Network pharmacology and bioinformatics analysis identified essential genes of Jingulian in the treatment of rheumatoid arthritis and COVID-19

Haiyan Zhou[1#], Changchao Zou[2#], Bing Wang[1], Chao Li[1], Muzhi Lin[1], Lili Mo[1], Bei Zhang[3], Niwen Huang[4], Bo Wei[1], Xiufang Yang[5], Wupeng Liu[1], Guobao Xiong[1], Zheng Shen[1], Wei Zhou[1], Xingde Liu[2], Wei Li[1], Mingzhu Gao[6,7]

[1]Department of Cardiovascular Medicine, The Affiliated Hospital of Guizhou Medical University, Guiyang, China; [2]Department of Cardiovascular Medicine, The Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang, China; [3]Department of Ultrasound, The Affiliated Hospital of Guizhou Medical University, Guiyang, China; [4]Department of Respiratory Medicine, The Affiliated Hospital of Guizhou Medical University, Guiyang, China; [5]Department of Laboratory Medicine, Sansui People Hospital, Kaili, China; [6]Department of Laboratory Medicine, The Affiliated Wuxi No. 2 People's Hospital of Nanjing Medical University, Wuxi, China; [7]Department of Laboratory Medicine, Affiliated Wuxi Clinical College of Nantong University, Wuxi, China

Contributions: (I) Conception and design: H Zhou, C Zou; (II) Administrative support: W Li, X Liu; (III) Provision of study materials or patients: Z Shen, W Zhou, W Liu, L Mo; (IV) Collection and assembly of data: C Li, B Wang, M Lin; (V) Data analysis and interpretation: B Zhang, N Huang, X Yang, B Wei; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Haiyan Zhou. No. 28 Guiyi Street, Yunyan District, Guiyang 550004, China. Email: zhouhaiyan12388@126.com; Wei Li. No. 28 Guiyi Street, Yunyan District, Guiyang 550004, China. Email: liwei249188@sina.com; Mingzhu Gao. The Affiliated Wuxi No. 2 People's Hospital of Nanjing Medical University, No. 68 Zhongshan Road, Wuxi, China. Email: gaomingzhujewel@163.com.

Background: Patients with rheumatoid arthritis (RA) may be more susceptible to infection by coronavirus disease-19 (COVID-19) due to immune system dysfunction. However, there are still insufficient treatment strategies for patients with RA and COVID-19. Since Jingulian is a traditional Chinese medicine (TCM) with anti-viral and immune regulatory functions, our study aims to explore the detailed mechanisms of Jingulian in treating patients with RA and COVID-19.

Methods: All the components of Jingulian were retrieved from pharmacology databases. Then, a series of network pharmacology-based analyses and molecular docking were used to understand the molecular functions, core targets, related pathways, and potential therapeutic targets of Jingulian in patients with RA/COVID-19.

Results: A total of 93 genes were identified according to the disease-compound-target network. We investigated that the main targets, signaling pathways, and biological functions of Jingulian in RA and COVID-19. Our results indicated that Jingulian may treat patients with RA/COVID-19 through immune processes and viral processes. Moreover, the results of molecular docking revealed that tormentic acid was one of the top compounds of Jingulian, which had high affinity with Janus kinase 1 (JAK1), signal transducer and activator of transcription 3 (STAT3), and epidermal growth factor receptor (EGFR) in patients with RA/COVID-19. Furthermore, 5 core targets of Jingulian were also identified, including JAK1, Janus kinase 2 (JAK2), STAT3, lymphocyte specific protein tyrosine kinase (LCK), and EGFR.

Conclusions: Tormentic acid in Jingulian may regulate JAK1, STAT3, and EGFR, and might play a critical role in RA/COVID-19.

Keywords: Jingulian; coronavirus disease-19 (COVID-19); rheumatoid arthritis (RA); network pharmacology; computational biology

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Introduction

Coronavirus disease-19 (COVID-19) has been a global pandemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new coronavirus discovered in 2019 (1). Remdesivir was the only drug approved by the U.S. Food and Drug Administration (FDA) to treat COVID-19 in adults and children aged 12 and older (2). However, this drug shows limited therapeutic effectiveness especially in patients with severe COVID-19. Therefore, more effective drugs need to be discovered to treat patients with complicated COVID-19.

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterized by synovial hyperproliferation and inflammatory cell infiltration, which can lead to progressive joint damage and even disability, seriously affecting the quality of life of patients (3,4). Furthermore, in-hospital patients with RA are more likely to be infected with COVID-19. In addition, patients with RA are more likely to have a higher risk of severe COVID-19 outcomes (5). Meanwhile, there is also some evidence that COVID-19 may increase the risk of developing RA (6). Treatment for patients with COVID-19 and RA is difficult due to a dysfunction of the immune system and lack of effective medicines. Hence, effective treatments should be explored in such patients.

Jingulian, a traditional Chinese medicine (TCM), can obviously dampen inflammatory responses and provides symptom relief for patients with RA. Jingulian consists of 5 TCMs, including Alangium (Alangiaceae; Chinese alangium), Sargentodoxa Caulis (Lardizabalaceae; Sargentodoxa cuneata), Speranskiae seulmpaticntis Herba (Ericaceae; Gaultheria trichophylla Royle), Psammosilenetunicoides (Caryophyllaceae; Psammosilene), and Guangxi schefflera twig and leaf (Araliaceae; Schefflera leucantha R. Viguier). However, the underlying mechanisms of Jingulian in the treatment of patients with RA/COVID-19 remain unknown.

Network pharmacology is a promising method used to explore all candidate targets and underlying mechanisms of a particular disease (7). Molecular docking is a useful bioinformatics tool used to explore the behaviors of ingredients at the binding site of a target protein (8). In our study, network pharmacology analysis and molecular docking were employed to evaluate the pharmacological and detailed mechanisms of Jingulian. The workflow is shown in *Figure 1*. This study reveals the potential targets and pathways of active compounds derived from Jingulian against patients with RA and COVID-19. Moreover, this study provides new insights into the detailed mechanisms of traditional Chinese medicine against RA and COVID-19. We present the following article in accordance with the STREGA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1665/rc).

Methods

Schematic diagram

The schematic diagram of the research methods in our study is shown in *Figure 1*. Network pharmacology approaches and molecular docking were employed to explore the pharmacological and detailed mechanisms of Jingulian in the treatment of RA and COVID-19. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Identification of the active chemical components

With the purpose of retrieving the chemical ingredients of components in Jingulian capsule, we conducted a complete search using the Traditional Chinese Medicine Systems Pharmacology database (TCMSP, https://old.tcmsp-e.com/tcmsp.php) (9), traditional Chinese medicine database@ TAIWAN database (TCM@TAIWAN, http://tcm.cmu.edu.tw/zh-tw/) (10), and China National Knowledge Infrastructure (CNKI, https://www.cnki.net). The names of herbs were used as the main words to acquire all components. Based on absorption, distribution, metabolism, and excretion, active compounds of Jingulian were screened. In screening out the compounds, oral bioavailability (OB) and drug-likeness (DL) were used as the main indicators to identify pivotal compounds. In our study, the active compounds of Jingulian were screened according to the criterion of OB ≥30% and DL ≥0.18.

Identification of active targets

The ingredients of active compounds were collected and imported into the Swiss Target Prediction Database (swisstargetprediction.ch) (11), Batman (12), and DrugBank (http://go.drugbank.com) (13). The names and ID of the target genes were uniformly obtained using UniProtKB (http://www.uniprot.org) (14).
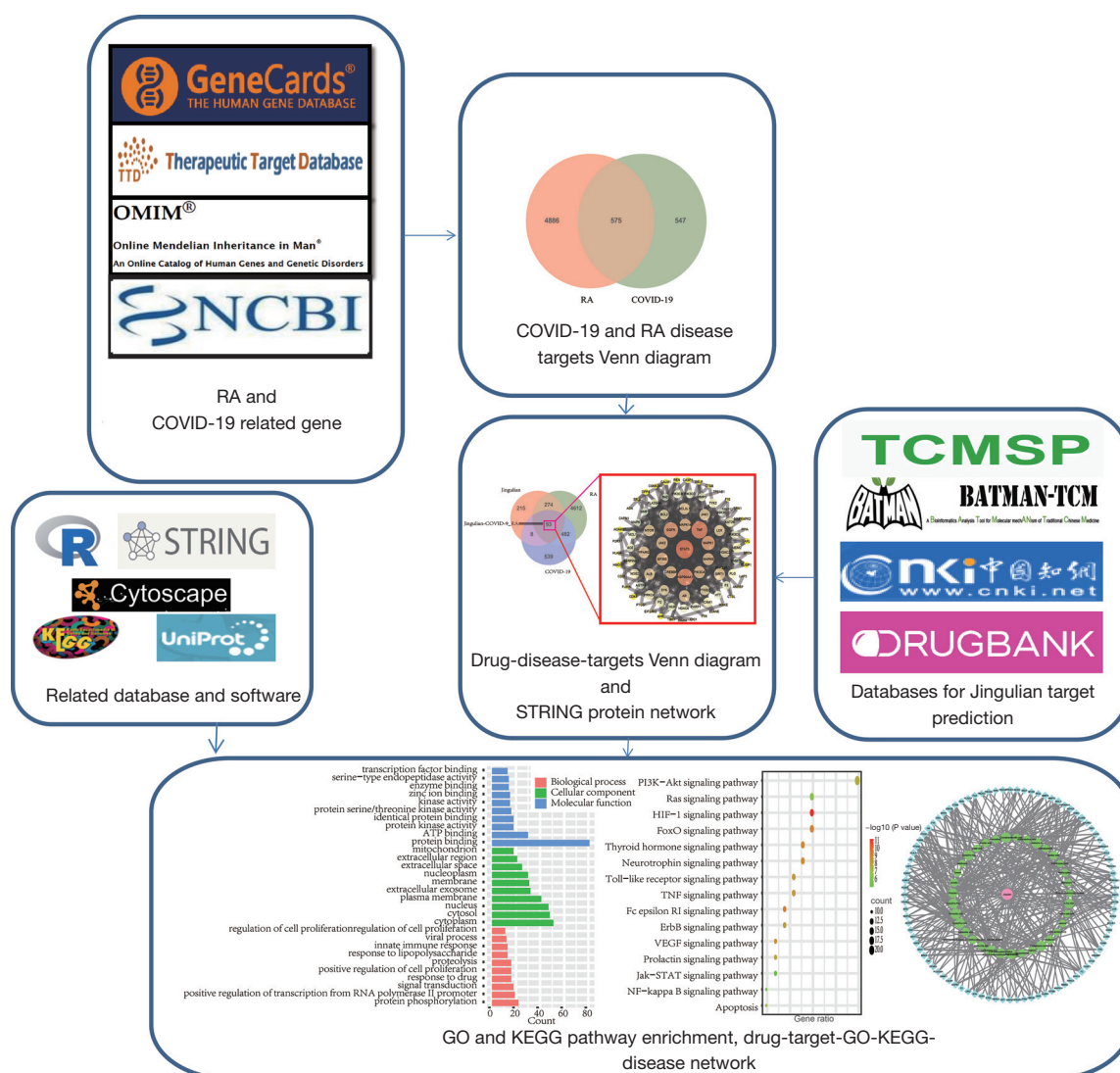
Figure 1 Workflow of the study. The underlying mechanism of Jingulian against COVID-19/RA would be investigated using network pharmacology and molecular docking. COVID-19, coronavirus disease-19; RA, rheumatoid arthritis; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Identification of RA/COVID-19-associated genes

To identify the RA/COVID-19-associated genes, genes related to RA and COVID-19 were retrieved from Genecards (https://www.genecards.org/) (15), the Online Mendelian Inheritance in Man (OMIM) database (https://www.omim.org/) (16), the Therapeutic Target Database (TTD, db.idrblab.net/ttd) (17,18) and the NCBI gene module. Then, overlapping targets of RA and COVID-19 were obtained. Finally, the intersection of retrieved targets of active compounds and RA/COVID-19-related genes

were then collected as the targets of Jingulian in the treatment of patients with RA/COVID-19.

Molecular docking

The three-dimensional (3D) structures of active compounds were acquired from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) (19). 3D structures of RA/COVID-19-related genes were downloaded from the Protein Data Bank (PDB) database (https://www.rcsb.org/). Autodock Vina (version 1.1.2) was used to dock
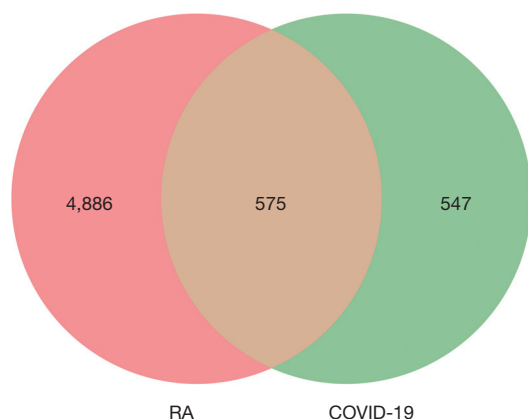
Figure 2 Venn diagram depicting the intersecting genes of RA and COVID-19. RA, rheumatoid arthritis; COVID-19, coronavirus disease-19.

small molecules. The best affinity was selected as the final docking conformation and visualized in Pymol 2.3.

Statistical analysis

The intersection genes of Jingulian and RA/COVID-19 were retrieved for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis in the DAVID database (https://david.ncifcrf.gov/) (18) with the criterion of P value >0.05. GO enrichment analysis included biological processes, molecular functions, and cellular components, and KEGG pathway analysis was performed using the 'ClusterProfiler', 'GOplot', and 'org. Hs.eg.Db' packages. Then, all intersected targets of active compounds and RA/COVID-19-related genes were put into the STRING database to build the protein-protein interaction (PPI) network. Cytoscape software (version 3.6.1) was used for visualization of the compound-target genes-RA/COVID19 network.

Results

Identification of Jingulian targets intersecting with RA and COVID-19

First, network pharmacology identified 5,461 genes associated with RA and 1,122 genes associated with COVID-19 from the Genecards, OMIM, TTD, and NCBI databases (*Figure 2*). In this study, 40 active compounds were identified through the absorption, distribution, metabolism, and excretion (ADME) screening. After

biological correction and deletion of repetitive genes using the UniProt database, a total of 590 targets were identified through the TCMSP database, traditional Chinese medicine database@TAIWAN, and CNKI database using these 40 compounds. An overlap of RA/COVID-19 genes with Jingulian-associated targets identified 93 intersecting genes.

GO and KEGG enrichment

To further explore the intersecting genes, GO enrichment was conducted, which indicated that Jingulian affected a series of biological processes including protein binding, adenosine triphosphate (ATP) binding, protein kinase activity, identical protein binding, and protein serine/threonine kinase activity. After the analysis of cellular components, the targets mainly consisted of the cytoplasm, cytosol, nucleus, and plasma membrane, among others. Furthermore, molecular functions mainly included protein phosphorylation, positive regulation of transcription from RNA polymerase II promoter, signal transduction, positive regulation of cell proliferation, innate immune response, and viral process, among others (*Figure 3*).

Additionally, KEGG enrichment terms related to the intersecting genes included the PI3K-Akt signaling pathway, Ras signaling pathway, HIF-1 signaling pathway, and FoxO signaling pathway, among others (*Figure 3*).

Identification of the main targets of Jingulian against COVID-19/RA

Then, STRING analysis was performed to obtain the PPI network mediated by 93 overlapped genes of Jingulian in the treatment of patients with COVID-19/RA. These intersection genes were input into Cytoscape software to determine 5 core gene targets related to Jingulian against COVID-19/RA, including signal transducer and activator of transcription 3 (STAT3), Janus kinase 1 (JAK1), epidermal growth factor receptor (EGFR), Janus kinase 2 (JAK2), and lymphocyte specific protein tyrosine kinase (LCK) (*Figure 4*). Finally, a Jingulian-compound-target network was constructed (*Figure 5*).

Results of molecular docking

In order to explore the possible binding of ingredients of Jingulian to the targets associated with RA/COVID-19, the 5 core proteins in the PPI network were selected to perform molecular docking with the top 5 active
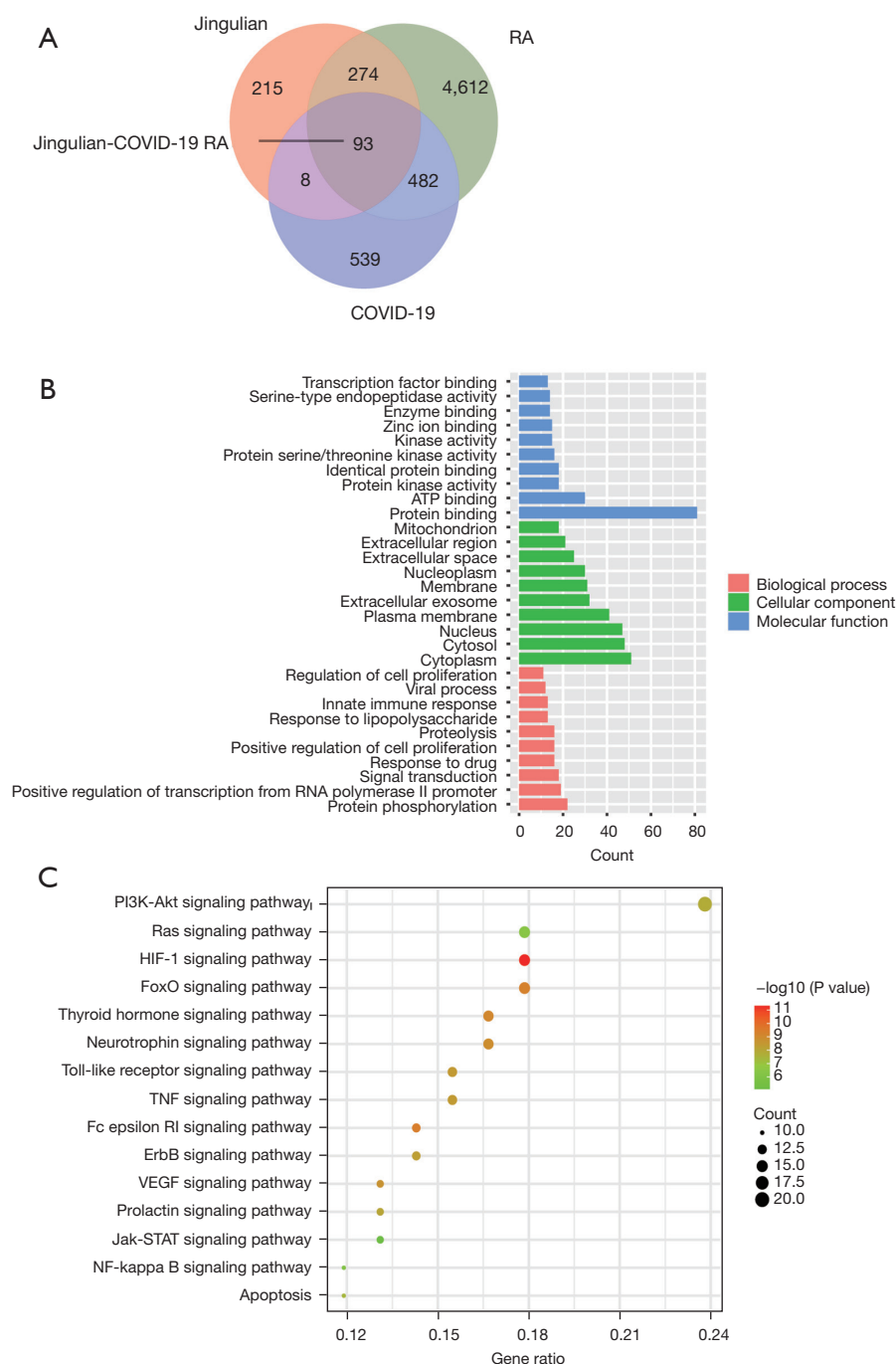
Figure 3 Functional characteristics of Jingulian against RA/COVID-19. (A) Venn diagram depicting the intersecting genes of Jingulian and RA/COVID-19. (B) GO analysis of overlapped genes of Jingulian and RA/COVID-19. (C) KEGG pathway analysis of overlapped genes of Jingulian and RA/COVID-19. RA, rheumatoid arthritis; COVID-19, coronavirus disease-19; ATP, adenosine triphosphate; HIF, hypoxia-inducible factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; NF, nuclear factor; STAT, signal transducer and activator of transcription; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

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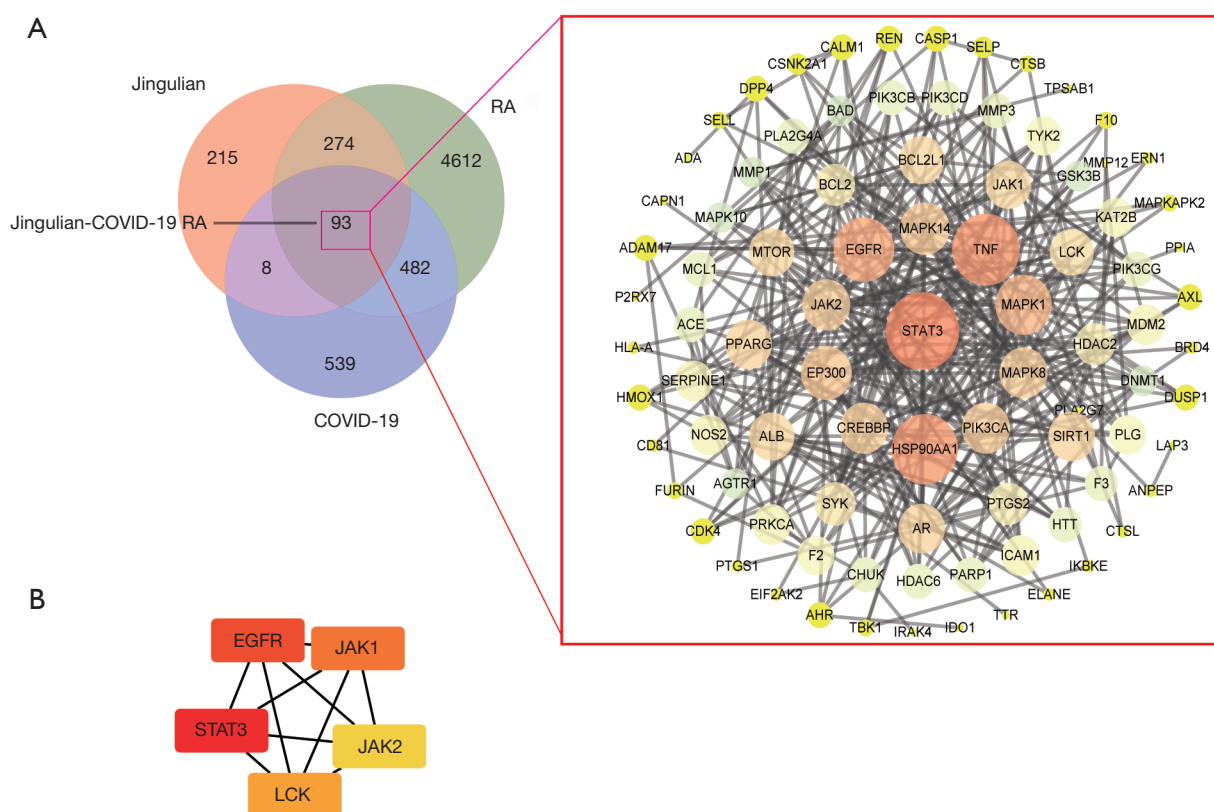

Figure 4 Gene network analysis of Jingulian against RA/COVID-19. (A) STRING analysis indicating protein-protein interaction networking mediated by 93 overlapped targets of Jingulian in the treatment of patients with RA/COVID-19. (B) Five targets, including JAK1, JAK2, STAT3, LCK, and EGFR, were screened using cytoHubba. RA, rheumatoid arthritis; COVID-19, coronavirus disease-19; STAT3, signal transducer and activator of transcription 3; JAK1, Janus kinase 1; LCK, lymphocyte specific protein tyrosine kinase; JAK2, Janus kinase 2; EGFR, epidermal growth factor receptor.

ingredients in the drug component-target-pathway network. Among the docking results, the main binding complexes are displayed in *Figure 6*, including STAT3-tormentic acid docking (−11.4 kcal/mol), JAK1-tormentic acid docking (−12.6 kcal/mol), EGFR-tormentic acid docking (−12.6 kcal/mol), JAK2-tormentic acid docking (−10.3 kcal/mol), and LCK-tormentic acid docking (−8.4 kcal/mol). The 3D structure of STAT3 was obtained from the PDB database (https://www.rcsb.org/structure/6TLC), and the active cavity box parameter setting center_x, y, z was 0.231, 37.283, and 33.516, respectively. Size_x, y, z was 126, 70, and 126, respectively, whereas the RMSD of the original ligand was 2.3Å. This suggested that tormentic acid had good binding activity with the STAT3 protein. Furthermore, we obtained the 3D structure of EGFR from the PDB database (https://www.rcsb.org/structure/1YY9). The active cavity box parameter

setting center_x, y, z was 35.548, 39.543, and 50.341, respectively. Size_x, y, z was 82, 72, and 126, respectively, whereas the RMSD of the original ligand was 2.7Å. The analysis suggested that hydrogen bonding was formed on 2 amino acid residues TRP-386 and SER-418 (*Figure 6C*), indicating the high-affinity association between tormentic acid and EGFR. In addition, we collected the crystal structure of COVID-19 main protease (https://www.rcsb.org/structure/5R84). The active cavity box parameter setting center_x, y, z was 11.891, 0.634, and 4.517, respectively. Size_x, y, z was 40, 70, and 72, respectively, indicating that tormentic acid had good binding activity with the COVID-19 main protease (*Figure 6*).

Discussion

The prevalence of COVID-19 has had a tremendous

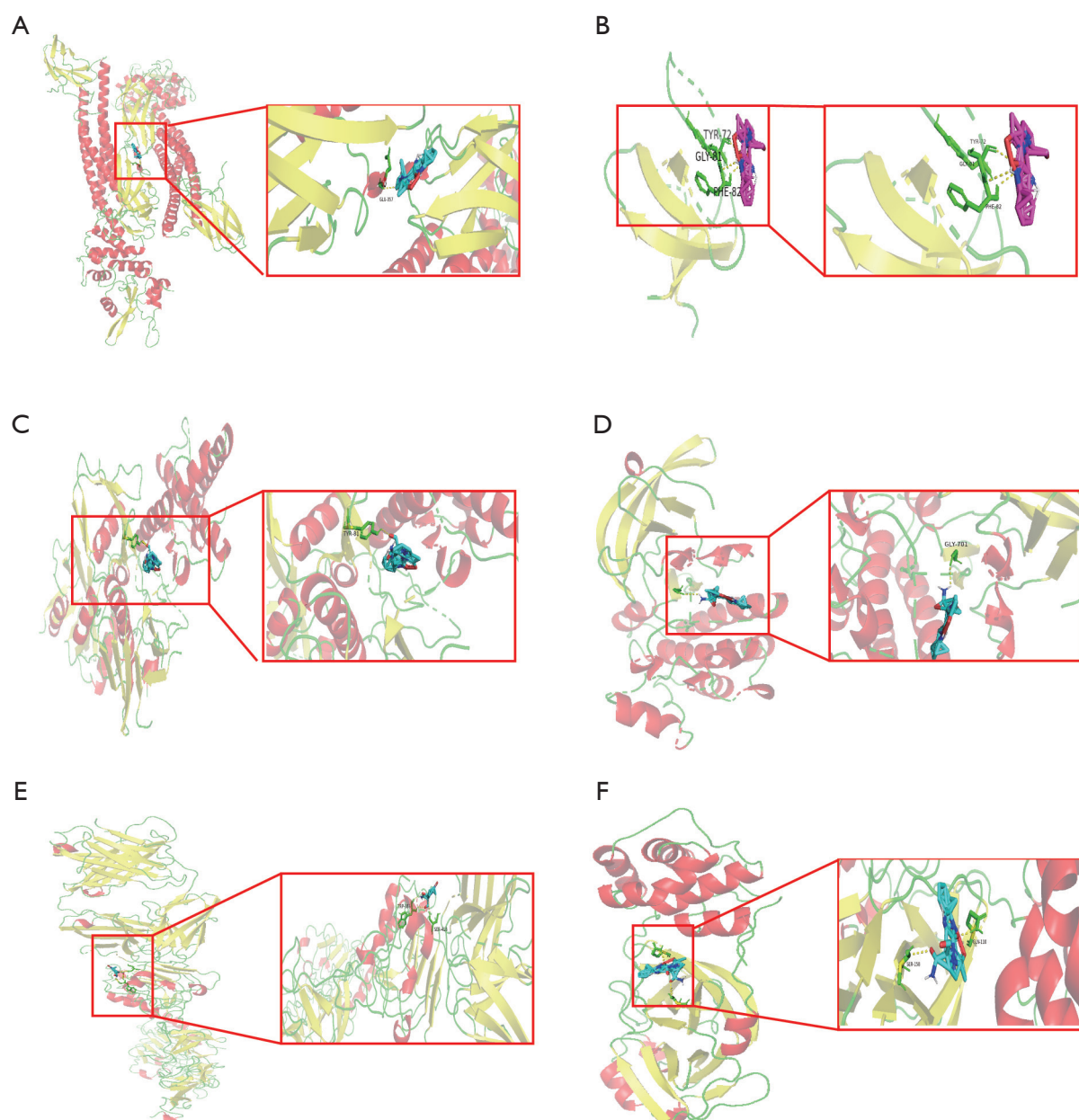*Ann Transl Med* 2022;10(11):635 | https://dx.doi.org/10.21037/atm-22-1665
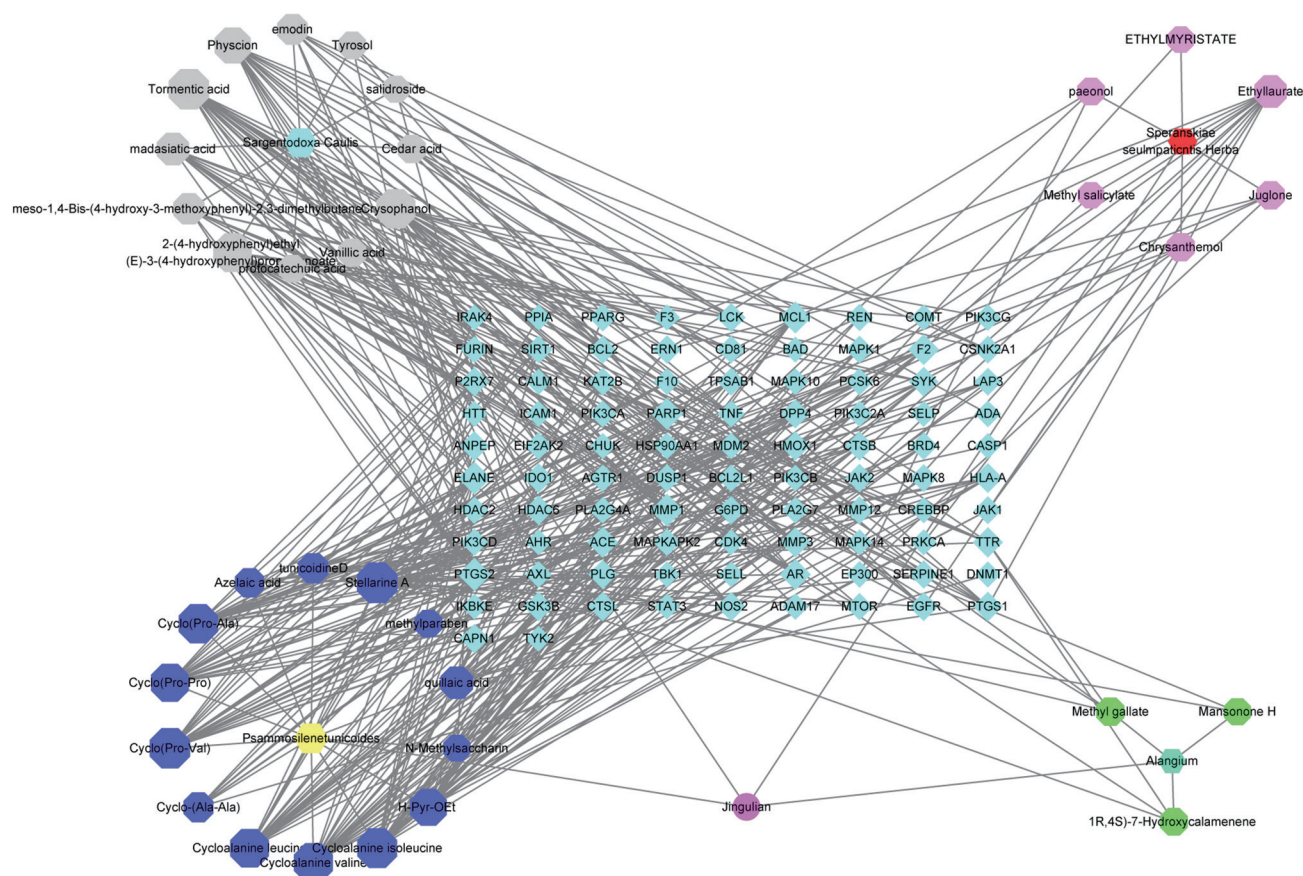
Figure 5 Jingulian-compound-target network (the octagon nodes represent all herbs of Jingulian, the circle nodes represent compounds of Jingulian, and the rhombus nodes represent targets of Jingulian).

impact, leading to a global health emergency with high morbidity and mortality. The treatment of COVID-19 patients includes general supportive care, symptomatic treatment, and respiratory support, among others (20). However, until now, limited specific therapies against COVID-19 have been developed to overcome this disease. A study has reported that COVID-19 can lead to severe inflammation and autoimmune dysfunction (21). Meanwhile, patients with active RA face a higher risk of severe COVID-19 outcomes. Moreover, the incidence of COVID-19 in RA patients may decrease the survival rate.

In the previous reference analysis, glucocorticoid treatment was associated with a higher risk of severe COVID-19 outcomes in RA patients (22). At present, there is no specific drug for RA/COVID-19. Thus, an alternative treatment was explored in patients with COVID-19 and RA. Jingulian, a TCM mainly made from Alangium, Sargentodoxa Caulis, Speranskiae seulmpaticntis

Herba, Psammosilene tunicoides, and Guangxi schefflera twig and leaf, has been used to treat RA with remarkable outcomes and few side effects, and can disperse swelling and has analgesic and anti-inflammatory effects. However, illuminating the mechanisms of TCM in treatment of RA and COVID-19 using traditional methods is challenging. Network pharmacology is a approach to understand the interaction network based on target molecules, biological function, and active compounds, which meets the natural feature of Jingulian formula, and enable elucidate the action mechanism of Jingulian at molecular level with systematic view point, expecting to be of great significance in the treatment of RA and COVID-19.

In our study, we screened out 40 active compounds of Jingulian, including protocatechuic acid (degree =103), vanillic acid (degree =26), and chrysophanol (degree =13), among others. Then, using a network pharmacology approach, 93 intersection genes were identified with

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Figure 6 Binding of tormentic acid, an effective compound of Jingulian, and the key targets using molecular docking. (A) Sites of tormentic acid with STAT3 (PDB ID 6TLC). (B) Sites of tormentic acid with LCK (PDB ID 1KIK). (C) Sites of tormentic acid with JAK1 (PDB ID 5L04). (D) Sites of tormentic acid with JAK2 (PDB ID 4Z32). (E) Sites of tormentic acid with EGFR (PDB ID 1YY9). (F) Sites of tormentic acid with COVID-19 main protease (PDB ID 5R84). COVID-19, coronavirus disease-19; STAT3, signal transducer and activator of transcription 3; JAK1, Janus kinase 1; LCK, lymphocyte specific protein tyrosine kinase; JAK2, Janus kinase 2; EGFR, epidermal growth factor receptor.

Jingulian treatment against COVID-19 and RA. KEGG enrichment analysis showed that the key targets were mainly concentrated on the PI3K-Akt signaling pathway, the HIF-1 signaling pathway, the Ras signaling pathway, and the FoxO signaling pathway, among others. The results

of the PPI network indicated that STAT3, JAK1, EGFR, JAK2, and LCK were the main proteins related to the ingredients of Jingulian against COVID-19/RA. PIK3CA encodes class I phosphatidylinositol-3-kinase (PI3K). A previous study has reported that the PI3K signaling pathway

is related to inflammatory responses and participates in RA-related chondrocyte proliferation, autophagy, and apoptosis (23). Protocatechuic acid, a pivotal component of Jingulian, can reduce inflammation and inhibit proliferation and migration through the PI3K/AKT/mTOR pathway, so as to protect the synovial tissue of the footpad in the rheumatoid joint of rats (24). STAT3 is activated in response to the phosphorylation of various cytokines and growth factors, such as IFN-γ, IL-5, IL-6, and LIF. A previous study reported that the novel synthetic peptide AESIS-1 could be an effective therapeutic for treating RA via the downregulation of STAT3 signaling (25). Therefore, we speculated that Jingulian may directly activate the PI3K pathway and inhibits the molecular function of STAT3 to reduce the inflammatory response.

In our data, GO enrichment analysis showed that the major molecular functions were innate immune responses and viral processes. Protocatechuic acid is a phenolic compound that induces a better antiviral effect by immune enhancement. Additionally, paeonol was shown to protect against cytokine release of FLS by upregulating the FOXO signaling pathway (26). These findings indicate that the anti-RA/COVID-19 action of Jingulian may be modulated by FoxO signaling pathway. Using a molecular docking approach, we identified good binding activity between tormentic acid and STAT3, which may indicate that the compound can effectively bind to specific proteins in COVID-19. However, further clinical and experimental research is still needed.

Conclusions

Taken together, the network pharmacology analysis and molecular docking results highlight anti-inflammation and immune regulation as the main targets of Jingulian treatment in patients with COVID-19/RA. Furthermore, based on the significant pathways and targets, our studies indicated that Jingulian may be used clinically to treat patients with RA/COVID-19.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1665/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1665/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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