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ORIGINAL RESEARCH

Analysis of the Network Pharmacology Mechanism and Clinical Efficacy of Qingre Jiedu Decoction (QJD) in the Treatment of Infectious Mononucleosis (IM) in Children

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Purpose: This study aimed to clarify the molecular mechanisms of Qingre Jiedu Decoction (QJD), a traditional Chinese medicine (TCM), in treating infectious mononucleosis (IM). By combining network pharmacology and clinical trial validation, the research sought to understand how QJD interacts with biological pathways to combat IM.

Methods: The research team identified active compounds and their targets in QJD using databases like TCMSP and STITCH. Genes related to IM were sourced from NCBI and DisGeNET. These data were used to construct a protein-protein interaction (PPI) network with STRING, visualizing interactions between QJD targets and IM-related genes. Functional enrichment analyses were conducted, including GO biological process analysis via Cytoscape ClueGo and KEGG pathway analysis using R's Clusterprofile package. A clinical trial involving 97 pediatric IM patients (53 in the experimental group, 44 in the control group) evaluated QJD's real-world efficacy.

Results: The study identified 156 active compounds and 401 targets in QJD, along with 15 potential therapeutic targets for IM. In the clinical trial, the experimental group showed a significantly higher negative rate of plasma EBV (Epstein-Barr virus)-DNA post-treatment, indicating a stronger antiviral effect. Peripheral blood lymphocyte counts, $CD3^+$ percentage, and $CD8^+$ percentage decreased in the experimental group, suggesting an immunomodulatory effect. Additionally, levels of inflammatory cytokines (IL-6, IL-1β, TNF-α) were significantly reduced post-treatment, supporting QJD's anti-inflammatory properties.

Conclusion: QJD's multi-component effects contribute to its antiviral activity against EBV by modulating cytokine-mediated signaling pathways. This finding provides a scientific basis for QJD's clinical use in IM and underscores the potential of integrating network pharmacology with clinical trials to elucidate TCM mechanisms.

Keywords: QJD, IM, EBV, network pharmacology, clinical efficacy, children

Introduction

Epstein-Barr virus (EBV) was first discovered by Anthony Epstein in a study of Burkitt's lymphoma in African children.[1] EBV belongs to the Herpesviridae family, Gammaherpesvirinae subfamily and is classified as human herpesvirus type 4 (HHV-4).[2] The World Health Organization (WHO) categorizes EBV as a Group I carcinogen.[3] EBV was the first human oncovirus to be discovered and is carcinogenic.[3,4] It is a highly prevalent virus worldwide, with transmission occurring in 90–95% of adults.[5,6] Humans are the only known host for EBV.[7] This ubiquitous virus is primarily spread through direct contact with an infected person's saliva, such as kissing (the main route of transmission), sharing eating and drinking utensils, etc.[8] EBV can also be transmitted through blood transfusions and organ transplants.[9]

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Primary EBV infection can lead to infectious mononucleosis (IM), as well as some severe non-neoplastic diseases that can significantly affect the health and quality of life of children, such as chronic active Epstein-Barr virus infection (CAEBV),[10] EBV-related hematologic disorders like Epstein-Barr virus associated hemophagocytic lymphohistiocytosis (EBV-HLH)[11] and Epstein-Barr virus associated lymphocytosis after transplantation (EBV-PTLD).[12] In addition, EBV is closely associated with a variety of tumors, including lymphomas (such as Burkitt's lymphoma, Hodgkin's lymphoma and B-cell lymphomas in immunocompromised patients),[13] certain types of epithelial cell carcinomas (such as nasopharyngeal carcinoma)[14] and certain types of gastric cancer.[15] The evidence also suggests a link between EBV infection and certain autoimmune diseases (such as Sjogren's syndrome (SS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and multiple sclerosis (MS)), but the exact mechanism of this relationship remains unclear.[16] It is awe-inspiring and intriguing that EBV possesses the remarkable ability to evade immune surveillance of the host and establish persistent latent infection, while also being able to cause a variety of diseases.[2,4]

It was confirmed that EBV is associated with IM.[17] IM occurs globally without seasonal patterns. The global annual incidence is 150–200/100,000,[18] with higher rates in Western countries (eg, US: 250/100,000) than in Asia (eg, Japan: 80/100,000; China: ~120/100,000).[19] In developed nations, IM peaks in adolescents/young adults,[20,21] whereas in China (a developing country), incidence is highest among preschool children (4–6 years).[22] While infantile EBV infection is usually asymptomatic, it can cause IM in 25% to 79% of infected adolescents and young adults.[20,21] IM is a clinical syndrome caused by primary EBV infection.[21] In children, the typical clinical presentation of IM is the triad of fever, pharyngitis and enlarged lymph nodes.[22] Some patients may have periorbital and/or eyelid edema,[23] hepatosplenomegaly,[24] rash,[25] hepatic dysfunction 6 and spontaneous splenic rupture,[26] etc. IM is a benign self-limiting disease with a favorable prognosis in the majority of cases.[8] Less than 1% of IM cases may experience life-threatening complications.[8,22] Patients with specific genetic and immune backgrounds may develop severe IM.[27] Wang et al found 5–10% of IM patients develop persistent symptoms.[19] Chronic EBV infection and post-IM sequelae (eg, chronic fatigue, lymphoma risk) impose a long-term health burden. Clinical manifestations of EBV infection in children involve multiple systems, and some patients may develop pneumonia, encephalitis, myocarditis with a few may experience serious complications such as HLH.[8,11,22] The treatment for IM mainly focuses on supportive care.[6,8] So far, antiviral drugs such as Ganciclovir (GCV) and Acyclovir (ACV) have been proven to inhibit the replication of EBV.[28] However, the clinical effectiveness of antiviral therapy for IM is still controversial.[12,22] While antiviral drugs can suppress virus replication, they do not affect the proliferation of latently infected cells.[12,29] The T lymphocyte subset is the main cell population that mediates the body's immune response, capable of secreting various immune factors and playing an important regulatory role in the pathological process of EBV infection.[4]

Although ancient traditional Chinese medicine (TCM) literature lacks explicit reference to "IM", its epidemiological and clinical features mirror TCM concepts like "febrile epidemic diseases" and "pestilential disorders".[30] Historical records from Chao Yuanfang's era attribute IM to "wind-heat pathogenic factors" affecting the throat and facial region, classified as "warm toxin" by Wu Jutong in the Qing Dynasty. Children, with their immature yin-yang balance and delicate zang-fu organs, are prone to pathogenic fire/heat, internal transmission of pathogens, and subsequent syndromes post-pestilential exposure. We simplify IM pathogenesis to "heat, toxin, phlegm, and stasis". In modern TCM, syndrome differentiation based on Wei-Qi-Ying-Xue and Triple Energizer frameworks classifies IM into four types for tailored treatment: lung-defense toxin stagnation, nutrient-blood heat infiltration, liver-gallbladder toxin-stasis, and qi-yin deficiency.[31,32] Currently, heat-clearing, detoxifying, blood-activating, and stasis-resolving herbs are commonly prescribed for pediatric IM.[31,32] Andrographolide (from Xiyanping injection) and emodin effectively inhibit EBV replication.[33,34] Ancient TCM insights offer a theoretical basis for modern IM management. Multiple domestic studies confirm TCM syndrome differentiation and integrated Chinese-Western medicine's efficacy in IM treatment. However, large-scale randomized controlled trials (RCTs) are still warranted to provide more robust evidence.[30–32]

TCM has provided an alternative perspective. With its synergistic effects on multiple targets, stages, and pathways, as well as fewer side effects compared to chemical drugs, TCM offers a unique advantage in clinical practice and can significantly improve the overall functional state of patients. In this study, the selected TCM preparation (QJD) is a pure Chinese herbal formula developed using modern technological processes in accordance with the principle of "clearing heat and detoxifying, cooling blood", tailored to the physiological characteristics of children. It mainly consists of ten

Chinese medicinal herbs: *Scutellariae Radix* (Huang Qin), *Forsythiae Fructus* (Lian Qiao), *Radix Isatidis* (Ban Lan Gen), *Gypsum* (Shi Gao), *Anemarrhenae Rhizoma* (Zhi Mu), *Radix Rehmanniae* (Sheng Di), *Pogostemon Cablin* (Blanco) *Bonth* (Guang Huo Xiang), *Curcumae Radix* (Yu Jin), *Acoritataninowi Rhizoma* (Shi Chang Pu), and *Ramulus Uncariae cum Uncis* (Gou Teng). This preparation has been granted a national invention patent.[35] As an in-hospital treatment option for respiratory tract infections, influenza, mumps, hand-foot-and-mouth disease, IM and viral encephalitis; it has shown significant therapeutic effects after more than 20 years of clinical application.[36–38] The QJD is convenient to take with significant therapeutic effects while having no obvious toxic side effects.[35] The etiology and pathogenesis of IM are characterized by heat, toxicity, phlegm, and stasis. The fundamental treatment method for this disease is clearing heat and detoxifying.[30] The heat-clearing and detoxifying mixture possesses the effects of drying dampness and clearing heat, purging fire and detoxifying, cooling blood and nourishing yin, as well as quenching thirst and generating body fluids.[35–38]

In recent years, there has been a growing interest in the treatment of diseases with TCM. The chemical components of Chinese herbs are numerous, and the molecular mechanisms are not clearly explained. With the continuous advancement of technology, network pharmacology is often used to reveal the pathogenesis of diseases and analyze the mechanisms of action of drugs from the perspective of TCM.[39] Through various networks of multi-level interactions, it guides drug discovery and development by providing a valuable basis for exploring the mechanisms of action of drugs and bridging the gap between Chinese medicine and chemical drugs.[39,40]

The aim of this study is to investigate the mechanism of action of QJD in the treatment of IM. The potential targets and underlying mechanisms involved in the treatment of IM have been analyzed through network pharmacology. Furthermore, a clinical trial involving pediatric patients was conducted to verify the efficacy of the QJD in treating IM. It is believed that the results of this study provide a solid theoretical foundation for the clinical application of QJD.

Materials and Methods

Exploring the Mechanism of Action of QJD in Treating IM Based on Network Pharmacology

Assessment of Drug-Likeness of QJD

The chemical components of nine Chinese medicinal herbs (excluding gypsum) were gathered from domestic and international literature, as well as Chinese medicine systems pharmacology databases and analysis platforms such as TCMSP (http://lsp.nwu.edu.cn/tcmsp.php),[41] Integrated Pharmacology Platform (TCMID, http://bidd.group/TCMID) and NIBI database. Active ingredients were screened based on oral bioavailability (OB) and drug likeness (DL) parameters.[40] This study adopts the standards of oral bioavailability (OB) ≥30% and drug-likeness (DL) ≥0.18 to screen active compounds. The PubChem database (https://pubchem.ncbi.nlm.nih.gov/) is used to standardize the above components. Save the SMILE chemical structure formula.[42]

Construction and Analysis of the Chinese Medicine Compound Active Ingredient-Target-Infectious Mononucleosis Network

The target information of active ingredients will be obtained and predicted directly through the TCMSP database, STITCH molecule-protein interaction database (http://stitch.embl.de/), and ChEMBL small molecule target prediction server. Both TCMSP and STITCH include targets from literature as well as predicted targets. The SMILE structure formula of the active ingredients will be uploaded to the target prediction server, with a high confidence level set, in order to return the top 10 targets. The target points of the components will be selected from the STITCH molecule-protein interaction database.

Retrieve host genes associated with infectious mononucleosis by utilizing keywords such as "infectious mononucleosis" in human disease databases like OMIM (Online Mendelian Inheritance in Man, OMIM, https://www.omim.org/)[43] and DisGeNET (https://www.disgenet.org/).[44]

Identify potential targets for the treatment of IM through the intersection of drug component targets and disease targets using the QJD.

Generate a PPI network diagram for potential therapeutic targets in the string database (https://string-db.org/) to analyze functional interactions between proteins. Develop the herbal material-component-target network based on Chinese medicine sources, active ingredients, and potential targets.

Identify nodes in the aforementioned network with three centrality parameters of network topology (degree value, betweenness centrality, and closeness centrality) greater than the median as core targets and core active ingredients.

Perform gene ontology (GO, http://www.geneontology.org) function and Kyoto Encyclopedia of Genes and Genomes (KEGG, https://www.genome.jp/kegg/) enrichment analysis for potential therapeutic targets. GO analysis includes biological process (BP), cellular component (CC), and molecular function (MF).[45]

Through the above analysis, elucidate the material basis and molecular mechanism by which the heat-clearing and detoxifying mixture exerts its pharmacological effects, providing evidence for further verification of its efficacy.

Clinical Efficacy Verification of QJD in the Treatment of IM

General Data

Study Population and Setting

This study included inpatients aged 1 to 14 years who met the inclusion and exclusion criteria for IM and were admitted to our hospital from January 1, 2023, to December 31, 2023. Clinical data were retrospectively collected from the patients' medical record, including demographic factors, clinical manifestations, laboratory parameters, disease management methods and outcomes.

Diagnostic Criteria for IM

The definition of IM in this study was based on the published diagnostic criteria for IM. These criteria are as follows: the presence of ≥3 characteristic symptoms (ie, fever, cervical lymph node enlargement, hepatomegaly, splenomegaly, pharyngitis, eyelid edema); atypical lymphocytes in the peripheral blood ≥10% of the total lymphocyte count and/or lymphocyte count ≥5.0×10^9/L; and the presence of specific antibodies: (1) positive for anti-viral capsid antigen (VCA)-IgM and anti-VCA-IgG antibodies, negative for anti-EBV nuclear antigen (EBNA)-IgG antibodies; (2) negative for anti-VCA-IgM antibodies and positive for anti-VCA-IgG antibodies with low affinity.[46,47]

Inclusion Criteria

Inpatients who meet the diagnostic criteria for IM; Guardians who agree to participate in the randomized controlled trial and sign the informed consent form; Case age ≤14 years old.

Exclusion Criteria

Patients with coexisting malignant hematological tumors, severe central nervous system damage, connective tissue disease, congenital immunodeficiency, congenital malformations, and hereditary metabolic diseases, etc.

Patients who have been or are currently using hormone or immunosuppressive therapy due to underlying diseases.

Patients who are participating in other clinical trials of IM.

Patients who cannot cooperate with oral TCM treatment.

Type of Intervention

All patients were randomly assigned to either the experimental group or the control group.

Experimental Group

Comprehensive Western medicine treatment, supplemented with QJD.

Control Group

Comprehensive Western medicine treatment according to the guidance plan, including symptomatic support and selection of antibiotics based on the condition.

QJD Treatment

Prescription of the Decoction

Forsythiae Fructus (Lian Qiao) 15g, *Radix Isatidis* (Ban Lan Gen) 30g, *Scutellariae Radix* (Huang Qin) 6g, *Gypsum* (Shi Gao) 25g, *Pogostemon Cablin* (Blanco) *Bonth* (Guang Huo Xiang) 15g, *Curcumae Radix* (Yu Jin) 6g, *Anemarrhenae Rhizoma*(Zhi Mu) 9g, *Radix Rehmanniae* (Sheng Di) 12g, *Acoritataninowi Rhizoma* (Shi Chang Pu) 9g and *Ramulus Uncariae cum Uncis* (Gou Teng) 6g. The medicinal materials were carefully selected from Liaocheng People's Hospital. They were decocted and concentrated using the best purification process. Each bottle contains 250mL with each milliliter of medicinal liquid containing about 2.13g of crude drug.

Method of Administration

Dosage-oral administration twice a day for different age groups as follows: 1–3 years old 20mL, 3–6 years old 30mL, 7–9 years old 35mL, 9–13 years old 40mL.

Course of Treatment

7 days.

Methods

Cytokine Detection

Flow cytometry is utilized for the detection of inflammatory factors, specifically IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17, TNF-α, and IFN-γ. The kits required for this process are supplied by Qingdao Raisecare Biological Technology Co., Ltd (Shandong Qingdao Medical Device Filing, 20180086).

(1) Sample Collection:

Venous blood samples are collected in EDTA anticoagulant blood collection tubes and then centrifuged at 1000g for 10 minutes to separate the plasma for testing.

(2) Method:

a. Calculate the number of samples (n = number of standard tubes 10 + negative control 1+ number of test samples). Take the 1kit's capture microsphere mixture (A), vortex for 3–5 seconds, take n*25ul (slightly more can be taken) in a test tube and mark it. Centrifuge at 200g for 5 minutes and carefully aspirate the supernatant with a pipette before discarding it. Then resuspend the microspheres with an equal amount of microsphere buffer (H). Vortex for 3–5 seconds and incubate in the dark for 30 minutes. Remove the standard tubes (B) from the kit and transfer them to test tubes; add 2mL of sample diluent and let stand for 15 minutes while marking as the highest standard concentration (be gentle; do not shake violently). Take 10 test tubes and label them as 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256, and 1:512. Add 300 ul of sample diluent (G) to each tube. Transfer 300ul of sample from the highest concentration standard tube to the 1:2 tube and gently mix by blowing. Then transfer 300ul from the 1:2 tube to the 1:4 tube and mix by blowing, continuing this process until reaching the 1:512 tube. Prepare a series of standard solutions with different concentrations in n test tubes labeled in order as standard tubes (0 for negative control), standard tubes (tubes numbered from "0" to "10"), and sample tubes (test tubes numbered from"test 1" to "test (n-11) "). Add 25ul of the corresponding concentration standard to each standard tube, and add 25ul of the sample to be tested to each sample tube. Add 25ul of fluorescent detection reagent (C) to all standard and sample tubes. After incubation, vortex the capture microspheres to mix, and add 25ul to all standard and sample tubes. Vortex all test tubes from step i, mix thoroughly, and incubate at room temperature in darkness for hours. Following incubation, add 1mL of PBS solution to each tube for washing. Centrifuge at 200g for 5 minutes and discard the supernatant. Add 100ul of PBS solution to each tube, vortex to resuspend, and prepare for machine processing. Operate the machine and analyze the results.

Four-color fluorescent staining method for absolute technical blood T lymphocyte subset detection

The BD FACSCanto flow cytometer is used to detect T lymphocyte subsets, including the levels of $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$, with the reagent kit being the instrument's matching reagent kit.

(1) Reagents

BD TriTEST CD3FITC/8PE/45Percp/4APC antibodies, BD TriTEST CD3FITC/16+56 PE/45Percp/19APC antibodies, TruCOUNT tubes containing a known number of fluorescent counting microspheres, and FACS Lysing solution for red blood cell lysis.

(2) Sample Collection

2mL of venous blood should be collected using an EDTA-K2/K3 vacuum blood collection tube, and staining treatment should be performed within 6 hours after collection.

(3) Immunofluorescence Staining

Add 20μL of TriTEST CD3FITC/8PE/45Percp/4APC, BD TriTEST CD3FITC/16+56 PE/45Percp/19APC antibodies, and 50μL of anticoagulant to the TruCOUNT tube. Mix well and allow to react at room temperature in the dark for 20 minutes. Then add 450μL of red blood cell lysing solution (1x FACS), mix well again, and allow to react at room temperature in the dark for 15 minutes before performing flow cytometry detection within 24 hours.

(4) Flow Cytometry Analysis

Conduct machine operation and analysis as per standard protocol.

EBV-DNA Detection

Quantitative detection of plasma EBV DNA is conducted using real-time fluorescent quantitative polymerase chain reaction (PCR). The reagent kits are sourced from Sansure Biotech Inc., Changsha, China (National Medical Device Registration Approval, 20173400077), and the fluorescence detection system utilized is the ABI7500 fluorescent PCR instrument.

(1) Sample Collection

A sterile syringe is used to draw 1mL of venous blood from the subject, which is then injected into a sterile collection tube containing EDTA and immediately mixed gently by inverting.

(2) Follow the operating procedures outlined in the reagent kit instructions, taking the appropriate amount of reaction liquid, enzyme mixture, and internal standard, mixing well to form the PCR mixture, and briefly centrifuging before use.

(3)Treat the peripheral blood sample with whole blood genomic extraction reagent; subsequently, utilize DNA obtained from extraction by Tianlong 96E as the sample for testing.

(4) Add 40μL of PCR mixture to a closed tube cap and centrifuge at 2000 rpm for 30 seconds.

(5) Place the PCR reaction tubes into the PCR amplification instrument for amplification; conduct UNG enzyme reaction at 50°C for 2 minutes followed by Taq enzyme activation at 94°C for 5 minutes. Then proceed with cycles of heating at 94°C for 15 seconds and annealing at 57°C for 30 seconds, totaling in a sequence of 45 cycles.

(6) Interpretation of results.

Collection of Clinical Data and Laboratory Test Results

Clinical Data Clinical data for pediatric patients includes the following

(1) Demographic indicators: age, gender, height, weight.

(2) Underlying comorbidities.

(3) Clinical symptoms: fever, sore throat, nasal congestion, snoring, difficulty breathing, cough, vomiting, diarrhea, headache, mental status, etc.

(4) Physical signs: rash, pharyngeal congestion, tonsillar enlargement, superficial lymph node enlargement, hepatomegaly, splenomegaly, etc.

Laboratory Test Results Gather the laboratory test results for pediatric patients, including: complete blood count, liver function tests (AST, ALT, TBIL, DBIL, ALB), renal function tests (Cr, BUN), cardiac enzymes (LDH, HBDH, CK, CKMB), peripheral blood cell count and morphology (percentage of atypical lymphocytes), EBV-DNA (plasma), EBV-DNA (mononuclear cells), EBV antibody panel, TORCH (Toxoplasma, Others, Rubella, Cytomegalovirus, Hepres), anti-O^+ rheumatoid factor, immunoglobulins, T cell subsets, interleukin measurement, abdominal ultrasound, etc.

Statistical Analyses

The analysis was conducted using IBM SPSS Statistics software. For measurement data that do not follow a normal distribution, they are presented as M (P25, P75), indicating the median with the interquartile range. Comparisons between two groups were performed using the Mann–Whitney U rank-sum test. Discrepancies between data are denoted by *P*-values, where $P > 0.05$ indicates no statistically significant difference, and $P \leq 0.05$ indicates a statistically significant difference.

Results

Network Pharmacology Based Analysis

Evaluation of Drug-Like Properties of the QJD

The chemical components of each medicinal material were obtained from the TCM Systems Pharmacology Database, Analysis Platform (TCMSP) and the TCM Information Database (TCMID). Active compounds were selected based on specific criteria, including oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18. The chosen active compounds were then cross-referenced with the PubChem database for validation and standardization of their names and structural formulas.

In the TCMSP database, chemical components of 10 herbs, including *Pogostemon Cablin* (Blanco) *Bonth* (Guang Huo Xiang), *Ramulus Uncariae cum Uncis* (Gou Teng), *Radix Rehmanniae* (Sheng Di), *Anemarrhenae Rhizoma* (Zhi Mu), *Curcumae Radix* (Yu Jin), *Acoritataninowi Rhizoma* (Shi Chang Pu), *Forsythiae Fructus* (Lian Qiao), *Scutellariae Radix* (Huang Qin), *Radix Isatidis* (Ban Lan Gen), and Gypsum were collected in varying numbers for each material. The number of chemical components contained in each herb are 94, 65, 8,81,222,105,150,38 and 169 respectively. After removing duplicates, a total of 159 unique components were obtained. It is important to note that calcium sulfate was identified as the main component of gypsum but was excluded from subsequent network construction due to a lack of clear target information. Furthermore, through literature review it was discovered that 17 chemical components in the QJD exhibited significant pharmacological activity despite not meeting the OB and DL screening criteria; therefore, they were still included in the research scope. These compounds include pogostone, acteoside, curcumenol, curzerene, forsythiaside, forsythoside B, acteoside, catalpol, beta-asarone, alpha-asarone, aaicalin, wogonoside, ursolic acid, chlorogenic acid, epigoitrin, indirubin and tryptanthrin.

Construction and Analysis of the Network of TCM Compound Active Ingredients, Targets and Infectious Mononucleosis

The action targets of the screened active compounds were comprehensively collected using the TCMSP database and STITCH database (http://stitch.embl.de). The UniProt database (http://www.uniprot.org) was utilized to standardize the names of the target. Compounds without targets were excluded from the analysis. Out of the 159 screened active compounds, 156 compounds with targets were identified, resulting in a total of 401 action targets.

By using "Infectious Mononucleosis (CUI: C0021345)" as the keyword, NCBI database (https://www.ncbi.nlm.nih.gov/gene) and DisGeNET database (https://www.disgenet.org) were queried to obtain targets related to infectious mononucleosis. After merging and de-duplication, these targets were compared with the action targets of QJD. An intersection gene Venn diagram (http://bioinformatics.psb.ugent.be/webtools/Venn/) was created (Figure 1), revealing 15 common genes. These genes are considered potential treatment targets for infectious mononucleosis by QJD.

The network diagram of the TCM- Component-Target (H-C-T) was constructed using Cytoscape 3.7 software (Figure 2). The network consists of 68 nodes and 148 edges, encompassing 9 types of Chinese medicines, 44 chemical components, and 15 common targets. A table presenting the topological parameters for network nodes has been compiled (Table 1). Notably, *Forsythiae Fructus* (Lian Qiao), *Scutellariae Radix* (Huang Qin) and *Radix Isatidis* (Ban Lan Gen) exhibit higher network degree values among the Chinese medicines. Key chemical components include Quercetin, Beta-Sitosterol, Kaempferol, Luteolin, and Stigmasterol. They may serve as the principal and ministerial medicinal herbs as well as important active ingredients in QJD.

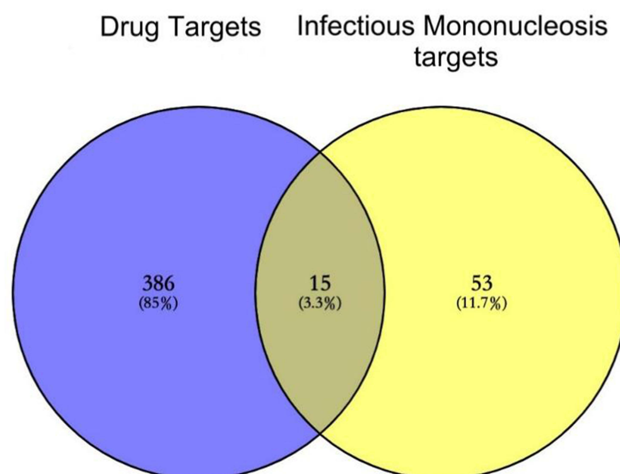

Figure 1 Venn diagram of the intersected targets of Qingre Jiedu Decotion (QJD) and infectious mononucleosis (IM) (QJD active component and IM-related genes overlap; 15 common targets found, potential for QJD in IM treatment).

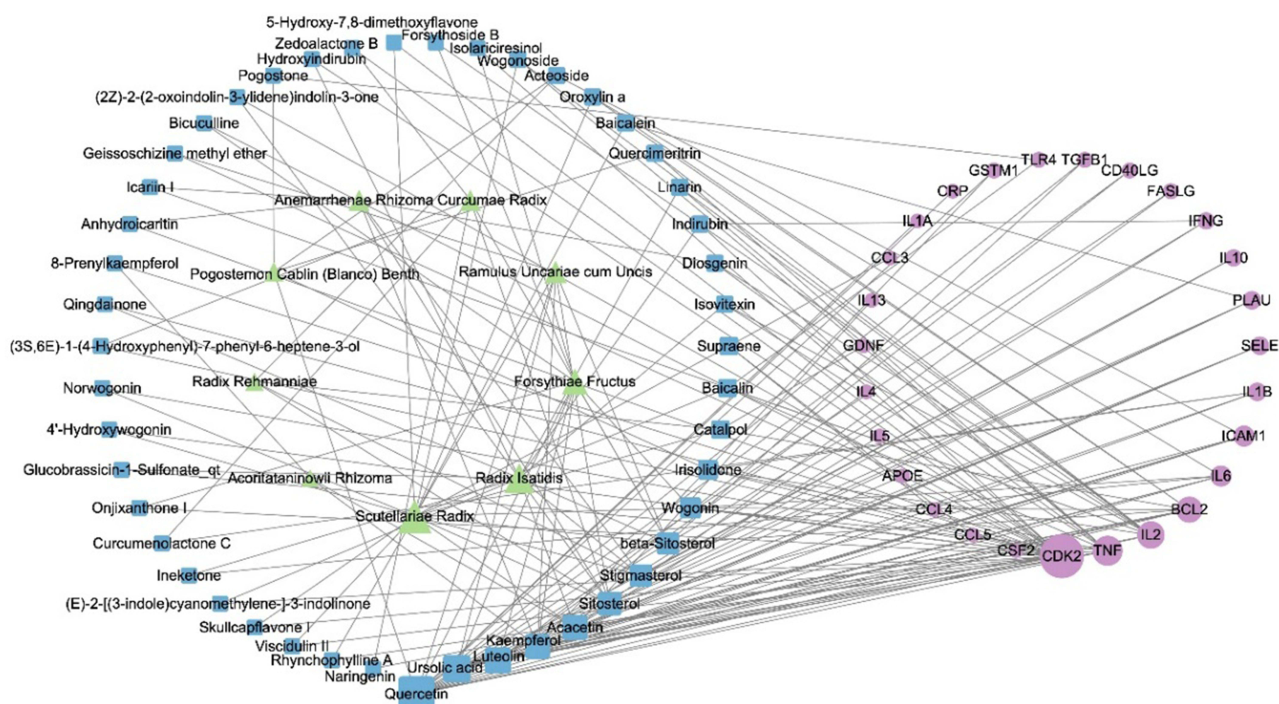

Figure 2 Traditional Chinese Medicine-active components-target (H–C–T) network of Qingre Jiedu Decotion (QJD) acting on infectious mononucleosis (IM) (Green triangles: 9 drugs (TCM). Blue squares: 44 chemical constituents. Purple circles: 15 common targets. Edges show interactions; node size indicates degree (68 nodes, 149 edges total). Larger node = higher degree.

Construction of PPI network for potential targets. The PPI network was established using the String database (https://string-db.org/) and the PPI network diagram was created (Figure 3). The target network degree value graph was generated using R language (Figure 4). Core targets include TNF, IL6, IL1B, IL10 and TGFB1.

Enrichment analysis of potential target GO terms. Enrichment resulted in 1247 Gene Ontology biological process (GO-BP) entries and 13 molecular function (GO-MF) entries. The top 20 enriched entries are listed separately (Figures 5 and 6).

Enrichment analysis of potential target KEGG pathways revealed enrichment in 79 entries. The top 20 enriched pathways are listed in the KEGG enrichment ranking chart (Figure 7).

Table 1 Network Topological Parameters of the Traditional Chinese Medicine-Component-Common Target (TCM-C-T)

Node	BC	CC	DC	Node	BC	CC	DC
Scutellariae Radix	0.1378	0.4136	14	Baicalin	0.0390	0.3602	4
Radix Isatidis	0.0930	0.3941	12	Catalpol	0.0392	0.3317	4
Forsythiae Fructus	0.0745	0.4085	10	Baicalein	0.0050	0.3284	3
Ramulus Uncariae cum Uncis	0.0309	0.3895	6	Diosgenin	0.0039	0.3160	3
Curcumae Radix	0.0243	0.3252	5	Indirubin	0.0099	0.3641	3
Anemarrhenae Rhizoma	0.0215	0.3490	5	Isovitexin	0.0078	0.3454	3
Pogostemon Cablin (Blanco) Bonth	0.0319	0.3641	4	Linarin	0.0078	0.3454	3
Acoritataninowi Rhizoma	0.0060	0.3284	3	Oroxylin a	0.0048	0.3350	3
Radix Rehmanniae	0.0026	0.2965	2	Quercimeritrin	0.0037	0.3160	3
Quercetin	0.1836	0.4295	15	Wogonoside	0.0079	0.3526	3
Beta-Sitoste	0.0636	0.4241	7	CDK2	0.3145	0.4589	24
Kaempferol	0.0454	0.3807	7	TNF	0.1120	0.4295	13
Luteolin	0.0552	0.4295	7	IL2	0.0817	0.4085	11
Stigmastero	0.0616	0.3988	7	BCL2	0.0958	0.4188	10
Ursolic acid	0.0277	0.3764	7	IL6	0.0264	0.3764	6
Wogonin	0.0455	0.4408	6	IL1B	0.0221	0.3641	4
Acacetin	0.0369	0.4188	5	PLAU	0.0107	0.3602	4
Irisolidone	0.0568	0.4136	5				

Notes: Network diagram ranked TCMs, compounds, and targets by descending DC values. Top items with high BC, CC, and DC were selected and listed in the table.

Abbreviations: BC, Betweenness Centrality;CC, Closeness Centrality; DC, Degree Centrality.

Validation of the Therapeutic Effect of the QJD

Ninety-seven eligible pediatric patients were included in our study. Of the 97 cases, there were 64 males (66%) and 33 females (34%), with a male-to-female ratio of 1.9:1. Among the patients, 39 (40%) were under the age of 3, 41 (42%) were aged between 3 and 6, and 17 (18%) were between the ages of 7 and 14 (Table 2).

There were no differences in clinical symptoms, signs, and laboratory indicators between the experimental group and the control group before medication ($P>0.05$) (Table 3). The post-treatment plasma EBV-DNA conversion rate in the experimental group was significantly higher than that in the control group ($P=0.006$). After treatment, the percentages of peripheral blood lymphocytes, $CD3^+$ cells, and $CD8^+$ cells in the experimental group decreased significantly (*P* values were 0.042, 0.0 19, 0.031 respectively). The levels of cytokines IL-1β, 2, 4, 6, 10; TNF-α; and TNF-γ were elevated in pediatric patients with mononucleosis. After treatment, IL6, IL-1β and TNF-α decreased faster in the experimental group than in the control group (*P* values were 0.001, 0.014 and 0.000 respectively) (Table 4).

Discussion

EBV is highly prevalent worldwide.[5,6] Following EBV infection, individuals become lifelong carriers of the virus.[7] The latent virus in the pharynx can be reactivated and shed,[8,9] making long-term carriers an important source of infection.[48] EBV infection can lead to a variety of serious non-neoplastic diseases and various tumors.[10–16] Annually, it causes approximately 145,000 deaths globally.[49]

For decades, EBV has posed a challenge for scientists.[2,5] The virus employs various strategies to evade detection and elimination by the host immune system, rendering it difficult to eradicate.[4,10] In response, the host's immune system deploys its most effective defense mechanisms including pattern recognition receptors,[50] natural killer cells[51] and T cells[52] in an effort to control and eliminate EBV. The interaction between EBV and the human immune system is complex and multifaceted.[4,53] Given that avoiding exposure to EBV is nearly impossible, researchers believe that the most effective approach to preventing EBV infection is through the development of an effective, safe and affordable vaccine which can confer lifelong immunity.[4,10] Furthermore, researchers believe that an effective prophylactic EBV vaccine has the potential to prevent EBV-related malignancies.[54] However, challenges such as the complexity of the EBV

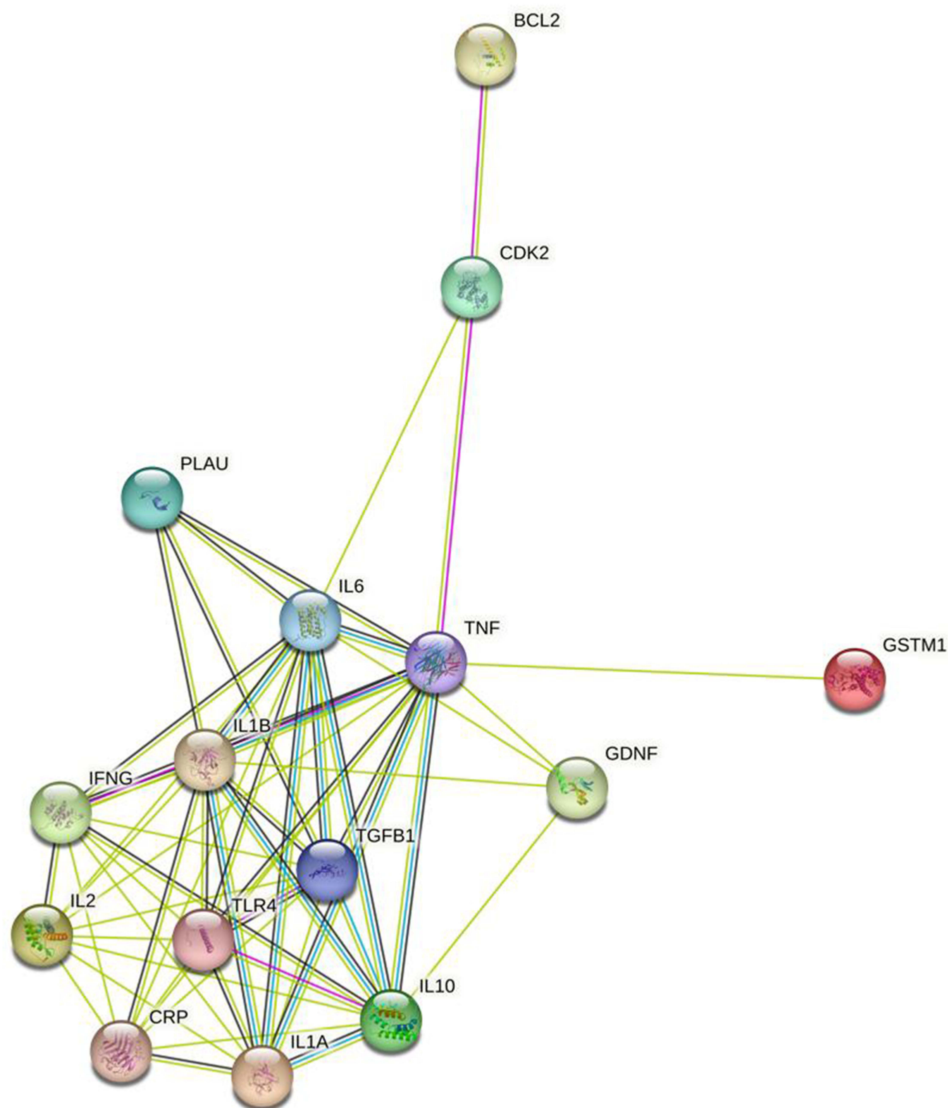

Figure 3 Protein-Protein Interaction (PPI) Network Diagram (The PPI network of 15 potential targets. Nodes denote proteins, edges represent PPIs, and line width between nodes indicates interaction strength).

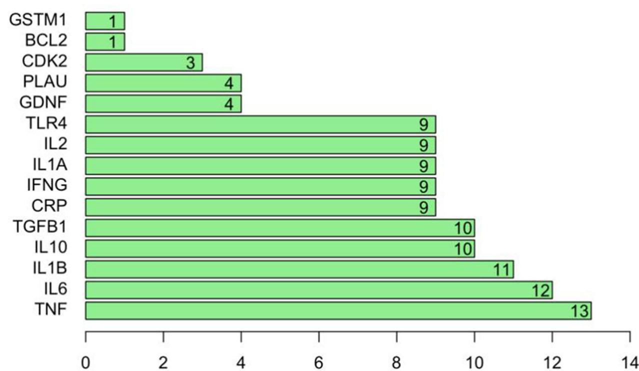

Figure 4 Bar chart of node degree values in the PPI network. (The horizontal axis shows node degree values (0–14), the vertical axis counts proteins per degree. Five proteins have high degrees (>10), likely potential drug targets.

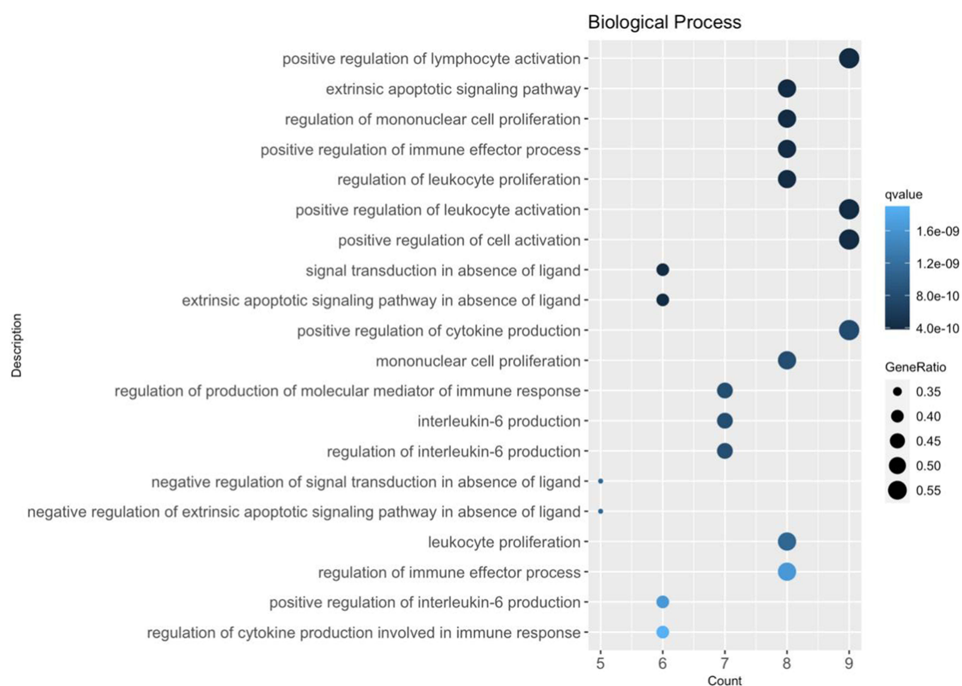

Figure 5 Enrichment Analysis of Potential Target Genes (GO Biological Processes) (GO biological process enrichment analysis of potential target genes found 1,247 enriched processes. Top 20 are shown. Node size = enrichment count; horizontal axis: biological process categories; vertical axis: -log10(Q-value); darker color = greater enrichment significance).

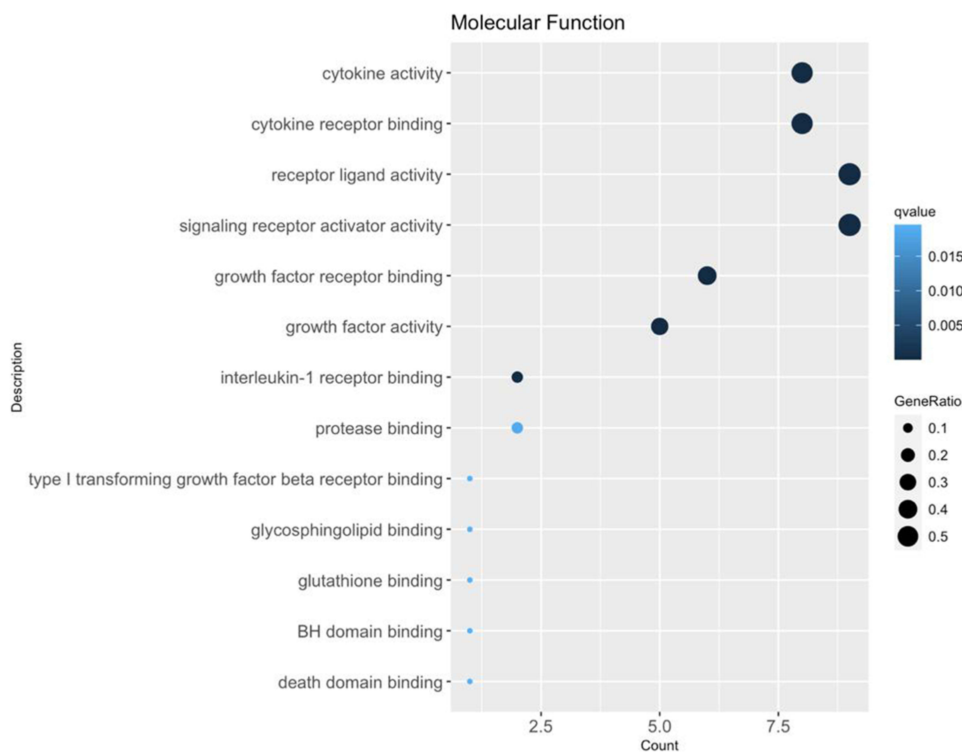

Figure 6 Enrichment analysis of potential targets in GO (Gene Ontology molecular function) (GO molecular function enrichment on potential targets gave 13 enriched functions. Node size: enrichment count; X-axis: function categories; Y-axis: -log10(Q-value); Color: darker = higher enrichment. Nodes sorted by function (ascending)).

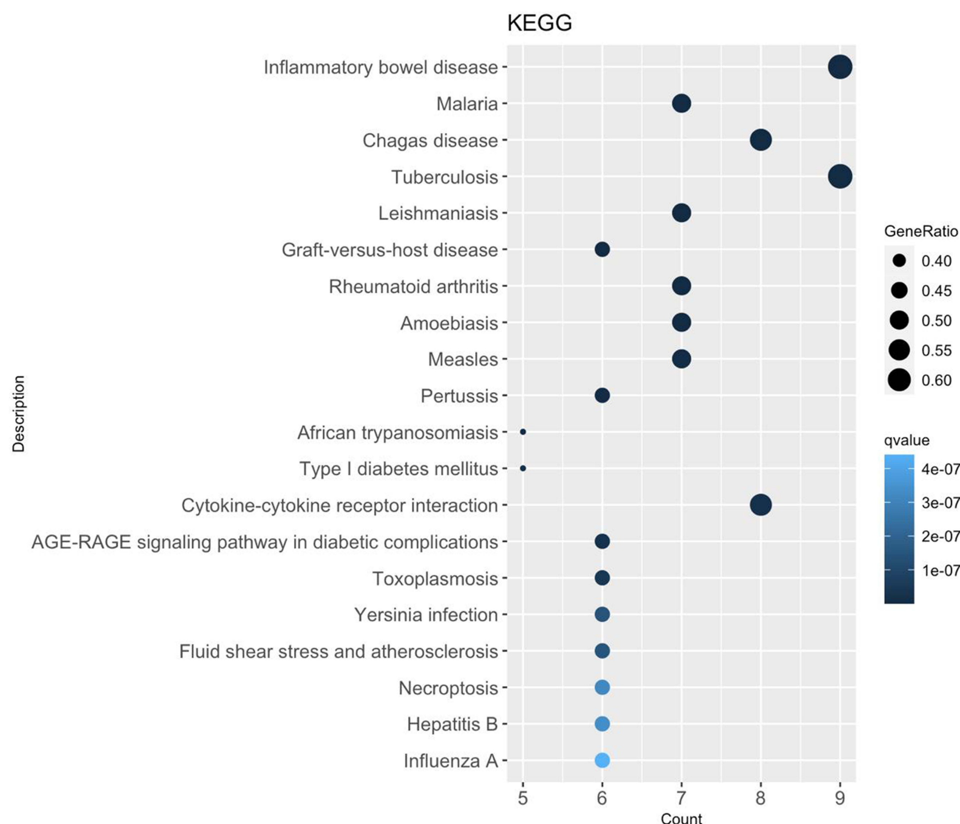

Figure 7 Enrichment Analysis of Potential Targets in KEGG (KEGG enrichment: Top 20 of 79 enriched pathways for potential targets. Node size: count of enrichments; X-axis: gene ratio; Color: darker = greater enrichment (-log10(Q-value)). Nodes sorted by gene count (ascending).

life cycle, lack of appropriate animal models and limited understanding of the required immune response have hindered progress in vaccine development.[4] Despite decades of effort, there remains no licensed commercial vaccine for preventing EBV infection at present time.[4,55]

We aim to initiate our study with patients suffering from IM caused by EBV, particularly those with a self-limiting prognosis. Our goal is to investigate the pathogenesis of EBV and explore potential treatment methods for this condition. The clinical efficacy of antiviral drugs such as ganciclovir (GCV) and acyclovir (ACV) in treating IM is currently a topic of debate.[12,22] In this study, we have chosen a detoxifying and heat-clearing prescription as our research drug, and we will examine the therapeutic effects of this prescription on IM through network pharmacology analysis. Network pharmacology allows for a comprehensive analysis of the interactions between drugs and their targets, providing insight into the potential mechanisms involved in the treatment of IM using our chosen prescription. Through network

Table 2 Clinical Features in 97 Patients with Infectious Mononucleosis (IM)

Items		Experimental group (53 cases)	Control group (44 cases)	*P*
Gender	Male	35	29	*P*>0.05
	Female	18	15	
Age(years)	0-3	22	17	*P*>0.05
	3-6	25	16	
	6-14	6	11	

Notes: No gender/age differences between experimental ($P > 0.05$) and control groups ($P > 0.05$).

Table 3 Pre-Treatment Indicators of the Experimental Group and Control Group

Items	Experimental Group Median (Quartiles)	Control Group Median (Quartiles)	*Z*	*P*
Fever (yes:1, no: 0)			−0.465	0.642
Number of days with fever	3(1,5.5)	3(1,5)	−0.421	0.674
Rash (yes: 1, no: 0)			−0.465	0.642
Degree of tonsillar enlargement (1 degree: 1, 2 degree: 2,3 degree: 3)	2(1,2)	2(1,2)	−0.494	0.621
Lymphadenopathy (no: 0 yes: 1)	1(1,1)	1(1,1)	−0.234	0.815
Hepatomegaly (Distance from the lower ribs (cm))	2(0,3)	1.5(0,3)	−0.966	0.334
Splenomegaly (Distance from the lower ribs (cm))	1(0,2.5)	1(0,2.5)	−0.456	0.648
WBC ($\times 10^9$ /L)	15.16(12.27,18.88)	16.04(11.73,18.79)	−0.214	0.831
Lymphocyte (%)	71.3(61.8,77.6)	68.6(58.57,76.17)	−0.757	0.449
ALC (%)	8.0(6.5,12.0)	8(6.5,12)	−1.145	0.252
ALT (U/L)	60(45,134)	58(34.5,98.75)	−1.286	0.198
AST (U/L)	69(42,130.5)	69(42,130.5)	−1.906	0.057
$CD3^+$ T cell (%)	84.32(81.6,87.8)	87.09(83.4,89.78)	−1.964	0.056
$CD4^+$ T cell (%)	15.65(10.57,27.89)	15.84(11.45,18.76)	−0.558	0.577
$CD8^+$ T cell (%)	65.34(52.08,72.22)	68.19(64.01,74.21)	−1.644	0.100
$CD4^+$ /$CD8^+$ (%)	0.22(0.14,0.59)	0.22(0.165,0.31)	−0.684	0.494
$CD3^+$ T cell (pcs/uL)	9645(5720,13,041)	8449(6549.5,13,311.5)	−0.044	0.965
$CD4^+$ T cell (pcs/uL)	1659(1169,2595)	1572(1129,2060)	−0.538	0.590
$CD8^+$ T cell (pcs/uL)	6443(3907,10,391)	6766(4518,10,568)	−0.276	0.782
NK cell (%)	7.16(5.31,10.07)	8.09(5.72,10.55)	−1.073	0.283
NK cell (pcs/uL)	722(417.5,1068.5)	670.5(444, 1041.75)	−0.246	0.805
B cell (%)	4.09(2.56,5.90)	4.52(3.05,6.51)	−1.228	0.219
B cell (pcs/uL)	403(205, 598)	392(230.75,665.25)	−0.366	0.714
IL2	0.89(0.305,1.865)	1.0(0.585,2.3)	−1.098	0.272
IL6	11.03(4.93,20.01)	9.92(3.55,21.80)	−0.040	0.968
IL10	4.71(3.5,11.72)	5.26(2.8,12.79)	−0.163	0.870
TNF-γ	40.91(22.64,78.63)	29.67(15.40,80.75)	−1.442	0.149
IL17	1.23(0.85,2.07)	1.36(0.79,2.30)	−0.429	0.668
IL-1β	0.39(0.1,3.74)	0.11(0.1,3.39)	−0.004	0.997
IL4	1.05(0.745,1.81)	1.01(0.635,1.887)	−0.551	0.582
IL12P70	1.27(0.52,1.65)	1.09(0.13,1.59)	−0.324	0.746
TNF-α	1.61(0.13,2.62)	1.98(0.61,3.00)	−0.958	0.338
EBV-DNA (in plasma) (copies/mL)	2600(1320,9515)	2490(655.5,22,975)	−0.446	0.656
EBV-DNA (in single nucleic cells) (copies/mL)	27700(4970,131,500)	27,700(4970,131,500)	−0.692	0.489
Cr (μmol/L)	26.6(22.4,32.1)	24.25(10.92,31.05)	−1.497	0.134
BUN (mmol/L)	3.45(2.83,4.19)	3.39(2.35,4.30)	−0.677	0.498
CK (U/L)	49(33,78)	46(36,59.7)	−0.999	0.318
CK-MB (U/L)	12.5(1.88,18.0)	10(1.75,16.8)	−0.452	0.652

Notes: Pre-treatment: No differences in clinical symptoms, signs, or lab indicators between exp. and control groups ($P > 0.05$). Data: Median (quartiles). *P*-values show discrepancies; $P > 0.05$: no diff., $P \leq 0.05$: diff.).

Abbreviations: WBC, white blood cell; ALC, atypical lymphocytes; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IL, interleukin; TNF-α, Tumor necrosis factor-α; TNF-γ, Tumor necrosis factor-γ; Cr, creatinine; BUN, blood urea nitrogen; CK, creatine kinase; CK-MB, creatine kinase-MB.

pharmacology analysis, we have identified that the mechanism by which our chosen prescription treats IM is related to the regulation of cytokines. Specifically, TNF, IL6, IL1β, IL10 and TGFB1 have been identified as core targets for treating IM.

Previous studies have also confirmed the involvement of cytokines in the process of EBV infection.[4] Immune cells are capable of secreting a variety of immune factors, which play an important regulatory role in the pathological development of EBV infection.[10,22] The significant increase in the proportion of lymphocytes and atypical lymphocytes in

Table 4 Relevant Indices of the Experimental Group and Control Group After One week of Medication

Items	Experimental Group Median (Quartiles)	Control Group Median (Quartiles)	*Z*	*P*
EBV-DNA negative (in plasma) (Day of admission, D)	12(9,15.5)	9(8,12)	−2.763	0.006
ALC (%)<5% (Day of admission, D)	7(4.5,9)	5.5(3,9)	−1.429	0.153
Liver function recovery (Day of admission, D)	7(0.10)	7(0,9)	−0.546	0.585
Tonsil secretions disappeared (Day of admission, D)	4(2,5)	4(0,5)	−0.498	0.619
Temperature stabilization (Day of admission, D)	2(1,4)	2(0,3)	−0.88	0.379
Liver retraction (Day of admission, D)	4(2.5,7)	4(0,6)	−1.097	0.273
Splenic retraction (Day of admission, D)	4(0,6)	2.5(0,6)	−0.694	0.488
Lymph node retraction (Day of admission, D)	4(3.5,5)	4(3,5)	−0.487	0.626
WBC ($\times 10^9$ /L)	9.55(7.37,10.89)	9.21(6.65,10.74)	−0.355	0.723
Lymphocyte (%)	72.9(64.45,79.25)	72.9(64.45,79.25)	−2.036	0.042
ALT (U/L)	25(15.5,47)	31.5(19.5,65.75)	−1.567	0.117
AST (U/L)	27(21,36.5)	27(21.25,39.00)	−0.041	0.968
$CD3^+$ T cell (%)	87.89(84.39,90.03)	85.22(81.78,88.27)	−2.355	0.019
$CD4^+$ T cell (%)	13.57(11.58,18.48)	15.25(10.45,24.49)	−0.645	0.519
$CD8^+$ T cell (%)	68.41(65.38,75.85)	65.88(53.82,72.21)	−2.152	0.031
$CD4^+/CD8^+$ (%)	0.2(0.16, 0.31)	0.22(0.14,0.45)	−0.921	0.357
$CD3^+$ T cell (pcs/uL)	8426(6549.5, 12,767.5)	9897(5799.5,13,442.25)	−0.529	0.597
$CD4^+$ T cell (pcs/uL)	1528(1103, 2015.5)	1626(1228.25, 2659.5)	−1.159	0.246
$CD8^+$ T cell (pcs/uL)	6793(4518,9888.5)	7928(3968,10,601.75)	−0.159	0.873
IL2	0.2(0.1, 0.4)	0.2(0.1,0.39)	−0.018	0.985
IL6	0.1(0.1,0.2)	0.35(0.1,0.8)	−3.423	0.001
IL10	0.2(0.1,0.36)	0.2(0.1,0.79)	−0.825	0.409
TNF-γ	0.4(0.19, 2.36)	0.98(0.2,2.4)	−0.996	0.319
IL17	0.1(0.1,0.2)	0.2(0.1,0.3)	−1.637	0.102
IL-1β	0.1(0.1,0.1)	0.1(0.1,0.37)	−2.460	0.014
IL4	0.1(0.1,0.2)	0.1(0.1,0.2)	−1.481	0.139
IL12P70	0.1(0.02,0.1)	0.1(0.1,0.1)	−1.408	0.159
TNF-α	0.1(0.02,0.2)	0.35(0.1,0.6725)	−4.076	0.000
Cr (μmol/L)	27(21.2,32.00)	23.2(19.7,27.7)	−1.805	0.071
BUN (mmol/L)	2.48(1.58,3.49)	2.24(1.47,3.2)	−0.571	0.568
CK (U/L)	26(21,39)	29(18,32)	−0.592	0.554
CK-MB (U/L)	0.75(0.5,13.5)	0.95(0.23,6)	−0.553	0.580

Notes: Posttreatment, the experimental group had a higher plasma EBV-DNA negative conversion rate (P = 0.006), and peripheral blood lymphocyte, $CD3^+$, $CD8^+$ percentages dropped significantly (P = 0.042, 0.019, 0.031). IL-6, IL-1β, TNF-α levels also fell fast (P = 0.001, 0.014, 0.000). Data: Median (quartiles). *P*-values show discrepancies; $P > 0.05$: no diff., $P \le 0.05$: diff.).

Abbreviations: WBC, white blood cell; ALC, atypical lymphocytes; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IL, interleukin; TNF-α, Tumor necrosis factor-α; TNF-γ, Tumor necrosis factor-γ; Cr, creatinine; BUN, blood urea nitrogen; CK, creatine kinase; CK-MB, creatine kinase-MB.

children with IM is attributed to the abnormal activation of the mononuclear-macrophage system caused by EBV, as confirmed by numerous domestic and international studies.[22,56] Our research revealed a significant decrease in the percentage of lymphocytes in patients who received QJD treatment, indicating a marked therapeutic effect. B cells are targeted by EBV, leading to induction of $CD4^+$ T cells to produce a large number of cytokines for defense. Th1 cells produce interleukin-2 (IL-2), while Th2 cells secrete interleukin-6 (IL-6). IL-2 promotes proliferation and differentiation of T cells as well as growth of NK cells; its levels are elevated after EBV infection.[4,57] Following EBV infection, there is a significant increase in the proportion of $CD4^+CD8^+$ regulatory T cells (Tr cells) in children, resulting in marked elevation in levels of IL-10 and IL-6 secreted by these cells.[58,59] After activation of the TRL receptor by the EBV, there is a significant increase in the level of IL-1β mRNA in peripheral blood mononuclear cells, leading to elevated levels of IL-1β in the body.[50] Additionally, TNF-α, a tumor cell-killing factor released by macrophages, shows a substantial increase in IM patients due to the proliferation of macrophages caused by EBV infection.[60] Furthermore, during the acute phase of IM, NK cells proliferate and accumulate with cytotoxic specificity mainly targeting B lymphocytes infected with EBV.[61] After being infected with EBV, NK cells secrete pro-inflammatory cytokines such as IFN-γ and TNF-α, or directly eliminate virus-infected cells.[62] The activation of NK cells is also considered to be crucial for the production of pro-inflammatory cytokines, particularly IFN-γ, which can aid in controlling the spread of the virus.[63]

Previous studies have compared TCM interventions with conventional treatments in diverse populations by assessing cytokine levels. For example, Zifu T et al[64] demonstrated that Jiedu Huoxue Decoction had notable clinical effects in non-ST segment elevation acute coronary syndrome (NSTE-ACS), mediated by modulating serum TNF-α and PIGF levels. Current research underscores the potential therapeutic benefits of TCM compound formulas for IM, acting via multi-target modulation of viral replication and host immune responses. Yan Y et al[65] found that Simiao Qinwen Baidu decoction inhibits EBV EA and VCA expression in Raji and B95-8 cells, suppressing EBV DNA replication by inhibiting DNA replication-related genes, thus playing a vital role in anti-EBV activity. It also induces apoptosis of EBV-transformed B cells by regulating EBV latent proteins, inhibiting EBV-induced B lymphoproliferative disorders and lytic viral replication.[66]

To validate this therapeutic effect, a clinical trial was conducted in children, which included an analysis of the changes in cytokine levels in patients before and after medication. The study observed that QJD had an impact on the levels of cytokines IL2, IL-1β, and TNF-α in the serum, consistent with previous research results.[4,45,48,58] Among these cytokines, IL6, IL-1β, and TNF-α are identified as core targets of QJD treatment for IM through network pharmacology methods. These findings highlight the close relationship between the therapeutic effect of QJD and cytokines. QJD exerts its anti-EBV effect by regulating the levels of cytokines.

However, this study has certain limitations. First, the rapid updates and diversity of network pharmacology databases hindered thorough exploration within time constraints. Second, the antiviral mechanisms of QJD against EBV lack experimental validation at the cellular or animal level, necessitating further studies. Third, the small sample size and single-center design limit generalizability. Future research should use a multicenter, larger cohort to improve robustness.

Conclusion

This study utilized network pharmacology analysis to explore the therapeutic effect of QJD on IM. The analysis revealed that the therapeutic effect of QJD on IM is closely related to the regulation of cytokine-mediated signaling pathways. QJD exerts its anti-EB virus effects by modulating cytokines. To validate this therapeutic effect, changes in cytokine levels before and after medication were analyzed in patients. The study observed that QJD influenced the levels of IL6, IL-1β, and TNF-α in serum. These results highlight the close relationship between the therapeutic effect of QJD and cytokines, indicating its potential as an anti-EB virus agent worthy of further exploration. Our findings contribute to a better understanding of the multi-component anti-EB virus effects of QJD, providing a solid theoretical basis for enhancing its clinical application. This achievement can serve as a reference for the clinical application and further research of QJD.

Our future research focus on: (1) In vitro Validation: Use EBV-infected B cells to confirm QJD's modulation of cytokine signaling pathways. (2) Preclinical Efficacy/Safety: Employ humanized mice to assess QJD's long-term antiviral effects and safety. (3) Dosage Form Optimization: Reformulate QJD into a standardized, convenient form

(eg, tablets/capsules) while preserving efficacy. These approaches provide actionable frameworks for advancing QJD research and clinical adoption.

Abbreviations

QJD, Qingre Jiedu Decoction; IM, Infectious Mononucleosis; EBV, Epstein-Barr Virus; TCMSP, TCM Systems Pharmacology database and analysis platform; OMIM, Online Mendelian Inheritance in Man; PPI, Protein-protein interaction network; GO, Gene ontology; KEEG, Kyoto encyclopedia of genes and genome; GCV, Ganciclovir; ACV, Acyclovir; CAEBV, chronic active Epstein-Barr virus infection; EBV-HLH, Epstein-Barr virus associated hemophagocytic lymphohistiocytosis; EBV-PTLD, Epstein-Barr virus associated lymphocytosis after transplantation; OB, oral bioavailability; DL, drug likeness; VCA, Viral Capsid Antigen; TCM, Traditional Chinese Medicine; WBC, white blood cell; ALC, atypical lymphocytes; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IL, interleukin; TNF-α, Tumor necrosis factor-α; TNF-γ, Tumor necrosis factor-γ; Cr, creatinine; BUN, blood urea nitrogen; CK, creatine kinase; CK-MB, creatine kinase-MB.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This study was approved by the Ethics Review Committee of Liaocheng people's Hospital. (No.67 West Dongchang Road, Liaocheng 252000, China) The registration number is 2024225. All legal guardian of a minor provided their written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors report that they have no conflicts of interest regarding the publication of this paper.

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