \( P < .05 \) as the test level.

The flowchart of this study is shown in Figure 1.

**Results**

**Screening the Active Compounds in SWQWD**

A total of 918 compounds were retrieved from the TCMSP database and SwissTargetPrediction database, yielding 113 active compounds with OB \( \geq 30\% \) and DL \( \geq 0.18 \) as the screening standard. Table 1 shows the literature-based information on the main active compounds in each SWQWD constituent medicinal material.

**TCM-Compounds-Target-Disease Interaction Network**

The Venn diagram above shows 73 common action targets between the SWQWD active compounds and COVID-19 genes (Figure 2a). The TCM Compounds-Target-Disease network chart has 162 nodes (including 10 TCMs, 79 compounds, and 73 common targets) and 693 edges. The top 10 chemical components are quercetin, kaempferol, luteolin, wogonin, beta-sitosterol, nobiletin, formononetin, naringenin, isorhamnetin, and 7-O-methylisomucronulatol (Table 2). The specific topological parameters show that these 10 chemical components may be the main active components preventing COVID-19 (Figure 2b).

**GO and KEGG Enrichment Analysis**

The 73 common targets enriched 470 GO entries (\( P < .05 \)), and the top 10 terms are illustrated in Figure 3. The GO terms suggested that these target genes are essential in hypoxia, inflammation, and immune responses (Figure 3a to c). Moreover, the KEGG enrichment analysis identified 119 (\( P < .05 \)) signaling pathways, including immune-related pathways such as TNF, Toll-like receptor, and PI3K-AKT (Figure 3d). The relationship between the above top 10 immune-related pathways, the genes that enrich these pathways, and TCM and their major active compounds are shown in Figure 4.

**PPI and Core Subnetworks Predicting the Potential Action Target**

A PPI network derived from the STRING database showed that the proteins encoded by the target genes had complex interactions. The PPI network generated 2 core subnetworks of 15 targets using CytoNca and CytoHub, ranking TNF on top (Figure 5).

**Active Ingredient-Target Molecular Docking Results**

We screened the key target TNF through the core sub-network to verify whether the main active ingredients in SWQWD fought new coronavirus through TNF as a potential target. The molecularly docked protein 1DU3 (encoded by TNF) with the top 10 compounds as potentially active compounds had low binding free energy to the TNF (Table 3). Quercetin, kaempferol, and lignan docked with the TNF receptor, showing that quercetin, kaempferol, and lignan enter the TNF binding pocket and maybe exert their anti-new coronavirus pneumonia effects by acting on the TNF receptor. The docking details are shown in Figure 6. Supplemental Figure S1represents the interactions formed between the best 3 herbal compounds with the target receptor-1DU3, while Supplemental Table S1 shows the details of the interactions formed.

**TNF-α in BALF and ALI Rats**

Further investigation of the TNF action through animal experiments showed that TNF-α significantly increased in BALF compared to the normal group (\( P < .01 \)). Moreover, TNF-α was significantly reduced in BALF from SWQWD high, SWQWD medium, and dexamethasone groups (\( P < .05 \); Table 4).

**Table 3. The Binding Energies of the First 10 Compounds.**

| CAS         | Molecule names          | Molecular formula | TNF docking score (kcal/mol) |
|-------------|-------------------------|-------------------|------------------------------|
| 117-39-5    | Quercetin               | C_{15}H_{10}O_{7}  | −8.2                         |
| 520-18-3    | Kaempferol              | C_{15}H_{10}O_{8}  | −8.1                         |
| 491-70-3    | Luteolin                | C_{15}H_{10}O_{8}  | −8.6                         |
| 632-85-9    | Wogonin                 | C_{16}H_{12}O_{5}  | −8.1                         |
| 83-46-5     | Beta-sitosterol         | C_{20}H_{16}O_{4}  | −9.7                         |
| 478-01-3    | Nobiletin               | C_{15}H_{12}O_{6}  | −7.5                         |
| 485-72-3    | Formononetin            | C_{16}H_{12}O_{4}  | −8.4                         |
| 480-41-1    | Naringenin              | C_{16}H_{12}O_{4}  | −8.6                         |
| 480-19-3    | Isorhamnetin            | C_{16}H_{12}O_{4}  | −8.4                         |
| 90-19-7     | 7-O-methylisomucronulat | C_{16}H_{12}O_{5}  | −8.5                         |

Abbreviation: TNF, tumor necrosis factor.
Discussion

Patients with COVID-19 show low immunity, fever, cough, sore throat, and diarrhea. Based on the characteristics of this disease, the expert group of Jingmen TCM Hospital used a compound formula composed of anti-diarrheal drugs such as Saposhnikoviae Radix, Atractylodes macrocephala, Astragali Radix, Lonicerae japonicae, Eupatorii Herba, and Atractylodis Rhizoma. Saposhnikoviae Radix, Atractylodes macrocephala, and Astragali Radix and found that this can enhance the immune function, while Lonicerae japonicae, Eupatorii Herba, and Atractylodis Rhizoma played an important role in the 2003 SARS outbreak. This formula improves the immunity of susceptible people as a whole while fighting the inflammation caused by COVID-19.

Figure 6. Molecular docking between quercetin (A, B), kaempferol (C, D), luteolin (E, F), and protein 1DU3 (encoded by tumor necrosis factor [TNF]).
Table 4. Contents of TNF-α in BALF of ALI Rats.

| Group                        | Dose (g/kg) | TNF-α      |
|------------------------------|-------------|------------|
| Normal group                 | –           | 99.8 ± 12.1** |
| Model group                  | –           | 48.4 ± 3.0**  |
| High-dose group of SWQWD     | 36.8        | 144.3 ± 71.0** |
| Middle-dose group of SWQWD   | 18.4        | 187.1 ± 51.9** |
| Low-dose group of SWQWD      | 9.2         | 215.5 ± 120.1*   |
| Positive drug (dexamethasone) group | 0.001      | 116.1 ± 34.1**   |

Abbreviations: TNF-α, tumor necrosis factor-α; BALF, bronchoalveolar lavage fluid; ALI, acute lung injury; SWQWD, Shiwei Qingwen decoction.

We screened several ingredients of SWQWD in the TCMSP database. This study generated 10 potential active compounds: quercetin, kaempferol, luteolin, wogonin, beta-sitosterol, nobiletin, formononetin, naringenin, isorhamnetin, and 7-O-methylisoumuronolactol from a TCM-medicine-compound-target-disease composite network screened by network topological parameters. Quercetin, abundantly found in Jujubae Fructus, Astragali Radix, and Lonicerae japonicae, has antioxidant, anti-inflammatory, and immune promotion effects, thus, inhibiting the expression of inflammatory factor IL-6 and reducing the inflammatory response. Recent studies have also shown that quercetin has the potential to treat COVID-19. Kaempferol is commonly found in Woodwardiae Rhizoma and Lonicerae japonicae and has antioxidation, anti-inflammatory, and antiviral effects, increasing autophagy and reducing silica-induced pulmonary fibrosis. Moreover, luteolin is abundant in Lonicerae japonicae and EupatoriHerba and has anti-inflammatory, anti-oxidation, and antiviral properties, which inhibit the expression of the NF-κB signaling pathway, thus reducing the contents of cytokines like TNF-α, IL-1β, and IL-6. Besides, luteolin is protective against LPS-induced ALI in mice. Wogonin is abundant in Saposhnikoviae Radix and Astragali Radix and exhibits anti-inflammatory effects. Wogonin inhibits iNOS expression, reduces NF-κB activity, and weakens the LPS-induced inflammatory response in macrophages. However, beta-sitosterol, commonly found in Saposhnikoviae Radix, Jujubae Fructus, and Lonicerae japonicae, has anti-inflammatory effects and inhibits the activation of NLRP3 in macrophages. Beta-sitosterol significantly reduces the activation of cellular inflammatory factors such as TNF-α, IL-1β, and IL-6 and protects against ALI. In summary, SWQWD contains active compounds that may prevent COVID-19 through its anti-inflammatory and immune-enhancing properties.

The enriched GO functions and KEGG pathways demonstrated that the SWQWD active components mainly regulate apoptosis, inflammatory response, oxidative stress processes, and other regulations, including enhancing immunity, anti-inflammation, and antiviral responses. The enriched functions and pathways are highly related to the PI3K-ATK, Toll-like receptor (TLRs), and TNF signaling pathways. Moreover, viral stimulation of PI3K-ATK and TLRs signaling pathways leads to the release of inflammatory mediators, enabling the inflammatory response. Stimulating PI3K-ATK and TLRs signaling pathways also activate NF-κB and regulate the transcription of inflammatory cytokine genes, thus, generating inflammatory factors such as IL-6 and TNF-α. When TNF reverses its effect on the expression of PI3K-ATK and TLRs, the inflammatory response and immune destruction escalate. Therefore, a possible mechanism is that SWQWD active components exert anti-inflammatory and immune-modulating functions by acting on the PI3K-ATK-NF-κB-TNF and TLRs-NF-κB-TNF signaling pathways preventing COVID-19 disease development.

The above analysis implied that SWQWD has a COVID-19 preventive effect, so we further discovered the core genes by generating core subnetworks. Tumor necrosis factor (TNF) was the highest-ranked target gene in the 2 core subnetworks. In addition, the molecular docking results showed that TNF has a high affinity toward the top ten potentially active compounds. TNF, as an endogenous pyrogen, mainly regulates immune cells that cause fever, preventing tumorigenesis and viral replication. Besides, TNF is a pro-inflammatory cytokine that can mediate MAPK, ERK, and NF-κB signaling pathways that are widely involved in physiological and pathological cell differentiation processes, apoptosis, and induced inflammation. Overexpressing TNF and IL-6 causes lung injury and increases the COVID-19 fatality rate. Therefore, inhibiting the overproduction of cytokines (such as TNF and IL-6) is the main treatment strategy for COVID-19. Rat experiments for ALI showed that SWQWD significantly reduces TNF-α contents in the BALF of ALI rats, possibly inhibiting the production of inflammatory factors and providing an anti-pneumonia effect.

Conclusion

In summary, this study demonstrated the preventive mechanisms of SWQWD on COVID-19. The study focused on the role of SWQWD in improving immunity and decreasing the inflammatory responses of infection and oxidative stress. In addition, we proposed a potential target for COVID-19 and verified the role of TNF targets in preventing COVID-19 in vivo and in vitro. We believe SWQWD can prevent and control COVID-19 through the target of TNF and these findings may aid the global fight against the COVID-19 pandemic.

Acknowledgements

We thank MogoEdit for its linguistic assistance during the preparation of this manuscript.

Authors’ Contributions

All authors have read and agreed to the published version of the manuscript.
Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Department of Science and Technology of Hubei Province (grant no. NO2020DEB016).

ORCID iD
Li Wen https://orcid.org/0000-0002-8647-851X

Supplemental Material
Supplemental material for this article is available online.

References
1. Hamed S-M, Elkhatib W-F, Khairalla A-S, et al. Global dynamics of SARS-CoV-2 clades and their relation to COVID-19 epidemiology. Sci Rep. 2021;11(1):8435.
2. Khan A-H, Tirth V, Fawzy M, et al. COVID-19 transmission, vulnerability, persistence and nanotherapy: a review. Environ Chem Lett. 2021;19(4):2773–2787. doi: 10.1007/s10311-021-01229-4. Epub 2021 Apr 7. PMID: 33846683; PMCID: PMC8026094.
3. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiol Genomics. 2020;52(11):549-557.
4. Fathi F, Sami R, Mozafarpoor S, et al. Immune system changes during COVID-19 recovery play key role in determining disease severity. Int J Immunopathol Pharmacol. 2020;34:2058738420966497. doi: 10.1177/2058738420966497. PMID: 33076729; PMCID: PMC7594220.
5. Tegally H, Wilkinson E, Giovanetti M, et al. Detection of a SARS-CoV-2 variant of concern in South Africa. Nature. 2021;592(7854):438-443.
6. Tao Q, Du J, Li X, et al. Network pharmacology and molecular docking analysis on molecular targets and mechanisms of Huashí Baidu formula in the treatment of COVID-19. Drug Des Ind Pharm. 2020;46(8):1345-1353.
7. Su J, Yang XH, Fu DQ, et al. Summary of clinical thinking on the prevention and treatment of COVID-19 with “Shiwei Qingwen Decoction”. J Bas Clin Med. 2020;26(3):389-390.
8. Habashi NM, Camporota L, Gatto LA, Nieman G. Functional pathophysiology of SARS-CoV-2-induced acute lung injury and clinical implications. J Appl Physiol. 2021;130(5):877-891.
9. Xiao K, He W, Guan W, et al. Mesenchymal stem cells reverse EMT process through blocking the activation of NF-κB and Hedgehog pathways in LPS-induced acute lung injury. Cell Death Dis. 2020;11(10):863.
10. Ru J, Li P, Wang J, et al. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. J Cheminform. 2014;6:13. doi: 10.1186/1758-2946-6-13. PMID: 24735618; PMCID: PMC4001360.
11. Uni Prot Consortium T. Uniprot:the universal protein knowledge-base. Nucleic Acids Res. 2017;45(D1):D158-D169.
12. Safran M, Dalah I, Alexander J, et al. GeneCards version 3: the human gene integrator. Database (Oxford). 2010;2010:baq020. doi: 10.1093/database/baq020. PMID: 20689021; PMCID: PMC2938259.
13. Amberger JS, Hamosh A. Searching online Mendelian inheritance in man (OMIM): a knowledgebase of human genes and genetic phenotypes. Curr Proteomics Bioinformatic. 2017;58:1.2.1-1.2.12. doi: 10.1002/cpbi.27. PMID: 28654725; PMCID: PMC5662200.
14. Rezaei-Tavirani S, Rostami-Nejad M, Yafaei R, et al. Introducing tumor necrosis factor as a prominent player in celiac disease and type 1 diabetes mellitus. Gastroenterol Hepatol Bed Bench. 2019;12(Suppl1):S123-S129.
15. Dennis G Jr, Sherman BT, Hosack DA, et al. DAVID: database for annotation, visualization, and integrated discovery. Genome Biol. 2003;4(5):P3. Epub 2003 Apr 3.
16. Cook HV, Doncheva NT, Szklarczyk D, von Mering C, Jensen LJ. Viruses. STRING: a virus-host protein–protein interaction database. Viruses. 2018;10(10):519.
17. Xia QD, Xun Y, Lu JL, et al. Network pharmacology and molecular docking analyses on Lianhua Qinqwen capsule indicate ACT1 is a potential target to treat and prevent COVID-19. Cell Prolif. 2020;53(12):e12949. doi: 10.1111/cpr.12949. Epub 2020 Nov 3.
18. Baswar D, Sharma A, Mishra A. In silico screening of pyridoxine carboxylates for anti-Alzheimer’s activities. Cent Nerv Syst Agents Med Chem. 2020;21(1):39-52.
19. Trost O, Olson AJ. Autodock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem. 2010;31(2):455-461.
20. Halder P, Pal U, Paladhi P, et al. Evaluation of potency of the selected bioactive molecules from Indian medicinal plants with MPro of SARS-CoV-2 through in silico analysis. J Ayurveda Integr Med. 2022;13(2):100449. doi: 10.1016/j.jaim.2021.05.003. Epub 2021 May 21. PMID: 34054246; PMCID: PMC8139275.
21. Jia CY, Li JY, Hao GF, Yang GF. A drug-likeness toolbox facilitates ADMET study in drug discovery. Drug Discov Today. 2020;25(1):248-258.
22. Jiang X, Pang LJ, Lv XD, et al. Treatment of viral pneumonia from spleen dampness and lung dryness. J Liaoning University Trad Chin Med. 2021;1-14.
23. Li Y, Yao J, Han C, et al. Quercetin, inflammation and immunity. Nutrients. 2016;8(3):167.
24. Kandere-Grzybowska K, Kempuraj D, Cao J, Cetrulo CL, Theoharides TC. Regulation of IL-1-induced selective IL-6 release from human mast cells and inhibition by quercetin. Br J Pharmacol. 2006;148(2):208-215.
25. Agrawal PK, Agrawal C, Blunden G. Quercetin: antiviral significance and possible COVID-19 integrative considerations. Nat Prod Commun. 2020. doi: 10.1177/1934578X20976293.
26. Devi KP, Malar DS, Nabavi SF, et al. Kaempferol and inflammation: from chemistry to medicine. Pharmacol Res. 2015;99:1-10. doi: 10.1016/j.phrs.2015.05.002. Epub 2015 May 14. PMID: 25982933.
27. Liu H, Yu H, Cao Z, et al. Kaempferol modulates autophagy and alleviates silica-induced pulmonary fibrosis. DNA Cell Biol. 2019;38(12):1418-1426.
28. Yan H, Ma L, Wang H, et al. Luteolin decreases the yield of influenza a virus in vitro by interfering with the coat protein I complex expression. *J Nat Med*. 2019;73(3):487-496.
29. Kuo MY, Liao MF, Chen FL, et al. Luteolin attenuates the pulmonary inflammatory response involves abilities of antioxidation and inhibition of MAPK and NFκB pathways in mice with endotoxin-induced acute lung injury. *Food Chem Toxicol*. 2011;49(10):2660-2666.
30. Huynh DL, Ngau TH, Nguyen NH, Tran GB, Nguyen CT. Potential therapeutic and pharmacological effects of Wogonin: an updated review. *Mol Biol Rep*. 2020;47(12):9779-9789.
31. Gong G, Wang H, Kong X, Duan R, Dong TTX, Tsim KWK. Flavonoids are identified from the extract of *Scutellariae Radix* to suppress inflammatory-induced angiogenic responses in cultured RAW 264.7 macrophages. *Sci Rep*. 2018;8(1):17412.
32. Liao PC, Lai MH, Hsu KP, et al. Identification of β-sitosterol as in vitro anti-inflammatory constituent in *Moringa oleifera*. *J Agric Food Chem*. 2018;66(41):10748-10759.
33. Blasius AL, Beutler B. Intracellular toll-like receptors. *Immunity*. 2010;32(3):305-315.
34. Ko JH, Yoon SO, Lee HJ, Oh JY. Rapamycin regulates macrophage activation by inhibiting NLRP3 inflammasome-p38 MAPK-NFκB pathways in autophagy- and p62-dependent manners. *Oncotarget*. 2017;8(25):40817-40831.
35. Quaresma JA, Barros VL, Pagliari C, et al. Revisiting the liver in human yellow fever: virus-induced apoptosis in hepatocytes associated with TGF-beta, TNF-alpha and NK cells activity. *Virology*. 2006;345(1):22-30.
36. Lai JL, Liu YH, Liu C, et al. Indirubin inhibits LPS-induced inflammation via TLR4 abrogation mediated by the NF-kB and MAPK signaling pathways. *Inflammation*. 2017;40(1):1-12.
37. Cheng SC, Huang WC, Pang JH S, Wu YH, Cheng CY. Quercetin inhibits the production of IL-1β-induced inflammatory cytokines and chemokines in ARPE-19 cells via the MAPK and NF-κB signaling pathways. *Int J Mol Sci*. 2019;20(12):2957.
38. Li M, Ye J, Zhao G, et al. Gas6 attenuates lipopolysaccharide-induced TNF-α expression and apoptosis in H9C2 cells through NF-κB and MAPK inhibition via the Axl/PI3K/Akt pathway. *Int J Mol Med*. 2019;44(3):982-994.
39. Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G. COVID-19: pathogenesis, cytokine storm and therapeutic potential of interferons. *Cytokine Growth Factor Rev*. 2020;53:66-70. doi: 10.1016/j.cytogfr.2020.05.002. Epub 2020 May 7. PMID: 32418715; PMCID: PMC7204669.
40. Soy M, Keser G, Aratgündüz P, Tabak F, Aratgündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol*. 2020;39(7):2085-2094.