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Similarity and Specificity of Traditional Chinese Medicine Formulas for Management of Coronavirus Disease 2019 and Rheumatoid Arthritis

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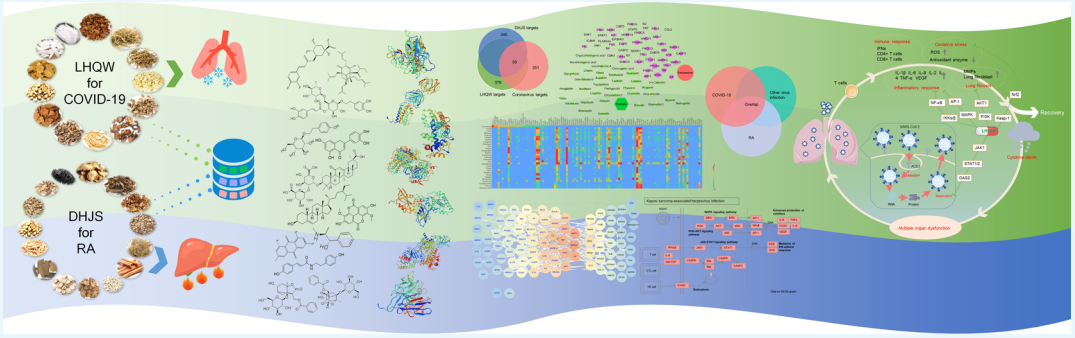

ABSTRACT: The pathogenesis similarity is leading to the introduction of drugs commonly used in rheumatoid arthritis (RA) into coronavirus disease (COVID-19) treatment. Traditional Chinese medicine (TCM) was widely used for the treatment of infectious diseases and rheumatic diseases. However, there is little knowledge of the relationship between COVID-19 and RA treatment employing TCM formulas. The present work was aimed to compare the similarity and specificity of TCM formulas for the management of COVID-19 and RA, as well as to deduce the potential mechanism of TCM for COVID-19 treatment. Two formulas including lianhuaqingwen (LHQW) and duhuojisheng (DHJS) were selected as the representatives of TCM for COVID-19 and RA treatment, respectively. An integrated network pharmacology was used to investigate their similarity and specificity. Although different herbs are present in the two formulas, they generated fairly similar ingredients, targets, interaction networks and enriched pathways, which were mainly involved in virus infection, inflammation, and immune dysregulation. Undoubtedly, they also exhibited their respective specificity. LHQW showed the cold property and lung channel tropism which dominated heat-clearing and lung-freeing, while DHJS showed the warm property and liver channel tropism. Herbal compatibility of LHQW was more in line with the rules of the TCM formula against coronavirus disease. Although both formulas suggested multifunctionality in virus infection and inflammation, LHQW was inclined to cope with virus infection, while DHJS was inclined to cope with inflammation. Therefore, LHQW was reliable for providing the desired efficacy in COVID-19 management because of its cold property, lung channel tropism, and multifunctionality for coping with virus infection and inflammation.

1. INTRODUCTION

Since December 2019, coronavirus disease 2019 (COVID-19) caused by the novel coronavirus SARS-CoV-2 has triggered an ongoing global pandemic. Although great effort has been made to develop vaccines or medications since the two prior coronavirus epidemics (SARS-CoV-1 and MERS-CoV), unfortunately, we have found ourselves unprepared. By 7th Sep, more than 27 million confirmed cases and over 881 thousand deaths have been reported worldwide, and the pandemic trend shows no signs of slowing.[1] COVID-19 is not only threatening the national health systems but also inevitably challenging global political and economic−financial future.

Based on the current knowledge, SARS-CoV-2 infects cells utilizing the cell-surface receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming.[2] SARS-CoV-2 infection can cause autoimmune derangement and cytokine release syndrome (CRS), which lead to multiple organ

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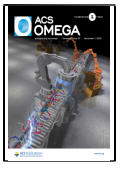

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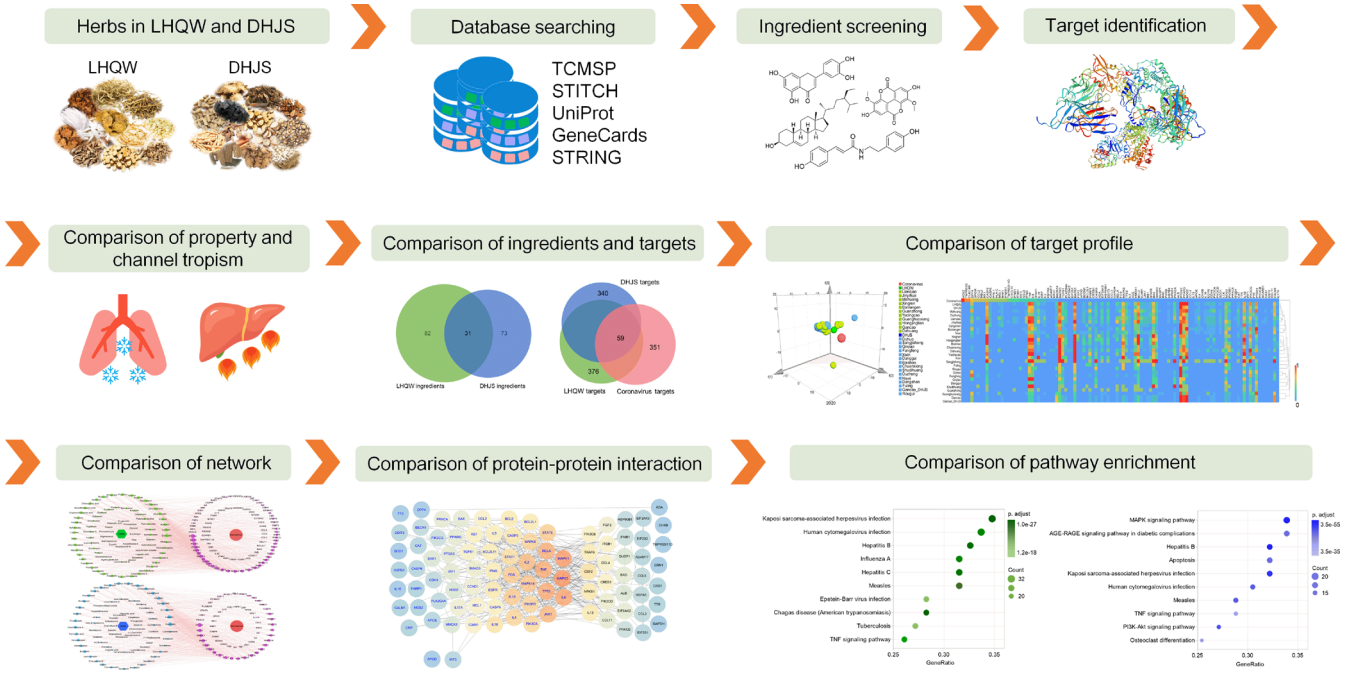

Figure 1. Workflow of the current study.

Table 1. Herbal Composition with the Property, Flavor, and Channel Tropism of LHQW and DHJS

formula	no.	herb name (Chinese)	property and flavor	channel tropism
LHQW	1	*Forsythia suspensa* (Lianqiao)	slightly cold, bitter	lung, heart
	2	*Lonicera japonica* Thunb. (Jinyihua)	cold, sweet	lung, stomach
	3	*Ephedra sinica* Stapf (Mahuang)	warm, pungent	lung, bladder
	4	*Prunus armeniaca* L. (Xingren)	slightly warm, bitter	lung, large intestine
	5	*Isatis indigotica* Fort. (Banlangen)	cold, bitter	heart, stomach
	6	*Dryopteris crassirhizoma* Nakai (Guanzhong)	slightly cold, bitter	liver, stomach
	7	*Houttuynia cordata* Thunb. (Yuxingcao)	slightly cold, pungent	lung
	8	*Pogostemon cablin* (Guanghuoxiang)	slightly warm, pungent	spleen, stomach
	9	*Rhodiola crenulata* (Hongjingtian)	natured, sweet,	lung, heart
	10	*Glycyrrhiza uralensis* Fisch. (Gancao)	natured, sweet,	heart, lung
	11	*Rheum palmatum* L. (Dahuang)	cold, bitter	spleen, stomach
	12	*Gypsum fibrosum* (Shigao)	cold, pungent	lung, stomach
	13	L-menthol (Bohenao)	cold, pungent	lung
DHJS	1	*Angelica pubescens* Maxim. (Duhuo)	slightly warm, pungent	kidney, bladder
	2	*Morws alba* L. (Sangjisheng)	natured, bitter	liver, kidney
	3	*Gentiana macrophylla* Pall. (Qinjiao)	natured, pungent,	stomach, liver
	4	*Saposhnikovia divaricata* (Trucz.) Schischk. (Fangfeng)	slightly warm, pungent	bladder, liver
	5	*Asarum sieboldii* Miq. (Xixin)	warm, pungent	heart, lung
	6	*Angelica sinensis* (Danggui)	warm, sweet	liver, heart
	7	*Paeonia tacti lora* Pall. (Baishao)	slightly cold, bitter	liver, spleen
	8	*Ligusticum chuanxiong* Hort. (Chuanxiong)	warm, pungent	liver, gallbladder
	9	*Rehmannia glutinosa* (Shudihuang)	slightly warm, sweet	liver, kidney
	10	*Eucommia ulmoides* (Duzhong)	warm, sweet	liver, kidney
	11	*Achyranthes bidentata* Blume. (Niuxi)	natured, bitter	liver, kidney
	12	*Codonopsis pilosula* (Franch.) Nannf. (Dangshen)	natured, sweet	spleen, lung
	13	*Poria cocos* (Schw.) Wolf (Fuling)	natured, sweet	heart, lung
	14	*Glycyrrhiza uralensis* Fisch. (Gancao)	natured, sweet	heart, lung
	15	*Cinnamomum cassia* Presl (Rougui)	hot, pungent	kidney, spleen

dysfunctions in the worst case.[3,4] Different from SARS-CoV-1 and MERS-CoV, most cases infected with SARS-CoV-2 were classified as mild. Early isolation, diagnosis, and management could be very important measures for the reduction of mortality.[3,4] However, currently, there is no specific medications for COVID-19. Clinical management mainly provides supportive therapy to alleviate the symptoms and prevent respiratory failure.[5,6] Therefore, there is an urgent need to find effective prophylactic intervention or pharmacological treatment. Because the development of vaccines or medications could take a long time,[7,8] reinvestigating existing drugs represents one of the most practicable strategies for rapid

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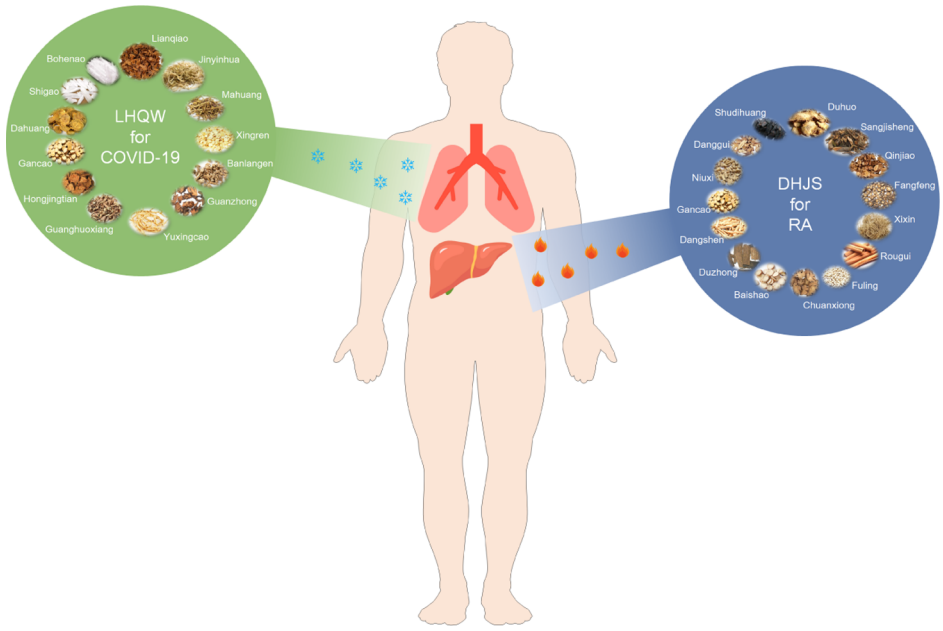

Figure 2. Main function and channel tropism of LHQW and DHJS based on TCM theory.

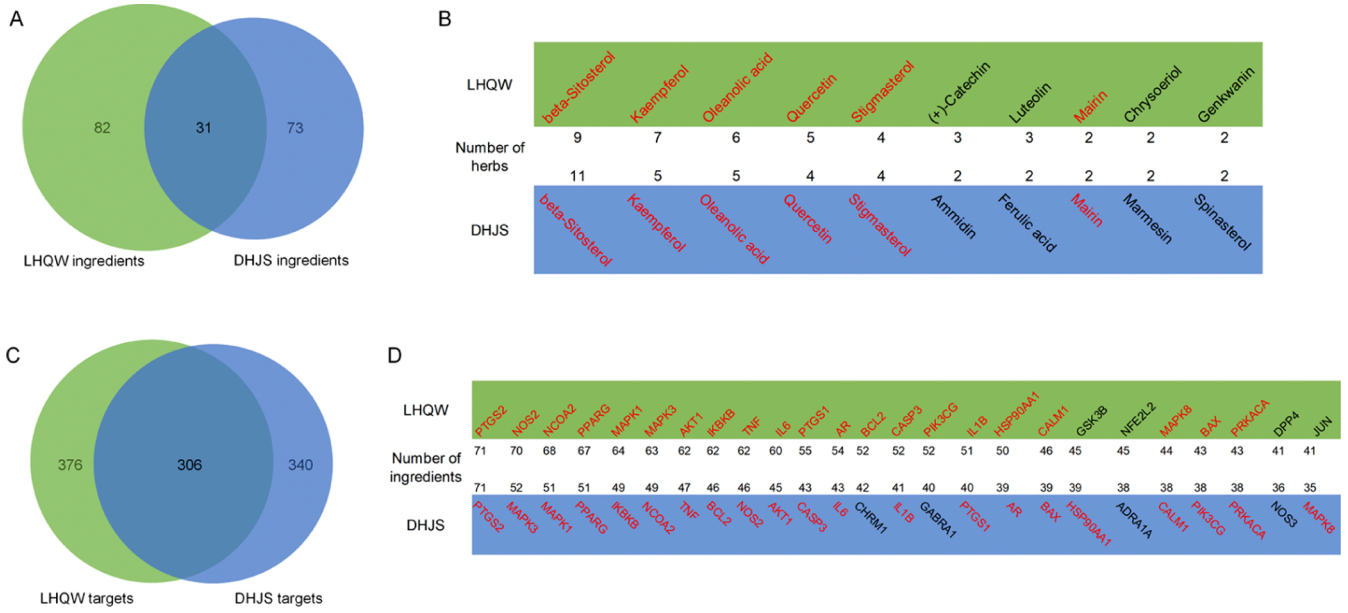

Figure 3. Chemical ingredients and putative targets of LHQW and DHJS. (A) Venn diagram of candidate ingredients; (B) top 10 ingredients from LHQW and DHJS; (C) Venn diagram of putative targets; and (D) top 25 targets from LHQW and DHJS. For panels B and D, items labeled with red color were shared by LHQW and DHJS.

deployment of COVID-19 treatment. Indeed, various drugs have been empirically used in COVID-19 treatment based on *in vitro* antiviral observations, anti-inflammatory properties, or application experience.[9−11]

Interestingly, the etiopathogenesis cascade of COVID-19 is reminiscent of systemic immune disturbances, particularly those in severe rheumatoid patients.[12] Correspondingly, the pathogenesis similarity is leading to the introduction of drugs commonly used in rheumatoid arthritis (RA) treatment into COVID-19 management. For instance, chloroquine and hydroxychloroquine with immunomodulating effects used in RA have now been evaluated for their use in mild cases of COVID-19.[13,14] Tocilizumab, an IL-6 receptor blocker licensed for both RA and CRS, has been preliminarily proven effective for decreasing C-reactive protein levels and alleviating symptoms in COVID-19.[15] Moreover, the JAK inhibitor baricitinib approved for RA therapy has been suggested to play a role in COVID-19 treatment,[16] while some opposed opinions also existed.[15,17]

Traditional Chinese medicine (TCM) was widely used for the treatment of infectious diseases,[18] inflammatory diseases, and rheumatic diseases.[19] Although a multitude of modern RA medications are now under investigation for COVID-19 treatment, there is little knowledge of the relationship between COVID-19 and RA treatment employing TCM formulas. Lianhuaqingwen (LHQW), a Chinese medicine formula composed of 13 herbs, was extended from two TCM prescriptions: Maxing Shigan Tang and Yinqiao San. Maxing

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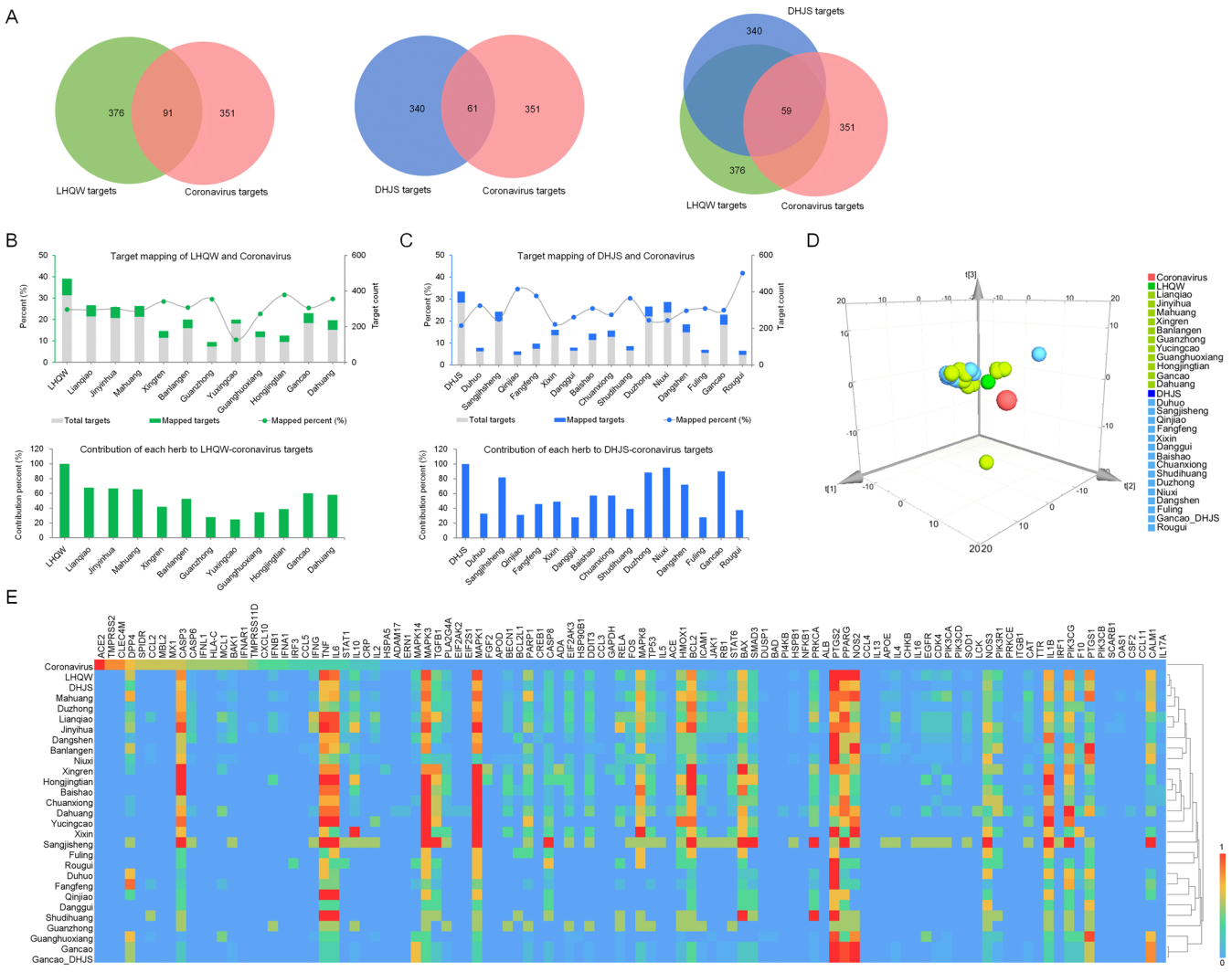

Figure 4. Integration analysis of drug targets and disease targets. (A) Target intersection of LHQW-coronavirus, DHJS-coronavirus, and LHQW-DHJS-coronavirus; (B) mapping and contribution of each herb in LHQW to the target integration of LHQW-coronavirus; (C) mapping and contribution of each herb in DHJS to the target integration of DHJS-coronavirus; (D) scores scatter 3D plot generated from PCA using the target profile data of drugs and disease; and (E) heatmap combined with HCA using the target profile data of drugs and disease.

Shigan Tang was originally described in a Chinese medical book Shanghan Lun for the treatment of febrile diseases. Yinqiao San was originated from the TCM monograph Wenbing Tiaobian for the treatment of "warm disease" characterized by fever and headache. LHQW has been widely used in treating influenza for decades.[20] Currently, it played a positive role in relieving cardinal symptoms and reducing the course of the COVID-19.[21] On the other side, duhuojisheng (DHJS) consisting of 15 herbs originated from the TCM book Prescriptions Valuable Prescriptions for Emergency. DHJS has been applied to the treatment of RA for a long time.[22] In the present work, the two formulas were selected as the representatives of TCM for COVID-19 and RA treatment. Based on integrated network pharmacology, we compared the similarity and specificity of TCM formulas, as well as clarified the holistic mechanism of LHQW for COVID-19 treatment. Our results could provide a deeper understanding of the relations between COVID-19 and RA treatment. The workflow of the current study with details of each procedure is shown in Figure 1.

2. RESULTS

2.1. Comparison of Herbal Composition. According to TCM theory, a formula could be composed of monarch, ministerial, adjuvant, and conductant herbs, which represent the function and position of one herb in a formula. The herbs in LHQW and DHJS are listed in Table 1. The property, flavor, and channel tropism of each herb are also given in Table 1. The sequence number of each herb in Table 1 corresponded to its position in the formula. The two formulas shared only one herb, *Glycyrrhiza uralensis* Fisch. (Gancao). In LHQW, the property of most herbs was cold; thus, this formula could be regarded as a cold medicine based on the TCM principle. In contrast, DHJS could be regarded as a warm medicine because the property of its most herbs was warm. Channel tropism is an important TCM term. Eight of 11 herbs in LHQW belong to the lung channel and five herbs belong to the stomach channel. On the other side, nine of 15 herbs in DHJS belong to the liver channel and six herbs belong to the kidney channel. In summary, LHQW appeared to exert a heat-clearing effect mainly through the lung channel, while DHJS appeared to

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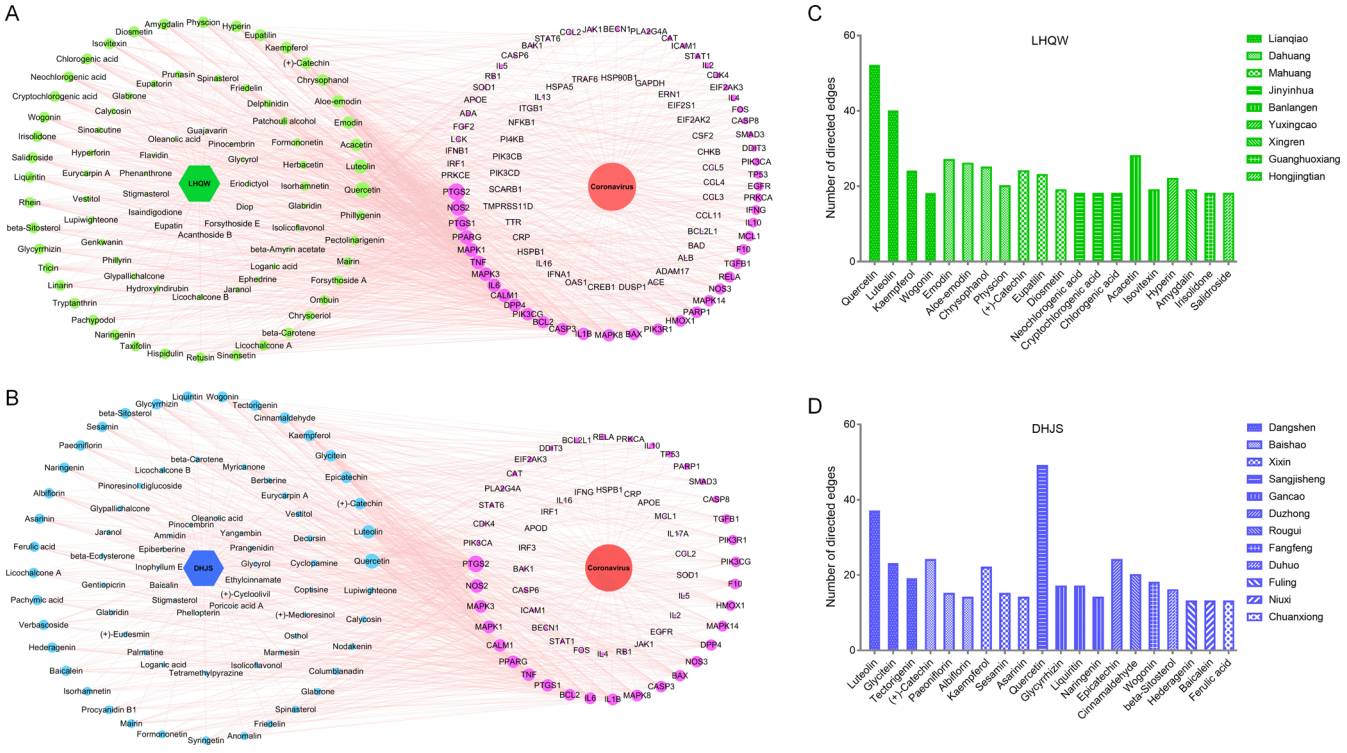

Figure 5. Comparison of drug−disease target interaction. (A) LHQW-ingredient-target-disease interaction network; (B) DHJS-ingredient-target-disease interaction network; (C) herbal affiliation of the top 20 ingredients in LHQW; and (D) herbal affiliation of the top 20 ingredients in DHJS.

exert a cold-dispelling effect mainly through the liver channel (Figure 2).

2.2. Comparison of Chemical Ingredients and Putative Targets. Based on screening, 11 herbs in LHQW generated 82 candidate ingredients, while 15 herbs in DHJS generated 73 candidate ingredients (Figure 3A). Besides the same herb containing the same ingredients, different herbs could also contain the same ingredients. Consequently, a total of 31 candidate ingredients were found in both LHQW and DHJS (Figure 3A). The occurrence numbers of the same ingredients in different herbs were counted. The top 10 ingredients from LHQW and DHJS are shown in Figure 3B. Interestingly, LHQW and DHJS shared up to six top ingredients, including beta-sitosterol, kaempferol, oleanolic acid, quercetin, stigmasterol, and mairin.

In LHQW, 82 ingredients generated total 376 putative targets, while 73 ingredients generated 340 putative targets in DHJS (Figure 3C). Among these targets, up to 306 targets were found in both formulas. The occurrence numbers of the same targets in different ingredients were counted, and the top 25 targets from LHQW and DHJS are shown in Figure 3D. It is not surprising that up to 21 top targets were shared by LHQW and DHJS.

2.3. Comparison of Formula−Disease Interaction Targets. A total of 351 targets associated with coronavirus disease were extracted from GeneCards database. The target intersection of LHQW-coronavirus, DHJS-coronavirus, and LHQW-DHJS-coronavirus was depicted by Venn diagrams (Figure 4A). There were 91 and 61 intersection targets in LHQW-coronavirus and DHJS-coronavirus, respectively. There were 59 intersection targets in LHQW-DHJS-coronavirus. These results suggested that LHQW contained more targets for interaction with coronavirus disease than DHJS.

By mapping formula targets with coronavirus targets, the mapped percent of each herb in LHQW was approximately 20% (Figure 4B). A similar result was observed in DHJS (Figure 4C). When it came to contribution percent, an obvious difference was found between LHQW and DHJS. The contribution percent of herbs in LHQW ranged from 68 to 25%, and on the whole, the contribution percent of herbs was consistent with their position in LHQW (Figure 4B). However, in DHJS, the contribution percent of herbs showed no clear pattern with their position (Figure 4C).

As shown in the 3D scatter plot generated from principal components analysis (PCA) (Figure 4D), the coronavirus group could be clearly separated from other groups. However, LHQW and its herb groups could not achieve clear separation from that of DHJS except two herb groups, suggesting that the two formulas shared a similar target profile for coronavirus disease. Based on the distance of formula groups to the coronavirus group, the LHQW group was nearer to the coronavirus group than the DHJS group, suggesting the higher integration degree of the LHQW target profile with the coronavirus disease target profile. Similar results were achieved from the heatmap combined with hierarchical cluster analysis (HCA), in which LHQW and DHJS were assigned into the nearest cluster because they shared a similar target profile (Figure 4E).

2.4. Comparison of the Drug−Disease Interaction Network. The formula-ingredient-target-disease interaction networks for LHQW and DHJS are shown in Figure 5A,B, respectively. In networks, green nodes represented LHQW targets, while blue nodes represented DHJS targets. The degree value of each node was determined using the Network Analyzer in Cytoscape. The size of each node had positive correlation with its degree value. The nodes were sorted counterclockwise according to their sizes. Interestingly, the

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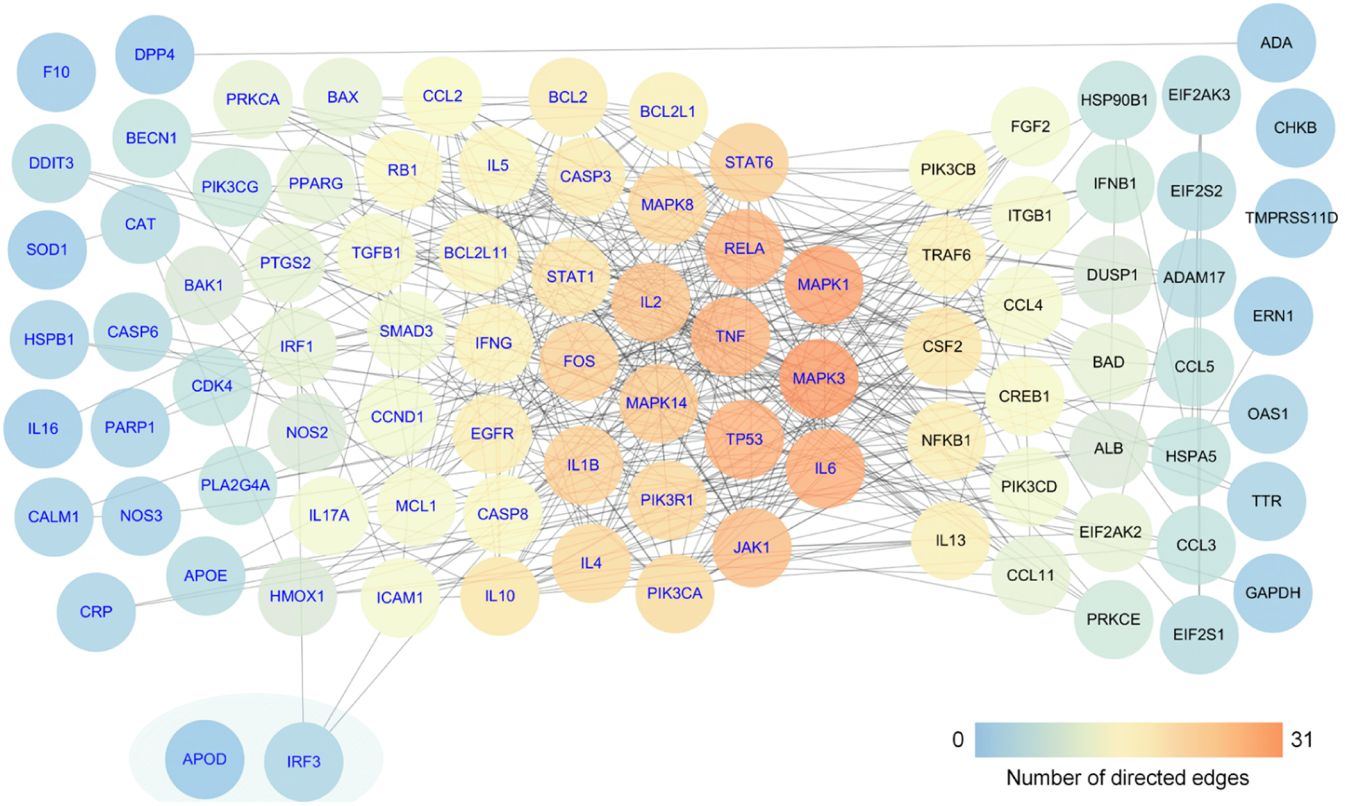

Figure 6. Merged PPI network of LHQW and DHJS. The left large part of the PPI network belonged to DHJS, while the entire PPI network belonged to LHQW except APOD and IRF3.

sorting of interaction targets showed high similarity in the two networks. The ingredients with high degree values were extracted and assigned to the corresponding herbs. The top 20 ingredients of LHQW and DHJS are shown in Figure 5C,D, respectively. The extracted ingredients of LHQW were mainly assigned to Lianqiao, Dahuang, Mahuang, Jinyinhua, and Banlangen. However, the extracted ingredients of DHJS were mainly assigned to Dangshen, Baishao, Xixin, Sangjisheng, Gancao, Duzhong, and Rougui. These results were coincident with the contribution of herbs to the interaction targets. Furthermore, the affiliation of top ingredients was more centralized to monarch herbs in LHQW, in comparison with DHJS. These results suggested that both LHQW and DHJS could act on coronavirus disease through multiple active ingredients and multiple action targets. However, the contribution to the interaction targets was mainly attributed to monarch herbs in LHQW, while DHJS was not.

2.5. Comparison of the Protein−Protein Interaction Network of LHQW and DHJS. The merged protein−protein interaction (PPI) network is shown in Figure 6. The left large part of the PPI network belonged to DHJS, while the entire PPI network belonged to LHQW except APOD and IRF3. Because of the considerable overlap of LHQW and DHJS targets, as well as LHQW generated more targets than DHJS against coronavirus, the PPI network of LHQW nearly completely covered the PPI network of DHJS. Based on the node degree, the top 20 targets were MAPK1, MAPK3, IL6, TNF, TP53, RELA, JAK1, STAT6, IL2, MAPK14, MAPK8, PIK3R1, PIK3CA, FOS, IL1B, IL4, IL10, STAT1, CFS2, and CASP3. Most of these targets were all shared by LHQW and DHJS except CFS2.

2.6. Comparison of Enriched Gene Ontology and KEGG Pathways. GO-based enrichment of LHQW yielded 106 gene ontology (GO) entries ($p < 0.05$), while DHJS yielded 118 GO entries ($p < 0.05$). The top 10 biological processes of LHQW and DHJS are shown in Figure 7A,B, respectively. A total of eight same entries including the response to the biotic stimulus, cellular response to the organic substance, response to the external stimulus, response to cytokine, response to stress, regulation of cell death, cytokine-mediated signaling pathway, and regulation of cell communication were found in both LHQW and DHJS. Additionally, two entries named response to the other organism and regulation of the immune system process were only found in LHQW, while two entries named the cell surface receptor signaling pathway and positive regulation of the nitrogen compound were only found in DHJS. Most of the enriched biological processes were associated with cellular responses after virus infection. However, the enriched biological processes of LHQW appeared to be more correlative with virus infection than DHJS.

KEGG pathways of LHQW and DHJS were enriched to yield 168 and 165 signal pathways, respectively. Most of these pathways were shared by LHQW and DHJS. The respective 10 most enriched signal pathways were screened out (Figure 7C,D). A total of five signaling pathways, including kaposi sarcoma-associated herpesvirus infection, human cytomegalovirus infection, hepatitis B, measles, and the TNF signaling pathway, were in the common ownership of LHQW and DHJS. The exclusive pathways of LHQW were mostly involved in virus infection, such as influenza A, hepatitis C, Epstein−Barr virus infection, and tuberculosis. The exclusive pathways of DHJS were mostly involved in inflammatory

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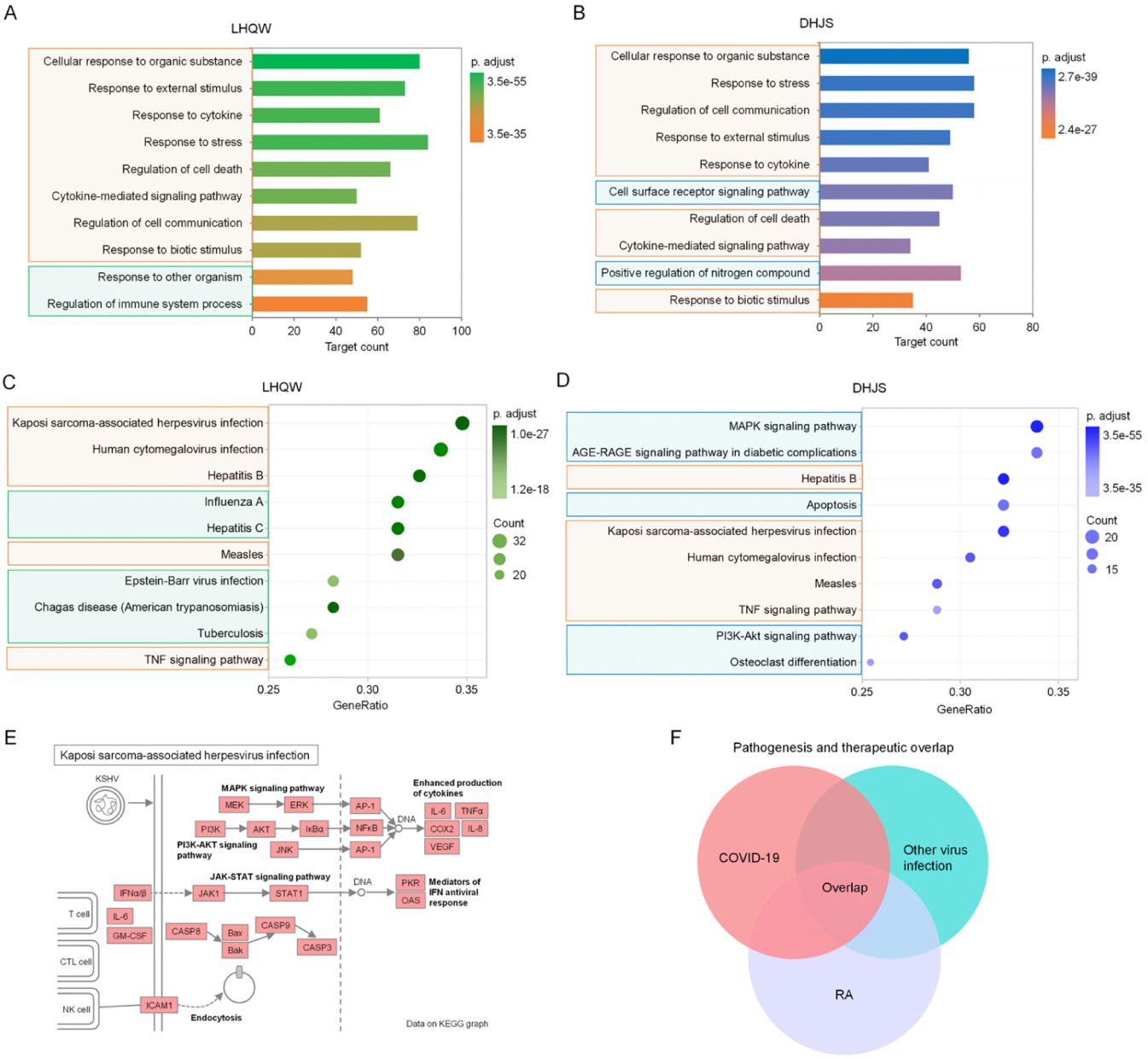

Figure 7. GO and KEGG enrichment. Top 10 GO entries of LHQW (A) and DHJS (B); top 10 KEGG pathways of LHQW (C) and DHJS (D); (E) representative KEGG pathway of LHQW rebuilt from the enriched KEGG graph; and (F) LHQW and DHJS shared extensive pathways involved in the pathogenesis and therapeutic of COVID-19, other virus diseases, and RA. For panels A, B, C, and D, items with an orange background were shared by LHQW and DHJS.

response, such as the MAPK signaling pathway, PI3K-Akt signaling pathway, and apoptosis. These results suggested that LHQW and DHJS shared a large proportion of enriched pathways. However, LHQW pathways were more enriched in virus infection, while DHJS pathways were more enriched in inflammatory regulation. Subsequently, the hit targets were extracted from the 10 most enriched signal pathways of LHQW. The enriched signaling pathways were refined and rebuilt based on the hit targets. A representative rebuilt KEGG pathway is shown in Figure 7E.

In summary, LHQW and DHJS showed extensive similarity in the cellular responses and signaling regulation, which were involved in the pathogenesis and therapeutic of COVID-19, other virus diseases, and RA (Figure 7F). Although the two formulas suggested multifunctionality for coping with virus infection, inflammation, and parasitic infection, the LHQW formula appeared to have much stronger links with virus infection, while the DHJS formula appeared to have much stronger links with inflammation.

3. DISCUSSION

The common symptoms of COVID-19 were fever, cough, fatigue, upper airway congestion, sputum production, shortness of breath, and myalgia/arthralgia.[3,4,23] According to TCM theory, COVID-19 could be classified into dampness pestilence which distressed the lung and arose heat. The compatibility of a herbal formula is commonly based on the symptom-based diagnosis. Therefore, the corresponding treatment using TCM should focus on clearing heat, obliterating the toxic material, eliminating dampness, and freeing the

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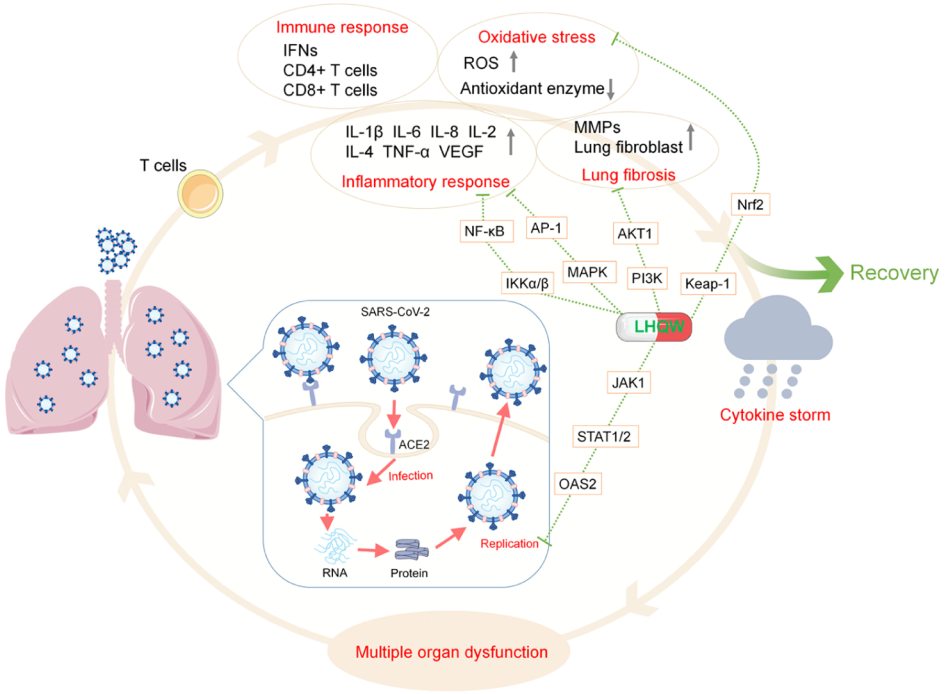

Figure 8. Deduced signaling network to decipher the mechanism of the LHQW formula for COVID-19 management.

lung.[24,25] According to TCM theory, channel tropism is considered as a very important basis of TCM applications. Based on this theory, Chinese herbs can be prescribed to achieve the desired therapeutic effects in clinical applications.[26] In this study, from the point of the property and channel tropism of herbs, LHQW could be regarded as a "cold" medicine and exert pharmacological effects in the lung channel. However, DHJS could be regarded as a "warm" medicine and exert pharmacological effects in the liver channel. Because clearing heat and freeing the lung are important measures for COVID-19 treatment, LHQW is more reliable for providing desired efficacy.

Although different herbs were used in the two formulas, they generated a similar target pattern against coronavirus disease. What is not coincidental is that the results of network analysis and enrichment analysis were fairly similar for LHQW and DHJS. Both formulas suggested multifunctionality for coping with virus infection, parasitic infection, inflammation, immune dysregulation, and cell apoptosis.

With regard to antiviral action, Ding *et al.*[27] reported that LHQW exerted anti-influenza A activity through inhibiting viral propagation and NF-κB activation. Runfeng *et al.*[28] indicated that LHQW significantly inhibited SARS-CoV-2 replication in Vero E6 cells. Although, currently, there were no antiviral studies using the DHJS formula, several medicinal herbs in the DHJS formula have been investigated for antiviral efficacy.[29−32] *Gentiana macrophylla* Pall. (Qinjiao) was suggested to increase the survival rate of mice infected with influenza A and ameliorate-related symptoms.[29] Different fractions divided from the extracts of *Saposhnikovia divaricata* (Trucz.) Schischk. (Fangfeng) were evaluated for anti-influenza virus activity, and several ingredients were identified to be responsible for the antiviral efficacy.[30] Moreover, *G. uralensis* Fisch. (Gancao), the herb contained in both LHQW and DHJS, was demonstrated to exhibit inhibitory activity against several viruses, such as influenza virus[31] and SARS-CoV-1.[32]

For LHQW and DHJS, numerous shared targets and pathways were involved in cytokine-mediated inflammation, suggesting that both formulas could play a promising role in anti-inflammation. Corresponding to this, immoderate inflammatory reaction occurred in COVID-19 patients, especially in those with more severe disease.[4,37] The overly released cytokines and chemokines (IL-6, TNF-α, IL-2, IL-7, CCL2, CXCL10, and MCP-1) could form a cytokine storm and lead to respiratory distress syndrome (ARDS) and multiple organ failure.[4,33] TCM intervention in the early stage of COVID-19 is critical to inhibit inflammatory response. As the present work suggested, both LHQW and DHJS could have the potential of exerting anti-inflammatory activity against COVID-19. Such a potential of LHQW was also confirmed by *in vitro* study.[28] Although there is no evidence for the efficacy of DHJS in suppressing inflammatory response in COVID-19, the anti-inflammatory effect of DHJS has already been widely presented in RA therapeutic studies.[34,35]

Although extensive similarity of targets was found between LHQW and DHJS, LHQW indeed possessed higher integration with coronavirus disease with regard to the target profile. Additionally, LHQW was more in line with the rules of the TCM formula, based on the herbal contribution for coronavirus disease. Despite the shared multifunctionality for coping with virus infection, inflammation, and parasitic infection, LHQW could have much stronger links with virus infection, while DHJS appeared to have much stronger links with inflammation. Latest, LHQW with the cold property and lung channel tropism could be more advisable for clearing heat and freeing the lung in COVID-19 treatment. Therefore, LHQW was more reliable for providing the desired efficacy in COVID-19 management, which has also been confirmed by the *in vitro* experiment[28] and randomized controlled trial.[36]

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Whether DHJS could really play a positive role in COVID-19 treatment still requires extensive and in-depth investigation.

Because LHQW showed superiority over DHJS in COVID-19 treatment, the key signaling pathways and embedded targets were refined and fused to generate an interactive signaling network (Figure 8), which could predict the multidimensional mechanism of LHQW for COVID-19 treatment. Although ACE2 and TMPRSS2 constitute potential targets for antiviral intervention,[2] the ingredients in LHQW did not show interaction with the two targets, suggesting that LHQW might be powerless to prevent SARS-CoV-2 infection. After infection, SARS-CoV-2 efficiently replicated in human lung tissue and caused direct cell injury.[37] LHQW was reported to significantly inhibit SARS-CoV-2 replication in Vero E6 cells,[28] and such an effect might be involved in the regulation of the JAK-STAT signaling pathway. Moreover, SARS-CoV-2 infection can also cause CRS and form a cytokine storm.[33] LHQW intervention in the early stage of this disease could suppress cytokine storm,[28] and the related mechanism could link with the inhibiting NF-κB signaling pathway and/or MAPK-AP-1 signaling pathway.[38,39] The severe inflammatory response could damage the immune system, resulting in a decrease in lymphocytes and CD4+ and CD8+ T cells.[40] Several herbs in the LHQW formula exhibited the immune regulatory function against virus infection, and the related mechanism could be associated with the upregulation of CD4+ and CD8+ T cell population.[41,42] In addition, severe COVID-19 could cause pulmonary and renal fibrosis and other complications.[43,44] Apart from anti-inflammation, herbal ingredients in LHQW could have the potential to inhibit fibrosis through suppressing the PI3K-AKT signaling pathway[45] and suppress oxidative stress through the Keap-Nrf2 signaling pathway.[46] Such effects could have positive significance to prevent COVID-19 complications and block COVID-19 progression. The abovementioned results indicated that the LHQW formula could have multitargets and multipathway-regulative effects and represent a promising application in COVID-19 management through immunomodulation, suppression of inflammatory response, and prevention of complications.

4. CONCLUSIONS

LHQW and DHJS, two widely used TCM formulas, were compared based on integrated network pharmacology to investigate their similarity and specificity. Fairly different herbs were present in the two formulas. Moreover, according to the property and channel tropism, LHQW could possess the heat-clearing effect mainly on the lung, while DHJS could exert the cold-dispelling effect mainly on the liver. Interestingly, extensive similarity of ingredients, targets, the interaction network, and enriched pathways were found in the two formulas, which were mainly involved in virus infection, inflammation, and immune dysregulation. However, LHQW was more reliable for providing the desired efficacy in COVID-19 management because of its cold property, lung channel tropism, fairly similar target pattern with coronavirus disease, and stronger links with virus infection and inflammation. Theses results were also mutually confirmed by reported preclinical and clinical evidence.

5. MATERIALS AND METHODS

5.1. Comparison of Herbal Composition and Chemical Ingredients. The information of herbal composition of LHQW and DHJS was obtained from the Chinese pharmacopoeia 2015,[47] in which the property, flavor, and channel tropism of each herb were also extracted. The chemical ingredients of each herb were collected from TCMSP database (http://tcmspw.com/tcmsp.php) which provides detailed information of various TCM ingredients, including oral bioavailability (OB), drug likeness (DL), and putative targets.[48] Ingredient screening was performed using OB and DL parameters. Based on previous reports,[49,50] the compounds with OB $\geq$ 30% and DL $\geq$ 0.18 are likely to exert desirable pharmaceutical activities. In the present work, OB and DL criteria mainly focus on two principles: (1) identifying medicinal substances of herbs using the least ingredients and (2) the extracted ingredients could represent the feature of herbs and explain the reported pharmacological data reasonably. Therefore, the ingredients in herbs with OB $\geq$ 25% and DL $\geq$ 0.18 were selected as candidate compounds for the following analysis.

5.2. Library Establishment of Putative Targets for LHQW and DHJS. Two specialized databases (TCMSP and STITCH (http://stitch.embl.de/cgi/input.pl)) were used to search the putative targets of the screened candidate ingredients. In the case that the databases hardly realize real-time update to incorporate latest studies, text mining of PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) for extracting relevant targets of candidate ingredients was performed. Subsequently, the official symbols of obtained targets were generated from UniProt database (https://www.uniprot.org/). For each ingredient, the repetitive target symbols were merged. Subsequently, for each herb and formula, the repetition number of each target symbol was counted as n, and then, the same target symbol was merged, and then, the values of n were normalized with the maximum n normalized to 1. Finally, the library of the formula-herb-ingredient-target value was constructed.

5.3. Library Establishment of Targets for Coronavirus Disease. The targets of coronavirus disease were exported from GeneCards database (https://www.genecards.org/). The items "Symbol" and "Score" of each gene were reserved. The "Score" values of genes were normalized through being divided by the maximum value. After normalization, the gene scores range from 0 to 1, and the target with normalized score 1 was the most relevant target to coronavirus disease. Finally, the library of the disease target value was established.

5.4. Integration and Comparison of Formula–Disease Targets. The target intersection of LHQW and DHJS was analyzed and identified. Then, the target intersection of LHQW-disease, DHJS-disease, and LHQW-DHJS-disease was identified and depicted using the Venn diagram. The target coverage and contribution degree of each herb to intersection targets were analyzed and compared. Finally, the dataset containing the herb target and disease target with the corresponding values was imported into the SIMCA (version 13.0) and Heml (version 1.0) to perform PCA and HCA, respectively. The pattern recognition models PCA and HCA were employed herein for evaluating the relevance of the target profile between LHQW, DHJS, and coronavirus disease.

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5.5. Construction and Comparison of the Drug–Disease Network. To explore the multiscale mechanisms of LHQW and DHJS formulas, a network consisting of "formula-ingredient-target-disease" was constructed by Cytoscape (version 3.4.0). In the network, formula, ingredient, target, and disease were described by nodes, and the intermolecular interactions were encoded by edges. Network Analyzer was used to analyze the degree values of nodes. The size of each node was positively associated with its degree value. Then, the top ingredient nodes were assigned to the corresponding herbs. Finally, the similarity and difference between LHQW and DHJS, regarding the network, top target nodes, and top ingredient nodes, were analyzed and compared.

5.6. Construction and Comparison of PPI. The drug–disease targets were imported into STRING database (https://string-db.org/) for predicting PPI. In PPI, the minimum required interaction score was set as 0.9 and the max number of interactors was set as 5. The interaction data were exported and then imported into Cytoscape for constructing the PPI network. Then, the node degree was analyzed using Network Analyzer. Finally, the PPI networks of LHQW and DHJS were merged and compared.

5.7. Comparison of Pathway Enrichment. GO and KEGG pathway enrichment were performed using R software to extract the canonical pathways and the corresponding proteins. p values were given in pathway enrichment, and smaller p values suggested greater enrichment. Subsequently, 10 most enriched GO and KEGG pathways were extracted. Finally, the similarity and specificity of enriched pathways of LHQW and DHJS were analyzed and compared.

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Notes

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