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Molecular mechanisms revealed by network pharmacology of Xuebijing on the treatment of acute respiratory distress syndrome caused by novel coronavirus infection

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Abstract. – OBJECTIVE: The study aims to predict the target and molecular mechanism of Xuebijing injection in the treatment of novel coronavirus-induced acute respiratory distress syndrome (ARDS), based on network pharmacology.

MATERIALS AND METHODS: Chinese and English studies were searched to obtain the main active components of Xuebijing injection. ETCM, TCMSP and Targetnet online databases were adopted used to predict Xuebijing therapeutic targets. GeneCards, CTD and OMIM databases were researched used to research for the novel coronavirus Disease-2019 (COVID-19) and ARDS-related targets. Integrate analysis was carried out to obtain the targets of Xuebijing injection in the treatment of ARDS caused by novel coronavirus. STRING was adopted to analyze the interaction of common target proteins. GO and KEGG enrichment analyses were carried out using Bioconductor bioinformatics software package based on R software. Network visualization was performed with Cytoscape software.

RESULTS: A total of 30 main active components in Xuebijing injection were collected in this study, which can act on 615 targets. The core components of Xuebijing injection in treating the coronavirus-induced ARDS are Ferulic acid, Ethyl ferulate, Albiflorin, Caffeic acid, Rosmarinic acid, Naringenin, Quercetin. Xuebijing injection has 56 target points for the treatment of ARDS caused by the novel coronavirus, among which AKT1, TNF, CASP3 and STAT3 are the core ones. The main molecular mechanisms of Xuebijing injection in treating the coronavirus-induced ARDs include PI3K-Akt, TNF, STAT3, NF-κB and apoptosis-related pathways.

CONCLUSIONS: Xuebijing mainly treats ARDS caused by the novel coronavirus through anti-inflammation, anti-apoptosis, and regulation of immunity since it has the characteristics of multi-component, multi-target and multi-pathway.

Key Words:

Xuebijing, Novel coronavirus, Acute respiratory distress syndrome, Network pharmacology, Novel coronavirus Disease-2019 (COVID-19).

Abbreviations

ARDS: acute respiratory distress syndrome; COVID-19: novel coronavirus Disease-2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Introduction

The novel coronavirus pneumonia (COVID-19) caused by the novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) has given rise to major public health emergencies in many countries around the world[1,2]. COVID-19 is highly contagious, and the severe incidence rate reaches as high as 18.1%, and about 15% to 30% of patients will rapidly deteriorate into acute respiratory distress syndrome (ARDS) in a short period of time[3,4]. ARDS, a clinical syndrome characterized by dyspnea, intractable hypoxemia, diffuse alveolar damage and rapid onset to acute respiratory failure, is the prime clinical manifestation of severe and critically ill patients with COVID-19, the proportion of which in intensive care units (ICU) is even as high as 61.1%[5]. Moreover, it is also one of the common causes of COVID-19 death[6]. At present, there is a lack of specific drugs for ARDS generated by SARS-CoV-2, and clinical treatment mostly adopts symptomatic support treatments, such as lung protection ventilation, anti-infection, anti-inflammatory and respiratory support. Thus, the treatment of ARDS from SARS-CoV-2 is still facing severe challenges.

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Traditional Chinese herbal medicine has shown good advantages in treating the COVID-19, reflecting the potential value of Chinese herbal medicine in the fight against SARS-CoV-2[7]. Current research also suggests that Xuebijing can significantly improve pulmonary lesions in patients with COVID-19, reduce serum inflammatory factor levels and patient mortality[8-10]. According to the prospective cohort studies[11,12] on the efficacy of Xuebijing injection in treating COVID-19 in China and China's New Coronavirus Pneumonia Diagnosis and Treatment Protocol, Xuebijing was proved to be an effective drug for the prevention and treatment of ARDS caused by COVID-19. Xuebijing is an important adjuvant drug for the treatment of ARDS caused by SARS-CoV-2 infection, although the molecular mechanism of its action remains unclear. Currently, network pharmacology is an important method to explore drug-disease interactions and molecular mechanisms[13]. Based on the network pharmacology, this study will explore the material basis and molecular mechanism of Xuebijing in the treatment of ARDS caused by SARS-CoV-2 and provide a theoretical reference for the clinical application of Xuebijing in treating SARS-CoV-2-triggered ARDS.

Materials and Methods

Active Ingredient and Target Screening of Xuebijing Injection

In this study, the main active components of Xuebijing injection were screened out by searching Chinese and English studies, and then verified and sorted *via* Pubchem database (https://pubchem.ncbi.nlm.nih.gov/). Component-related targets were obtained online from the ETCM (http://www.nrc.ac.cn:9090/ETCM/), TCMSP (http://tcmspw.com/) databases. The unlisted components adopted the Targetnet database (http://targetnet.scbdd.com/) to predict targets online.

The screening conditions were AUC $\geq$ 0.7, predicted probability (Prob) > 0.9, and corrected by Uniprot (https://www.uniprot.org/); the screening species was "Homo sapiens" target. Then, the top 10 components and targets were obtained through the Network Analyzer plug-in by degree value.

Disease Candidate Target Screening

The OMIM, Drugbank, and Genecards databases were adopted to search with "Corona Virus Disease 2019", "novel coronavirus Disease-2019", "Novel coronavirus pneumonia", and "Acute respiratory distress syndrome" as keywords to obtain disease targets. Then the Venn diagrams of drug-disease common targets were drawn on the Venny 2.1 online software mapping tool platform.

PPI Network Analysis and Core Target Identification

With Cytoscape 3.8.2 software, a "disease-target-component" network diagram was constructed, and a drug-disease common target protein interaction network diagram was drawn. Then, drug-disease common targets were inserted into the STRING database to form a PPI network of protein interactions, which was later imported into Cytoscape 3.8.2, while the topological analysis was performed by the Network Analyzer tool. Next, genes with a degree above the average score were selected as the core targets by degree sorting, and R 4.0.5 was adopted to draw a bar graph.

Biological Function and Pathway Enrichment Analysis of Core Biological Targets

Based on R software, the Bioconductor bioinformatics software package was adopted to carry out gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analysis of key target genes with p-value < 0.05 and q-value < 0.05. The results were output in the form of bar chart and bubble chart. *Via* utilizing Cytoscape 3.8.2 software, the components, targets, and signaling pathways were integrated altogether to construct a "component-target-pathway" network map. The top 10 ingredients and targets are obtained through the Network Analyzer plugin by degree value. Then, through the Venny 2.1 online software mapping tool platform, the Venn diagram of screening components and KEGG enrichment components, and that of screening targets and KEGG enrichment targets were drawn.

Results

Active Ingredient Screening and Target Prediction of Xuebijing Injection

By searching Chinese and English works, 30 active components in Xuebijing injection quantitatively detected by LC-MS were selected and consistent with the main active components of Xuebijing injection reported in the litera-

ture[16-18]. As shown in Table I, the components of safflower, Salvia miltiorrhiza, Angelica sinensis, red peony root, and Ligusticum wallichii corresponded to 11, 13, 4, 6, and 4, respectively (Table I). These 30 active ingredients were then adopted to predict the target points through the ETCM, TCMSP and Targetnet databases. After the correction of Uniprot, 615 target points in total were achieved and then imported into Cytoscape software to draw a "component-target" network. Results are shown in Figure 1. The Network Analyzer plug-in was applied to obtain the top 10 components and targets in terms of degree value. The result has been illustrated in Table II.

Screening of Therapeutic Targets of Xuebijing Injection in the Treatment of ARDS Caused by Novel Coronavirus

Through searching with "Corona Virus Disease 2019", "novel coronavirus Disease-2019", "Novel coronavirus pneumonia" as keywords, removing duplicate targets, and integrating within Uniprot, 1638 targets in total, related to COVID-19, were obtained. Besides, a total of 1257 ARDS-related targets were gained by searching keywords "Acute respiratory distress syndrome", removing duplicate targets, adjusting and integrating with Uniprot. After the intersection of drug targets and disease targets, 56 common drug-disease targets were obtained (Figure 2A) and then were input into Cytoscape software to draw the network diagram of "disease-target-component" interaction (Figure 2B), protein interaction (Figure 3A, the larger the node, the darker the color, higher value of the degree parameter), and PPI (Figure 3B). As illustrated in Figures 4A and 4B, based on PPI topological and cluster analyses, we found that AKT1, TNF, ALB, VEGFA, TLR4, CASP3, STAT3, ICAM1, PPARG, and IL-2 are the main factors involved in Xuebijing's treatment of coronavirus-induced ARDS.

Table I. Major active compositions of Xuebijing injection.

No	Composition	Ingredient	Molecular formula	Pubchem ID
X1	5-Hydroxymethyl-furfural	Safflower	$C_6H_6O_3$	237332
X2	Hydroxysafflor yellow A	Safflower	$C_{27}H_{32}O_{16}$	49798103
X3	Hyperoside	Safflower	$C_{21}H_{20}O_{12}$	5281643
X4	Rutin	Safflower	$C_{27}H_{30}O_{16}$	5280805
X5	Quercetin	Safflower	$C_{15}H_{10}O_7$	5280343
X6	Ferulic acid	Angelica sinensis, safflower	$C_{10}H_{10}O_4$	445858
X7	Chlorogenic acid	Salvia, Safflower	$C_{16}H_{18}O_9$	1794427
X8	Luteolin	Salvia, Safflower	$C_{15}H_{10}O_6$	5280445
X9	Apigenin	Salvia, Safflower	$C_{15}H_{10}O_5$	5280443
X10	Sodium Danshensu	Salvia	$C_9H_9NaO_5$	23711819
X11	Tanshinol	Salvia	$C_9H_{10}O_5$	439435
X12	Protocatechuic acid	Salvia	$C_7H_6O_4$	72
X13	Protocatechuic aldehyde	Salvia	$C_7H_6O_3$	8768
X14	Salvianolic acid B	Salvia	$C_{36}H_{30}O_{16}$	51066555
X15	salvianolic acid A	Salvia	$C_{26}H_{22}O_{10}$	5281793
X16	Cryptotanshinone	Salvia	$C_{19}H_{20}O_3$	160254
X17	Tanshinone II A	Salvia	$C_{19}H_{18}O_3$	164676
X18	Senkyunolide I	Ligusticum wallichii, Angelica sinensis	$C_{12}H_{16}O_4$	11521428
X19	Butylidenephthalid	Ligusticum wallichii, Angelica sinensis	$C_{12}H_{12}O_2$	642376
X20	Caffeic acid	Ligusticum, wallichii	$C_9H_8O_4$	1549111
X21	Gallic acid	Red peony	$C_7H_6O_5$	370
X22	Oxypaeoniflorin	Red peony	$C_{23}H_{28}O_{12}$	21631105
X23	Catechinic acid	Red peony	$C_{15}H_{14}O_6$	9064
X24	Albiflorin	Red peony	$C_{23}H_{28}O_{11}$	51346141
X25	Benzoylpaeoniflorin	Red peony	$C_{30}H_{32}O_{12}$	21631106
X26	Paeonol	Red peony	$C_9H_{10}O_3$	11092
X27	Galuteolin	Salvia, Safflower	$C_{21}H_{20}O_{11}$	5317471
X28	Rosmarinic acid	Salvia	$C_{18}H_{16}O_8$	5281792
X29	Naringenin	Safflower	$C_{15}H_{12}O_5$	932
X30	Ethyl ferulate	Ligusticum wallichii, Angelica	$C_{12}H_{14}O_4$	736681

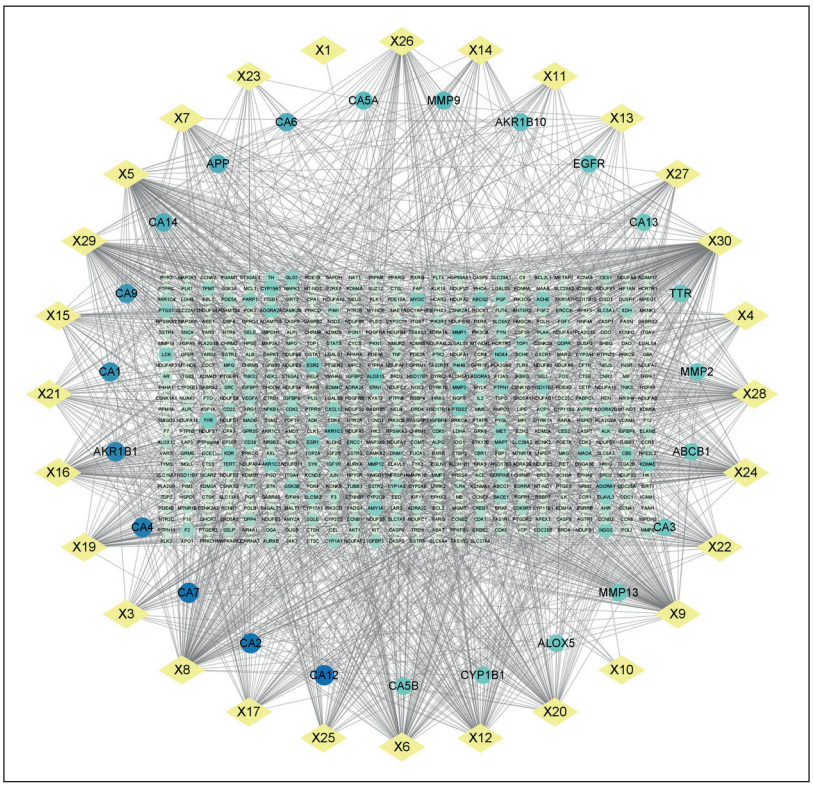

Figure 1. Compositions-Targets network of Xuebijing injection. Square and circle represent the active component and the target, respectively. The target degree value changes with the size and color of the figure.

GO Target Enrichment Analysis

The results of GO enrichment analysis suggested that 56 intersecting genes were enriched in 1486 biological process pathways **(Supplementary Table I),** 25 cellular components **(Supplementary Table II)**, 85 molecular functions **(Supplementary Table III)**. As illustrated in Figure 5, the top 20 GO enrichment results are taken according to the combined score and displayed in a bar graph. The main enrichments in the biological processes include: response to molecule of bacterial origin and to lipopolysaccharide, regulation of inflammatory response, cell-cell adhesion, leukocyte migration, etc. The major molecular functions involve endopeptidase activity, protease binding, serine-type peptidase activity, serine hydrolase activity, cytokine receptor binding, etc.

KEGG Target Pathway Annotation Analysis

KEGG pathway annotation analysis demonstrated that 56 intersecting genes were enriched ~~to~~ by 144 KEGG pathways **(Supplementary Table IV)**. As shown in Figure 6, top 20 KEGG enrichment results were taken according to the combined score and displayed in a bar graph.

Table II. Major compositions and targets in Xuebijing injection (Top 10).

Composition	Degree value	Target	Degree value
Ethyl ferulate	175	CA12	20
Quercetin	124	CA7	19
Luteolin	120	CA2	19
Apigenin	117	CA4	18
Naringenin	105	AKR1B1	17
Ferulic acid	96	CA1	16
Protocatechuic acid	83	CA9	15
Albiflorin	82	CA6	13
Caffeic acid	78	CA14	13
Rosmarinic acid	74	APP	13

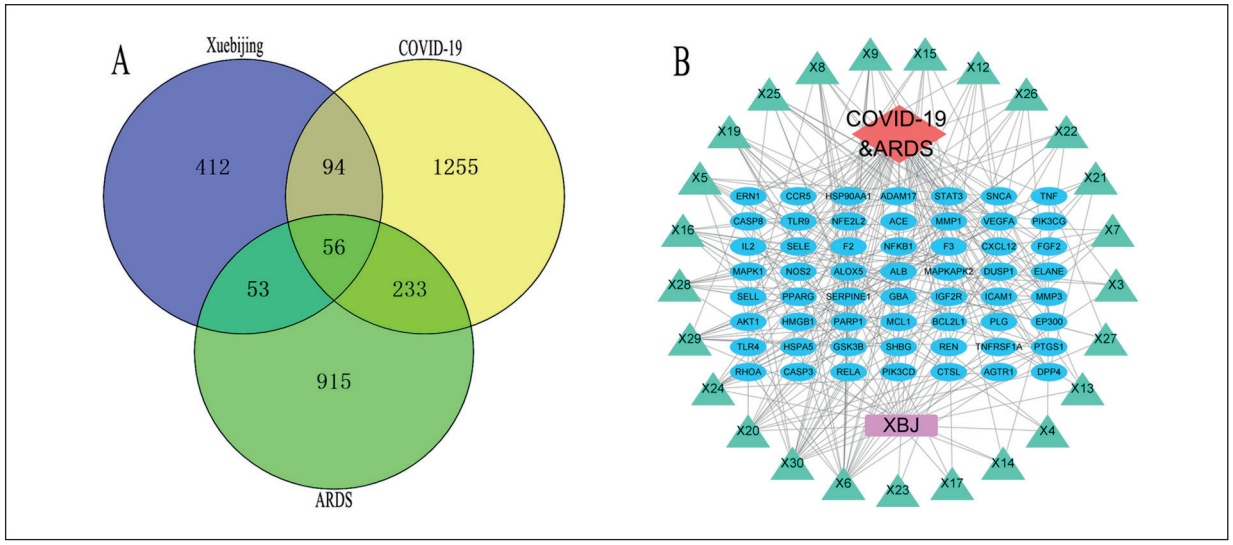

Figure 2. Screening analysis of common drug-disease targets. **A**, Venn diagram of common drug-disease targets. **B**, Network diagram of drug-ingredient-target-disease interactions.

Simultaneously, we adopted the top 20 pathways according to the *p*-value in the enriched KEGG pathways, integrated and constructed a "component-target-pathway" network map (Figure 6B, the size of the circle in the picture represents the size of the degree value). As shown in Figure 6, the enrichment of the KEGG pathway is mainly lipid and atherosclerosis, viral infection, apoptosis, PI3K-Akt signaling pathway, TNF signaling pathway, HIF-1 signaling pathway, etc. With the Network Analyzer plugin, we ranked the top 20 pathway components and targets enriched by KEGG by degree value. Table III illustrates the top 10 Xuebijing components and main targets for the treatment of COVID-19 triggered ARDS. Then, we conducted an intersection analysis of the active ingredients and found that Ferulic acid, Ethyl ferulate, Albiflorin, Caffeic acid, Rosmarinic acid, Naringenin, and Quercetin were the major components of Xuebijing in the treatment of ARDS caused by novel coronavirus (Figure 7A). Meanwhile, we also conducted an intersection analysis aimed at core targets and discover

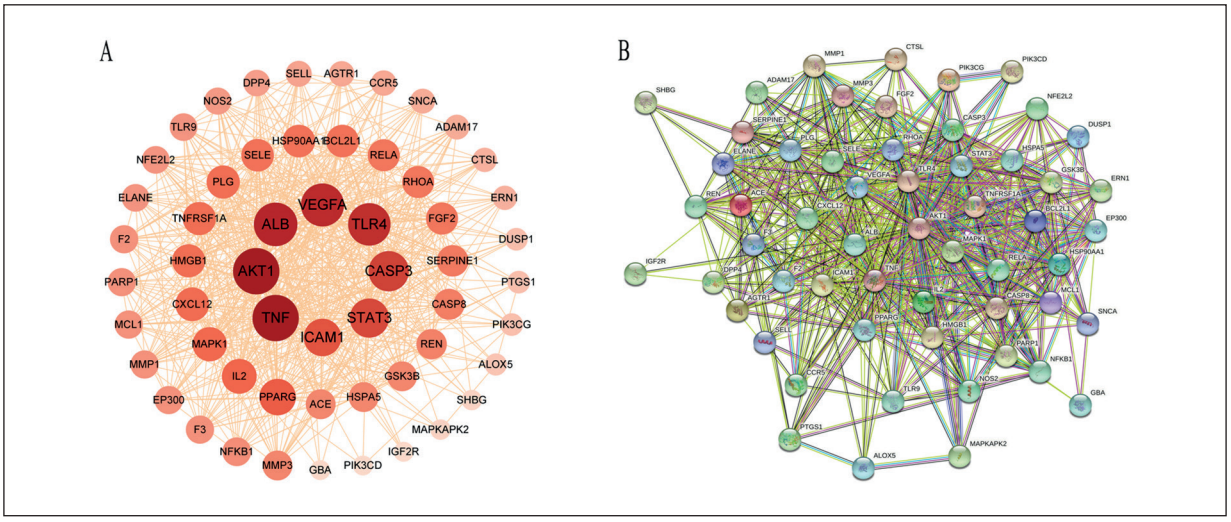

Figure 3. Drug-disease common target protein interaction analysis. **A**, core target protein PPI network diagram. **B**, core target protein interaction network diagram.

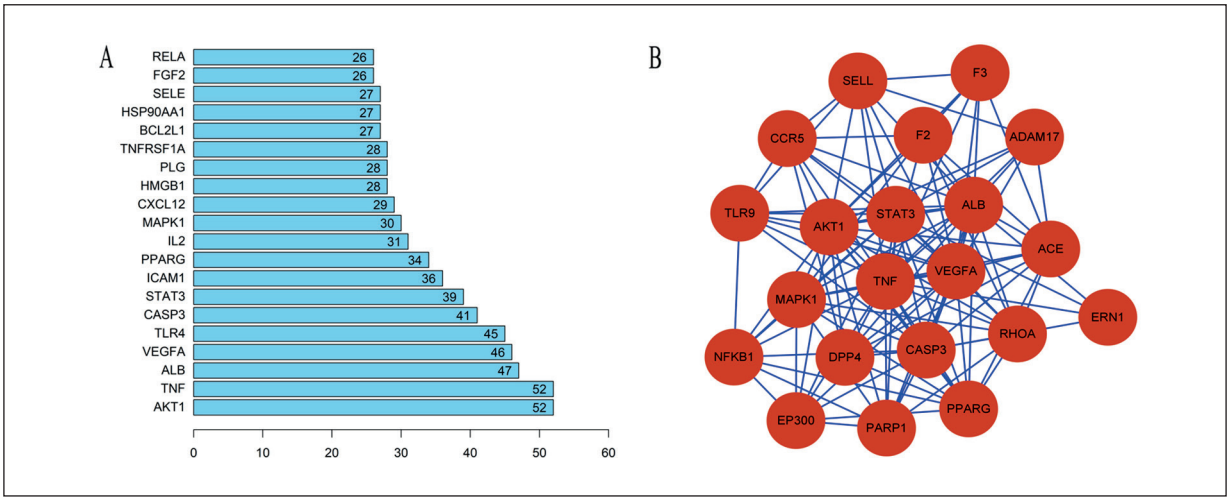

Figure 4. Core target topology and protein interaction analyses (Top 20). **A**, top 20 core target molecular bar graph; and **B**, top 20 core target protein protein interaction network diagram.

that AKT1, TNF, CASP3, and STAT3 were the main targets of Xuebijing in the treatment of the coronavirus-ARDS (Figure 7B).

Discussion

Xuebijing is mainly composed by five traditional Chinese medicines, including safflower, red peony, Ligusticum wallichii, Salvia miltiorrhiza and Angelica sinensis, which is also the only Chinese medicine injection approved for treating sepsis, systemic inflammatory response syndrome, and multiple organ dysfunction in China[20-22]. Studies[23-25] have found that Xuebijing can improve the organ function of ARDS patients, reduce the incidence of ventilator-associated pneumonia, shorten the duration of mechanical ventilation and ICU stay, and improve the prognosis of patients. Besides, recent studies[8-12] have also shown that Xuebijing has an outstanding curative effect on SARS-CoV-2-triggered ARDS. Nevertheless, the molecular mechanism of Xuebijing in treating the SARS-CoV-2-induced ARDS has not been reported yet. Therefore, in-depth analysis on the composition and molecular mechanism of Xuebijing injection in treating COVID-19 is of great value to provide a scientific basis for its clinical application.

In this study, 30 main active chemical components and 615 predicted targets of Xuebijing drug were obtained through network pharmacology. After the intersection analysis of these active components, seven core components were screened out, followed by Ferulic acid, Ethyl ferulate, Albiflorin, Caffeic acid, Rosmarinic acid, Naringenin, Quercetin. Most of them were flavonoids that widely exist in various plants and contain multiple functions, as for instance, anti-inflammatory, anti-infection, antioxidant activity, regulation of angiogenesis, and regulation of immunity. These components are widely applied in the treatment of inflammatory diseases, cardiovascular diseases, diabetes, cancer and other diseases[26,27]. Among them, Ferulic acid and Quercetin can protect against lipopolysaccharide-induced ARDS *via* anti-inflammatory and modulating heme oxygenase-1-dependent pathways[28,29]; Caffeic acid, Rosmarinic acid and Naringenin can reduce ARDS by blocking the activation of NF-κB, anti-inflammatory and antioxidant[30,31].

Through the PPI network map, the common target-enrichment pathway network map and the intersection analysis of core target components, we found that AKT1, TNF, CASP3, and STAT3 are the core targets of Xuebijing in the treatment of ARDS caused by SARS-CoV-2 infection. Meanwhile, KEGG analysis also showed that main enriched signaling pathways are Lipid and atherosclerosis, viral infection, apoptosis, PI3K-Akt signaling pathway, TNF signaling pathway, HIF-1 signaling pathway, etc. Then, by analyzing the pathway map of them, we discovered that the signaling pathway of PI3K-Akt, TNF, STAT3, NF-κB, and that related to apoptosis were all notably enriched. PI3K-Akt signaling pathway is involved in the occurrence

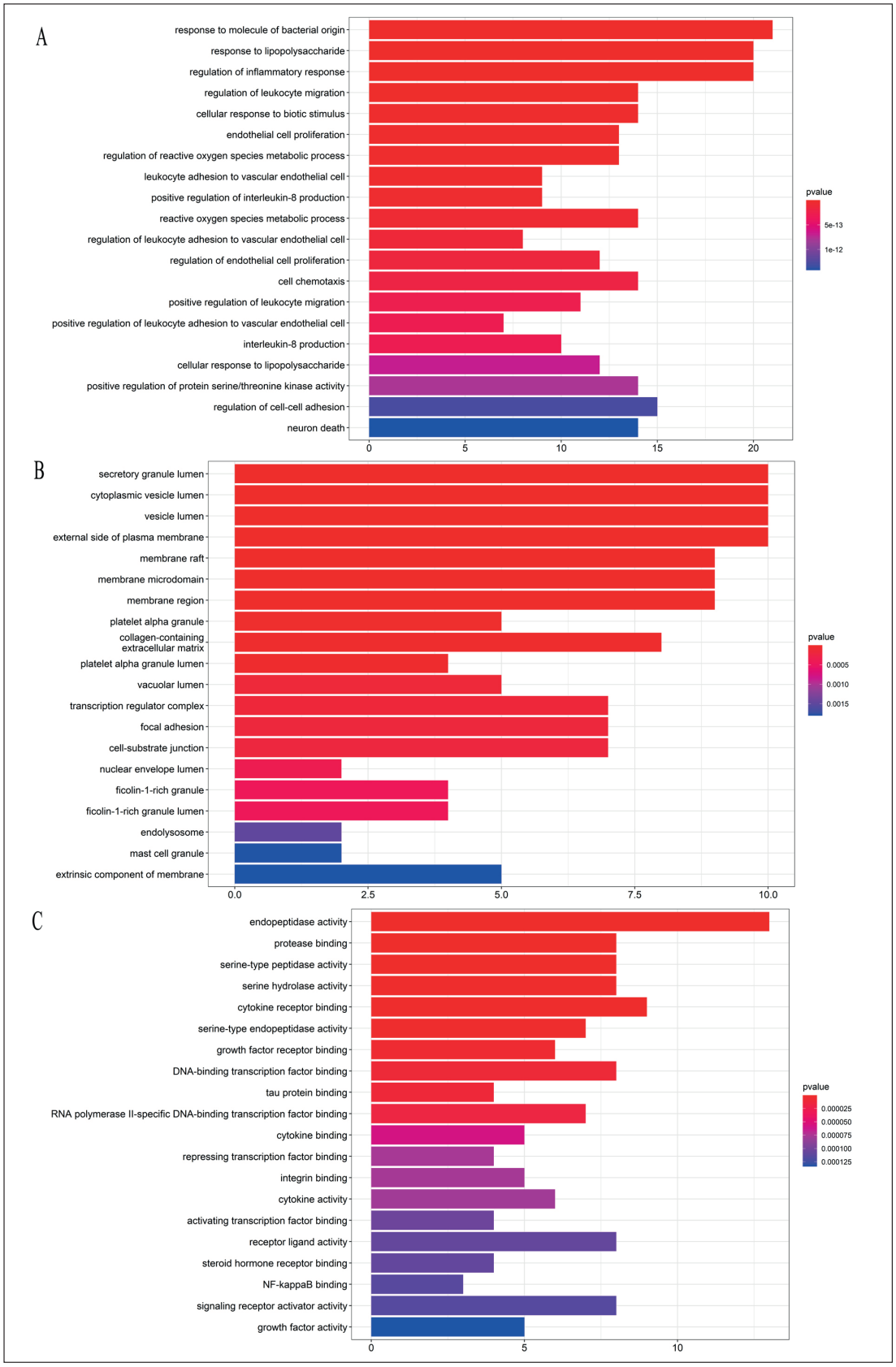

Figure 5. GO target enrichment analysis (Top 20). **A**, biological process; **B**, cellular component; and **C**, the molecular function.

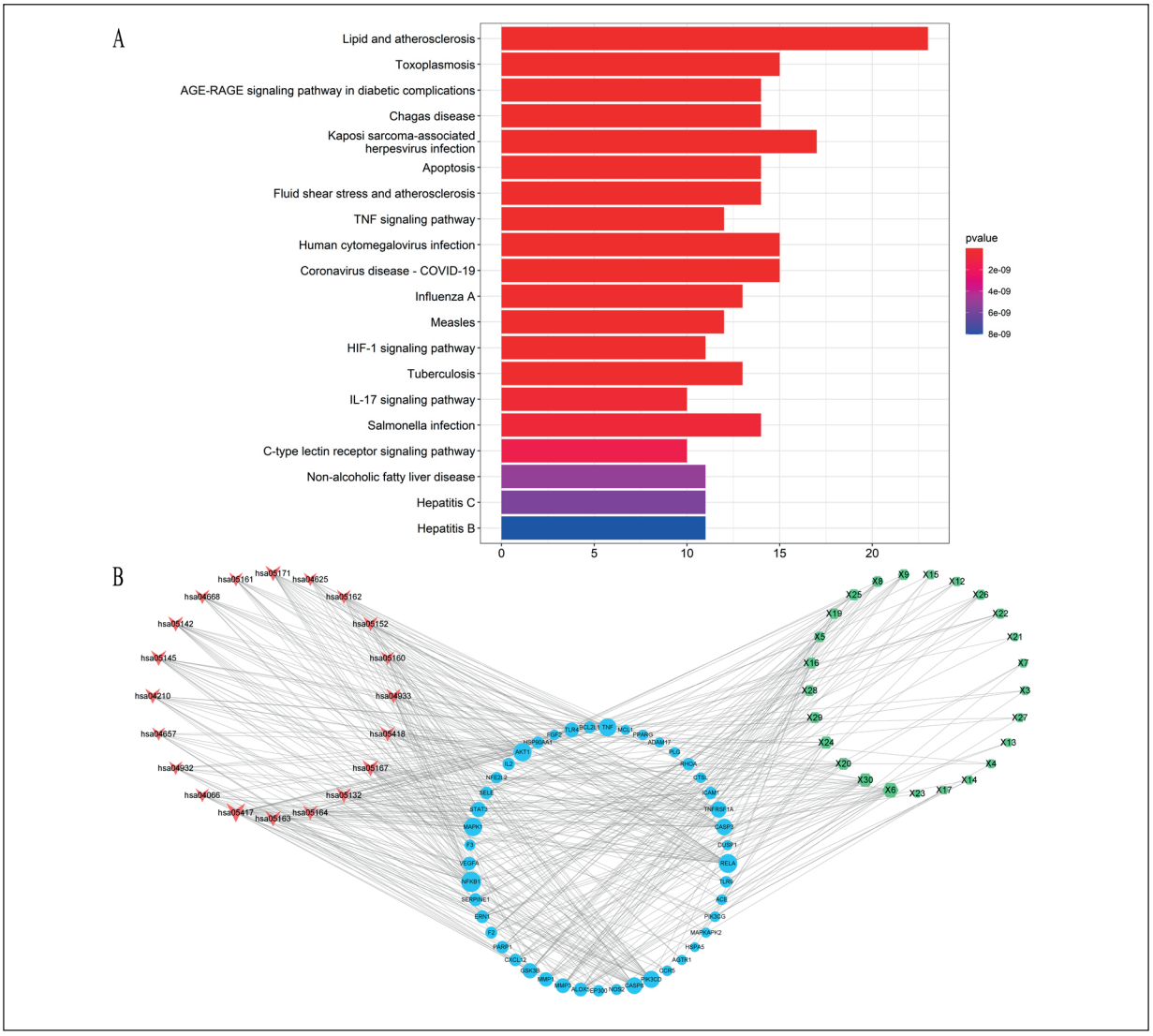

Figure 6. KEGG target pathway annotation analysis. **A**, KEGG pathway enrichment bubble map (top 20). **B**, Interaction network diagram of Composition-Target- Pathway (green the active component; blue the target; red the KEGG pathway; the size of the circle in the picture represents the size of the degree value).

and development of SARS-CoV-2-induced ARDS, which has been confirmed[32]. Blocking the PI3K-Akt signaling pathway from signaling can significantly curb the inflammatory response and reduce body damage in ARDS[33-36]. TNF signaling pathway is considered to be the core of cytokine storm, as TNF can stimulate the chemotaxis of neutrophils, T lymphocytes, and eosinophils, damage endothelial cells, promote tissue necrosis, and cause damage to organ functions[37,38]. The content of TNF in ARDS patients infected with SARS-CoV-2 was significantly increased, but it decreased significantly after the patients improved[37,38]. Simultaneously, in animal experiments, blocking the expression of TNF improved ARDS caused by SARS-CoV-2 infection[37,38]. Acute lung injury can activate the PI3K/Akt signaling pathway, thereby inducing apoptosis signaling molecules and apoptosis-related proteins to regulate epithelial cell apoptosis in lung tissue[39]. Among them, Casp3 plays a key role downstream of Caspase cascade activation in the apoptosis pathway. Abnormal apoptosis of lung epithelial cells may cause damage and loss of lung barrier function, and ultimately promote and accelerate the progression of ARDS[40,41]. Conversely, blocking apoptosis of alveolar epithelial cells significantly improves ARDS

Table III. Potential compositions and targets of Xuebijing injection in the treatment of ARDS caused by novel coronavirus.

Composition	Degree value	Target	Degree value
Ferulic acid	17	NFKB1	25
Ethyl ferulate	14	RELA	22
Albiflorin	11	MAPK1	21
Caffeic acid	10	AKT1	21
Benzoylpaeoniflorin	8	TNF	20
Rosmarinic acid	8	PIK3CD	18
Naringenin	8	CASP8	17
Cryptotanshinone	8	CASP3	17
Butylidenephthalid	7	TNFRSF1A	16
Quercetin	7	STAT3	14

progression[40,41]. STAT3 is a signal transduction and transcriptional activation cytoplasmic protein, which is not only involved in biological processes such as inflammation and immune regulation, but also in SARS-CoV-2-induced ARDS by regulating the expression of inflammatory factors[42,43]. Antagonizing the activation of it can reduce the secretion of inflammatory factors in lung tissue and the inflammatory response of ARDS[42,43]. NF-κB signaling pathway is a key pathway in inflammatory diseases, and its activation is involved in the occurrence and development of ARDS caused by SARS-CoV-2 infection[44,45]. Current studies[44,45] suggest that blocking NF-κB signaling pathway can significantly reduce the occurrence of SARS-CoV-2-triggered ARDS. As shown above, we found that the core components of Xuebijing play a role in the treatment of coronavirus-induced ARDS, mainly acting on PI3K-Akt signaling pathway, TNF signaling pathway, STAT3 signaling pathway, NF-κB signaling pathway and apoptosis-related pathways.

Conclusions

This study screened the main components, targets and molecular mechanisms of Xuebijing while treating SARS-CoV-2-induced ARDS through network pharmacology. Our research suggests that Xuebijing injection contains the characteristics of a multi-component, multi-target and multi-pathway treatment for ARDS triggered by SARS-CoV-2 infection. Meanwhile, we also discovered that the main mechanism of Xuebijing in the treatment of SARS-CoV-2-triggered ARDS is that multiple components act synergistically on PI3K-Akt, TNF, STAT3, NF-κB and apoptosis-related pathways.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

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

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Authors' Contribution

Pan Tao and Liu Jiming: Study conception and design, literature search, acquisition, interpretation and analysis of data, drafting and critically revising the article for important intellectual content and final approval of the version to be published.

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