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A Systematic Review and Analysis of the Mechanism and Clinical Effects of LIAN HUA QING WEN in the Treatment of Sars-cov-2 Infections

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ABSTRACT

LIAN HUA QING WEN(LHQW) is derived from two classic formulas of Han Dynasty and Qing Dynasty, namely, Ma Xing Shi Gan Tang and Drinking Qiao San, which is a heat-clearing and detoxifying proprietary Chinese medicine with the efficacy of clearing plague and removing toxins and promoting the lungs to release heat, and is mainly used for the treatment of influenza, which is a syndrome of heat and toxin attacking the lungs, and in the routine treatment of the new coronavirus pneumonia, it is used for the fever, cough and malaise caused by the mild and common types.LHQW consists of 13 components, 61 main compounds , the mechanism of action involves the intervention of immune system processes, cell proliferation, apoptosis and invasion, toxic metabolism, cytokine activity, and regulation of synthetic processes, etc., and has shown good clinical therapeutic efficacy and safety. The research method based on the combination of experiment and histology has greatly promoted the development of traditional Chinese medicine drugs and provided research ideas for the modernisation and internationalisation of Chinese medicine.

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Abbreviations: LHQW，LIAN HUA QING WEN Preparations.

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Introduction

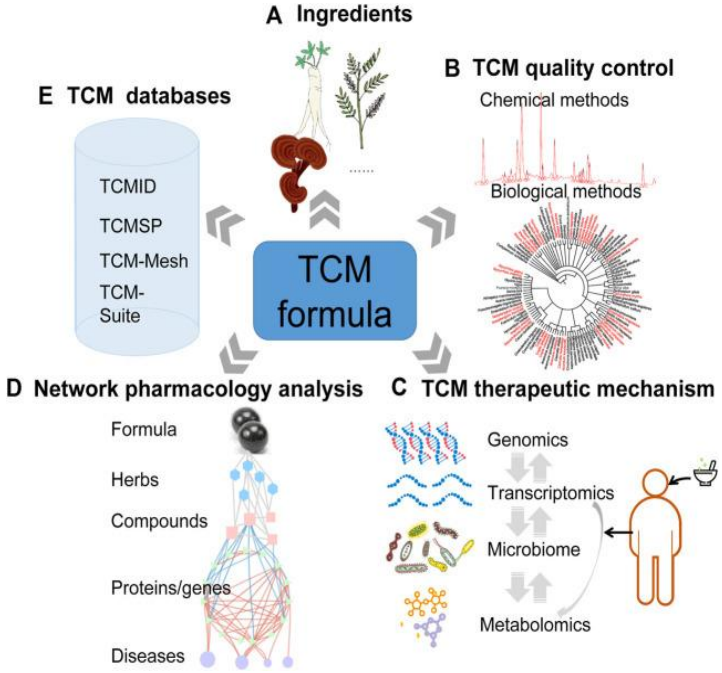
LIAN HUA QING WEN(hereinafter referred to as LHQW) originated from two classic formulas, Ma Xing Shi Gan Tang and Drinking Qiao San, in the Han and Qing Dynasties, and according to the theory of Chinese medicine pathology, LHQW is a good medicine for promoting the lungs through the collaterals, painstakingly opening up the orifices, and clearing away heat and detoxifying the toxins[1]. According to the Chinese Pharmacopoeia, LHQW consists of 13 ingredients, including forsythia 255g, honeysuckle 255g, sizzling ephedra 85g, fried bitter almonds 85g, gypsum 255g, platycodon 255g, Mianma guanzhong 255g, fritillaria japonica 255g, guanghuoxiang 85g rhubarb 51g, rhodiola rosea 85g, menthol 7.5g, licorice 85g, etc., and the auxiliary materials are Corn starch, made by decoction, distillation, filtration, refrigeration, mixing with icing sugar, dextrin or starch thoroughly, and drying[2].LHQW dosage form is granule capsule and oral liquid, which is used for the treatment of influenza belonging to the evidence of heat and toxicity attacking the lungs, and is widely used in the treatment of respiratory disorders[3].The main symptoms are: fever, malignant cold, muscle aches and pains, nasal congestion and running nose, cough, headache, dry and painful pharynx, red tongue with yellow moss or yellowish greasy. In the routine treatment of the patients with Sars-cov-2 infection, it can be used for fever, cough and malaise caused by mild and common type.

Currently, LHQW has been identified to contain 61 compounds (including cyclic enol ether terpenes, flavonoids, anthraquinones, phenylpropanes, triterpenoids, etc.), which have been clarified by fast ultra-high-performance liquid chromato--graphy coupled with diode-array detector and quadrupole time-of-flight mass spectrometry[4], among which, amygdalin, coniferin E, rhodiola rosea glycosides, glycyrrhetinic acid, chlorogenic acid, ginkgolides, rutin, coniferin A , crypto--chlorogenic acid, sweroside, forsythia glycoside and rhubarbic acid, twelve representative compounds have been quantified as chemical markers. In recent years, LHQW has played an important role in the prevention and control of viral public health events and is widely regarded as a representative antiviral herbal medicine in China [5].

Sequencing technology, systems biology and other multi-omics methods are now widely used in TCM. The mechanism of action of TCM and the side effects of TCM formulas can also be elucidated at the molecular level[6], and these new approaches promote the modernisation of TCM and enhance the applicability of TCM formulas in personalised treatment[7]. The rise of network pharmacology in recent years with the aim of identifying active compounds and targets has provided a new direction for drug discovery and development for the effective treatment of various diseases[8]. This analytical method based on the "compound--protein/gene-disease" network, together

with the high-throughput approach to elucidate the regulatory principles of small molecules, provides a new platform for accelerating the mechanistic study of TCM formulations. To meet the needs of TCM research, we have successfully developed TCM-related databases containing TCM formulations, herbal ingredients, bioactive compounds, targets, and TCM-disease interactions. Based on these digital platforms, the internationalisation and digitisation of TCM formulas can be achieved (Figure 1).

The treatment of diseases by LHQW involves many key targets and biological processes, such as the intervention of immune system processes, cell proliferation, apoptosis and invasion, toxicity metabolism, cytokine activity and regulation of synthetic processes. Based on the multi-omics research method combined with the traditional Chinese medicine concept of "treating different diseases with the same treatment", the mechanism of action of LHQW in treating diseases has been



- Fig. 1 Systems biology of Chinese medicine research. (A) The Chinese Pharmacopoeia (2020 edition) contains the formulas and ingredients of Chinese medicines. (B) Establishment of a modern quality control system for TCM. (C) Application of multi-omics approach in the study of therapeutic mechanism of Chinese medicine. (D) Screening of biologically active compounds and potential targets for the treatment of various diseases by TCM based on network pharmacological analyses. (E) Establishment of a database for Chinese medicine research.

experiments and clinical practice, and the results of the current study have confirmed that LHQW has a clear clinical efficacy, which can effectively alleviate the disease progression, and with little side effects, and can be used as an effective treatment for broad-spectrum respiratory diseases. effective therapeutic agent for broad--spectrum respiratory diseases. In this paper, the unique role of LHQW in the Sars-cov-2 epidemic and the related mechanism of action are summarized as follows.

Mechanistic studies on the treatment of Sars-cov-2 by LHQW clearing disease

Fatal pneumonia caused by highly pathogenic coronaviruses such as SARS--CoV is mainly associated with rapid viral replication, massive inflammatory cell infiltration and elevated pro-inflammatory cytokine/chemokine responses, and cytokine storms play a crucial role in lethal pneumonia. Clinical studies have confirmed the presence of excessive pro-inflammatory cytokines in the serum of SARS patients, such as IL-1 β , IL-6, IL-12, IFN- γ , IP-10, and MCP-1, and that cytokine storms occurred mostly in ICU patients[9]. Based on the excessive cytokine response, it was earlier suggested that IL-6 and IL-10 levels could be used as one of the bases for predicting Sars-cov-2 treatment and prognosis[10]. Therefore, at the early stage of the outbreak, scholars investigated the antiviral activity of LHQW against SARS-CoV-2 virus and its potential role in modulating host immune responses[11], assessing its antiviral activity in Vero E2 cells using CPE and null-spot reduction assays, observing its effect on the morphology of viral particles under transmission electron microscopy, and observing its effect on the morphology of viral particles by real-time fluorescence quantitative PCR assay to measure the expression levels of pro-inflammatory cytokines during viral infection in Huh-7 cells. The results showed that LHQW significantly inhibited viral replication in Vero E6 cells and significantly reduced the production of pro-inflammatory cytokines TNF- α , IL-6, CCL-2/MCP-1 and CXCL--10/IP-10 at the mRNA level, in addition to leading to abnormal morphology of viral particles in the cells.

In addition, the bioactive compounds of LHQW inhibit a combination of the viral target Spike and the human target ACE2, thereby preventing viral invasion and attachment to host cells, inhibiting viral replication and pro-inflammatory cytokine levels of IL6, TNF- α and chemokine levels, leading to improved symptoms in COVID-19 patients[12].

Multi-omics is a powerful weapon in the mechanistic study of modern Chinese medicine (Figure 2). Based on network pharmacology and the concept of "treating different diseases with the same treatment" of traditional Chinese medicine, Su[13] explored the mechanism of action of LHQW in treating influenza viral pneumonia and neocoronaviral pneumonia, which explored the biological activities of 31 main components of LHQW and obtained 68

common targets for the treatment of neocoronavirus， the study explored the biological activities of 31 key components of LHQW, and identified 68 common targets for the treatment of novel coronavirus pneumonia (NCP) and influenza virus pneumonia (IVP). 20 key targets, including COX2, IL-6, Mapk14, and TNF, were identified by using the component-target--disease network constructed by Cytoscape 3.2.1 software, and the KEGG and GO analyses showed that 115 signaling pathways were related to LHQW, and the KEGG analysis revealed that LHQW was a key component in the treatment of Sars-cov-2. KEGG and GO analyses showed that 115 signalling pathways were related to LHQW treatment, including IL-17, T-cell receptor, Th17 cell differentiation, TNF, Toll-like receptor, MAPK, and apoptosis, were closely related to the occurrence and development of neocoronavirus and influenza virus infections, and molecular docking showed that the components of each component were closely related to the development of 3C-like protease (3CL), angiotensin-converting enzyme 2 (ACE2), COX2 (3CL), angiotensin converting enzyme 2 (ACE2), COX2, haemagglutinin (HA), IL-6, neuraminidase (NA) and other six targets to varying degrees, among which rutin, isoguanoside A, hesperidin, and isochlorogenic acid B of LHQW are the best components for docking to the core targets mentioned above, and the top five

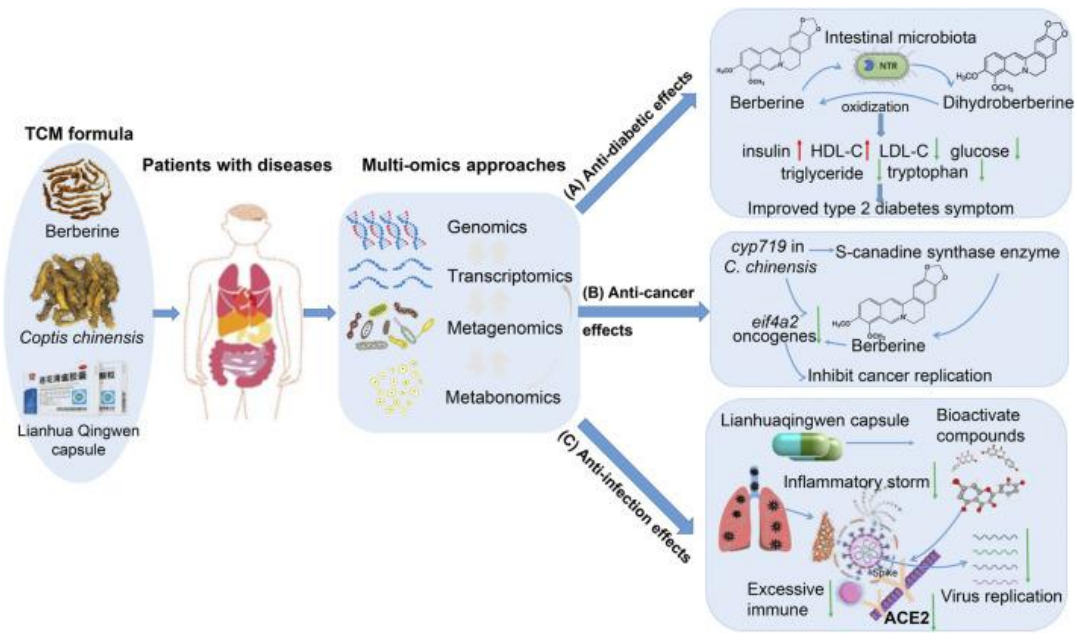


Fig. 2 Application of network pharmacology in the study of therapeutic mechanism of diseases treated by Chinese medicine

isoguanoside, hesperidin, isochlorogenic acid B, hesperidin E, and quercetin, so that LHQW has broad-spectrum antiviral properties. The results of Xu[14] showed that the six active herbal compounds of LHQW could regulate the intestinal flora and inhibit the immune-inflammatory response through Toll-like receptor (TLR) and nuclear factor-κB (NF-κB) signalling pathways in the lungs.

Yang[15] used a network pharmacological approach to predict, and validated by in vitro and in vivo experiments, demonstrated that a total of 80 genes were associated with LHQW in ALI treatment.After the PPI network was constructed, four active ingredients (quercetin, lignocerotoxin, kaempferol, and hansenin) and 10 target genes (AKT1, TP53, IL6, VEGFA, TNF, JUN, STAT3, MAPK8, MAPK1 and EGF) are essential for ALI, GO and KEGG analyses showed that the apoptotic pathway is mainly involved in the LHQW-ALI network, and animal experiments demonstrated that LHQW attenuates LPS-induced ALI, with the most dramatic effect of medium-dose LHQW, which can reduce the effects of LPS on ALI by decreasing the levels of Bax, caspase-3 and LHQW inhibited LPS-induced p53 overexpression by decreasing the levels of Bax, caspase-3 and caspase-9 in ALI, increasing the expression of Bcl-2, and attenuating the release of cytochrome C. LHQW inhibited the intrinsic p53-mediated apoptotic pathway in mice.

Li[16] systematically compared the similarities and differences in the mechanisms of Lianhua Qingwu (LHQW) and Qingfeng Pulmonary Detoxification (QFPD) for the treatment of COVID-19. Based on the tools of network pharmacology and systems biology, it was hypothesised that LHQW and QFPD contain 196 and 310 active compounds, respectively, and some of these active compounds have the same targets. These targets are enriched with pathways related to inflammation, immunity, apoptosis, oxidative stress and others. Among the specific active compounds and targets of these two herbal formulations, burdock glycosides, umbelliferin and aloe rhodopsin contained in LHQW mainly target neurological disease-related genes (GRM1 and GRM5), whereas isoprostanol, baicalein, chuanchengpiin, mu-mu-xuein A, epiberberine, and piperocarpine contained in QFPD target immune and inflammation--related genes (mTOR and PLA2G4A). The findings suggest that LHQW may be suitable for the treatment of mild to moderate SARS-CoV-2 with neurological symptoms, while QFPD can effectively modulate the oxidative stress damage and inflammatory symptoms induced by SARS-CoV-2.

Hong[17] explored the therapeutic mechanism of LHQW against SARS-CoV-2 mutant strain using tools such as molecular docking, medicinal properties of compounds and network pharmacology. The study screened and obtained 280 compounds, 16 targets related to SARS-CoV-2, 54 targets related to cytokine storm, and the key pathways Toll-like receptor signalling

pathway, NOD-like receptor signalling pathway, Jak-STAT signalling pathway, and the core target IL6 were obtained through the PPI network and KEGG pathway enrichment analyses, and the network analyses were predicted and discussed 16 major anti-SARS-CoV-2 active compounds and 12 major anti-inflammatory active compounds were identified, among which Ochnaflavone and Hypericin were potential anti-mutagenic compounds in LHQW. The results of this study suggest that the active compounds in LHQW can inhibit or activate the targets to produce resistance to SARS-CoV-2 mutant strains and modulate signalling pathways to exert anti-inflammatory effects.

Review of studies on the clinical therapeutic effects of LHQW in the treatment of Sars-cov2

Huang[18] compared the six most effective herbs/components for COVID-19 treatment in "San Zhong Tang Tripartite Chinese Medicine" and summarised the common herbal components (Figure 3). Among them, liquorice, ephedra, gypsum and bitter almond were the common components between LHQW, LCDD, XFBD, HSBD and JHQG.

Sun[19] included nine trials involving 1152 patients in a meta-analysis of the efficacy and safety of LHQW in the treatment of COVID-19 patients. The CT recovery rates

Components	Six Traditional Chinese Medicine (TCM) recipes					
GANCAO甘草	JHQG	LHQW	XFBD	HSBD		LCDD
MAHUANG麻黄	JHQG	LHQW	XFBD	HSBD		LCDD
SHIGAO石膏	JHQG	LHQW	XFBD	HSBD		LCDD
KUXINGREN苦杏仁	JHQG	LHQW	XFBD	HSBD		LCDD
DAHUANG大黄		LHQW		HSBD		
JINYINHUA金银花	JHQG	LHQW				
LIANQIAO连翘	JHQG	LHQW				
GUANGHUOXIANG广藿香		LHQW	XFBD			
CHISHAO赤芍				HSBD	XBJ	
HUANGQIN黄芩	JHQG					LCDD
QINGHAO青蒿	JHQG		XFBD			
SHEGAN射干			XFBD			LCDD
FULING茯苓				HSBD		LCDD
HUOXIANG藿香				HSBD		LCDD
TINGLIZI葶苈子			XFBD	HSBD		

Fig. 3 Common components of the six TCMs (JHQG, LHQW, XFBD, HSBD, XBJ and LCDD)

were 1.36 and 1.32 times higher than those of chemotherapeutic drugs, respectively (P<0.05). LHQW combined with chemical drugs significantly increased the disappearance rate of fever, cough, malaise, sputum, shortness of breath, and muscle aches and pains compared with chemical drugs (P<0.05). LHQW also significantly reduced the rate of exacerbation, which was 0.45 times higher than that of chemical drugs alone (P<0.05). There was no significant difference between the adverse effects of LHQW combined with chemical drugs and chemical drugs (P>0.05).

Wu[20] included 15 studies, seven randomised controlled studies and eight retrospective cohort studies, involving a total of 1,623 patients in a META analysis of systematic evaluations of TCM-assisted treatment of patients with mild and common COVID-19. Compared with the control group, TCM treatment improved the clinical effectiveness of the primary index (advantage ratio [OR] = 2.64, 95% confidence interval (CI) [1.94,3.59], P < .00001). The results of Begg's test (Pr > z = 0.266) and sensitivity analyses indicated more stable results. Penetrating and dispelling plague (OR = 4.9, 95%CI [1.9,14.0]), dispersing wind and removing toxins (OR = 2.9, 95%CI [1.5,5.7]) and clearing plague with Lianhua (OR = 2.4, 95%CI [1.6,3.6]). The Chinese medicines were effective in improving the main clinical symptoms (fever, cough, malaise and time to remission of the three symptoms), the rate of conversion to severe illness, and the rate of CT improvement. Their safety was not significantly different from conventional treatment. However, in terms of the safety of single herbs, the safety of wind-sparing and detoxification (OR = -0.86, 95% CI [-1.89,0.09]) and LHQW (OR = -0.49, 95% CI [-0.94,-0.05]) was poorer than that of conventional treatment.

Zhuang[21] included three studies involving a total of 245 patients with COVID-19 in a meta-analysis of LHQW for the treatment of coronavirus disease 2019 (COVID-19). Compared with the control group, the LQ group demonstrated a significant difference in reducing the rate of clinical conversion to severe or critical illness [RR = 0.38, 95 % CI (0.17 ,0.85), P < 0.05] and the duration of fever (SMD = -0.57,95 % CI (-0.96,-0.17), P<0.05),and the rate of disappearance of the clinical symptomatic fever was significantly improvement [RR = 1.36,95 %CI (1.14,1.61), P < 0.05], cough [RR = 1.99,95 %CI (1.39,2.86), P < 0.05], fatigue [RR = 1.52,95 %CI (1.15),2.01), P < 0.05] and coagulation [RR = 4.18, 95 %CI (1.99),-0.17). 95 %CI (1.99,8.81), P < 0.05], but no significant improvement in cough [RR = 2.46,95 %CI (0.81,7.51), P < 0.05].

In a rapid systematic evaluation and meta-analysis of randomised controlled trials of the efficacy and safety of oral CPMs for the treatment of COVID-19, Shi[22] included seven RCTs comprising 1079 participants, and the overall bias of all the included trials was assessed to be "high risk of bias". The oral CPMs studied were LHQW

capsule/granule (LHQW), Jinhua Qingdian granule (JHQG), Huoxiang Zhengqi drip pill (HXZQ), Tuanxie Dispelling Plague granule (TJQW), and Lianhua Qingcheng granule (LHQK). Compared with conventional western medicine alone for COVID-19 patients: regarding the primary outcome, the results showed that oral CPM combined with conventional western medicine increased the cure rate (RR = 1.20, 95 % CI 1.04-1.38, involving LHQW and TJQW) and decreased the deterioration rate (RR = 0.50, 95 % CI 0.29 - 0.85, involving LHQW, JHQG, LHQK and TJQW). In terms of additional outcomes, the results showed that additional oral CPM shortened the duration of fever, cough and malaise, increased the rate of recovery from cough and malaise, and increased the rate of improvement and recovery from chest CT performance. For the same COVID-19 outcomes, there was some variation in treatment outcomes across CPMs. The use of TJQW and LHQG does not appear to increase the risk of adverse events, but JHQG may cause mild diarrhoea.

Lei[23] included a total of 13 randomised controlled trials conducted in China involving 1,398 patients in a meta-analysis of randomised trials of TCM-assisted treatment of COVID-19 patients. Cross-sectional data from the studies were plotted, and the results showed statistically significant improvements in overall efficiency (RR, 1.357; 95% CI, 1.259-1.464; P < 0.001), chest CT improvement (RR, 1.249; 95% CI, 1.259-1.464; P < 0.001). 95% CI, 1.143 to 1.356; P < 0.001), improvement in cough (RR, 1.228; 95% CI, 1.057 to 1.570; P = 0.012), and lower incidence of conversion to severe cases (RR, 0.408; 95% CI) , 0.275 to 0.605; P < 0.001) in the Chinese herbal medicine group than in the control group. Notably, the LHQW (LQ) specific TCM subgroup showed that the experimental group was associated with a higher overall efficacy rate (RR, 1.248; 95% CI, 1.136 to 1.371; P < 0.001) and an improvement in CT of the chest. (RR, 1.226; 95% CI, 1.110 to 1.356; P < 0.001) and a lower rate of conversion to severe cases (RR, 0.469; 95% CI, 0.311 to 0.707; P < 0.001). However, there was no significant difference in fever improvement (RD, 0.110; 95% CI, -0.063 to 0.283; P = 0.213). The results of this meta-analysis suggest that combining Chinese and Western medicine in the treatment of COVID-19 may be more effective in relieving symptoms, promoting recovery, and decreasing the chances of patients developing serious illness.

Li[24] included seven studies involving 916 participants in a meta-analysis of the efficacy and safety of the traditional Chinese medicine LHQW for the treatment of patients with COVID-19. Overall, compared with the control group, the overall efficacy (OR = 2.23, 95% CI 1.56, 3.18), adverse events (OR = 0.42, 95% CI 0.18, 0.97), chest CT manifestations (OR = 1.74, 95% CI for the intervention group (1.12, 2.72), and conversion to severe disease rate (OR = 0.47, 95% CI (0.30, 0.75)) were better. In addition,

the intervention group had an advantage over the control group in improving clinical symptoms (fever, cough, malaise, chest tightness, shortness of breath, and sputum) and shortening the duration of fever ($p < 0.05$). The findings suggest that LHQW combined with western medicine may be more effective in treating COVID-19.

Wang[25] included 6 in a Meta-analysis of the effect of LHQW combination of western medicines in the treatment of patients with 2019 coronavirus disease, including a total of 856 COVID-19 patients. The meta-analysis showed that LHQW combination therapy achieved a high rate of fever reduction (OR = 3.43, 95% CI [1.78, 6.59], P = 0.0002), cough suppression (OR = 3.39, 95% CI [1.85, 6.23]) , P < 0.0001), and shortness of breath recovery (OR = 10.62, 95% CI [3.71, 30.40], P < 0.0001) and fatigue recovery (OR = 2.82, 95% CI [1.44, 5.53], P = 0.003), higher overall efficiency (OR = 2.51, 95% CI [1.73, 3.64], P < 0.00001), and shorter time to fever reduction (MD = -1.00, 95% CI [-1.04, 0.96], P < 0.00001), and no increase in the incidence of adverse reactions compared with the monotherapy control (OR = 0.65, 95% CI [0.42, 1.01], P = 0.06). The combination of LHQW and western medicines has significant efficacy in neocoronitis -19 patients with a favourable clinical safety profile.

Li[26] systematically analysed the results of clinical studies of LHQW for the treatment of viral diseases, and comprehensively evaluated the broad-spectrum therapeutic efficacy of LHQW by Meta-analysis of LHQW for influenza, novel coronavirus and hand, foot and mouth disease. Among the clinical studies involving the treatment of influenza, novel coronavirus pneumonia, and hand, foot, and mouth disease, 13 were finally included, and 75 outcome indicators were obtained. The results showed that (1) in the treatment of influenza, the clinical efficacy rate of LHQW formulation was superior to that of other proprietary Chinese medicines and ribavirin, while the difference with oseltamivir was not statistically significant; the indicators of improvement in clinical symptoms of LHQW were superior to those of other proprietary Chinese medicines, oseltamivir and ribavirin; and the differences in the time to viral nucleic acid turnover and turnover rate of LHQW were not statistically significant compared with that of oseltamivir or the conventional treatments of traditional Chinese and western anti-influenza medicines . (2) In the treatment of novel coronavirus pneumonia, LHQW with or without conventional treatment was superior to conventional treatment in overall effective rate, major symptom abatement rate, secondary symptom abatement rate, and major symptom abatement time, and was also superior to conventional treatment in the improvement rate of fever improvement, duration of fever, time of fever abatement, rate of cough abatement, time of cough abatement, rate of malaise abatement, time of malaise abatement, rate of myalgia abatement, sputum abatement, chest

tightness abatement, and so on. and chest tightness subsiding rate were better than conventional treatment; while in terms of sore throat subsiding rate, nausea subsiding rate, diarrhoea subsiding rate, decreased appetite subsiding rate, headache subsiding rate, dyspnoea subsiding rate, and shortness of breath subsiding rate, the difference between LHQW and conventional treatment was not statistically significant; and in terms of improvement of chest CT rate, clinical conversion rate, cure time and hospitalization time, LHQW alone or in combination with conventional treatment was better than conventional treatment. (3) In the treatment of HFMD, LHQW was superior to conventional treatment in terms of overall effective rate, average fever reduction time, herpes receding time and viral nucleic acid conversion time. (4) In terms of safety, the incidence of adverse reactions in the LHQW group was low and all of them were mild, and could be cured with drug withdrawal. Available evidence suggests that LHQW can reduce clinical symptoms, shorten hospitalisation time and improve chest CT indexes in patients with influenza, novel coronavirus pneumonia and hand-foot-mouth disease, and has a certain degree of efficacy in the treatment of viral infectious diseases, and has a good safety profile.

Hu[27] conducted a systematic study of adverse reactions occurring in the treatment of LHQW capsules/granules, and the results of the Meta-analysis of adverse reactions in the clinical application of LHQW versus conventional drugs showed that in a total of 217 included experimental studies comparing the LHQW versus conventional drug groups, the risk of adverse reactions in the LHQW group was significantly lower than that in the conventional drug group (RR = 0.63, 95% CI = 0.58-0.69, $p < 0.001$); in the assessment of treated diseases, the incidence of detected influenza A (H1N1) and adverse reactions during influenza treatment was significantly lower in the LHQW group than in the conventional drug group; and in the assessment of safety indices (see table below), the LHQW group had a significant impact on the patients' respiratory, dermatological (incidence of rash), and neurological (incidence of dizziness or headache from neurological injury) and digestive (incidence of nausea or vomiting from digestive injury) injuries and other adverse reactions were lower in the LHQW group than in the conventional drug group.

Discussion

LHQW Capsule/Oral Liquid is a kind of heat-clearing and detoxifying Chinese patent medicine, which has the efficacy of clearing the plague and detoxifying the toxin, promoting the lungs and draining the heat, mainly used for the treatment of influenza belonging to the heat and toxin attacking the lungs syndrome, with fever or high fever, malignant chills, muscle aches and pains, nasal congestion and runny nose, cough, headache, dry pharynx, sore throat, reddish

tongue, moss yellow or greasy yellow, etc. It is used for the fever, cough and fatigue caused by mild and common type of the new type of Coronavirus Pneumonia in the routine treatment, The formula of LHQW is based on the formula of "Asako Shi Gan Tang" from "Treatments of Typhoid Miscellaneous Diseases" of the Han Dynasty, "Yin Qiao San" from "Articles on Warm Diseases" of the Qing Dynasty, and the commonly used medicine of rhubarb for the treatment of epidemic diseases from "Treatments of Warm Epidemics" of the Ming Dynasty, which is the essence of the medicines used in the treatment of exogenous warm diseases and epidemic diseases in the past three dynasties. The "Asako Shi Gan Tang" was created by Zhang Zhongjing, the ancient Chinese medical sage, and is a famous formula for the treatment of febrile infectious diseases; the "Yin Qiao San" was created by Wu Jutong, a famous Chinese medicine practitioner, and is a representative formula for clearing away external evils; and rhubarb is the most commonly used formula for the treatment of the plague by the famous medical doctor Wu Yike, which is capable of It can help to expel heat and poison from the body as soon as possible and effectively interrupt the further development of the disease. On this basis, Rhodiola rosea, which clears the lungs and removes blood stasis, regulates the immune system, and Dongxiang, which aromatises and removes dampness, dispels evils and avoids filth, and strengthens the spleen and the stomach.

LHQW was first approved by China's State Food and Drug Administration (CFDA) in 2004, and was the first traditional Chinese medicine to go through the CFDA's fast-track drug approval channel for the treatment of Severe Acute Respiratory Syndrome (SARS), and was included in the National Health and Wellness Commission's "Diagnostic and Treatment Programme for Novel Coronavirus Pneumonia (Trial Sixth Edition)" in February 2020[28],and has been continued In April 2020, the Supplemental Application Approval for Drugs issued by the State Drug Administration (SDA) showed that LHQW capsules (granules) manufactured by Ealing Pharmaceuticals were approved for use for fever, cough, and malaise caused by mild and common types of neocoronaviral pneumonia, with a course of treatment of 7 to 10 days.

Traditional Chinese medicine (TCM) is widely used in clinical practice because of its therapeutic and preventive effects on a wide range of diseases. With the development of high-throughput sequencing and systems biology, TCM research has shifted from the traditional experimental-based approach to a combined experimental and histological--based approach, and a standardized research protocol has been established. The research methodology consists of three steps, firstly, establishing a modern quality assessment method for commonly used TCM based on chemical and biological composition analysis, secondly, applying multi--histological methods such as network pharmacology to elucidate the therapeutic

mechanisms of TCM formulations, and finally, constructing a database to store data and analytical resources. Finally, a TCM research database is constructed to store the histological data and analysis resources. With the development of systems biology-driven histological analysis, histological analysis methods will accelerate the unravelling of the mysteries of TCM. In addition, with the help of network analysis, the connection between TCM and diseases can be visualized from components to compounds to targets, thus enhancing our understanding of the relationship between TCM and diseases. By deconstructing the data in the database, it is possible to provide critical technical support for clinical diagnosis, drug development and precision medicine.

Conclusions

Based on the above combined experimental and histological approach, multi-omics tools such as network pharmacology have fully demonstrated that LHQW treatment of diseases involves numerous key targets and biological processes, such as intervention of immune system processes, cell proliferation, apoptosis and invasion, toxic metabolism, cytokine activity and regulation of synthetic processes, etc., and the available evidence has also shown that LHQW has demonstrated high in vitro and in vivo antiviral activity. Clinically, LHQW reduced clinical symptoms, shortened hospitalization time and improved CT scan of the chest in patients with influenza, neococcal pneumonia and hand-foot-mouth disease. Therefore, the clinical results are a full affirmation of the theoretical study, and also prove the value of the combined experimental and histological research method in TCM research, which greatly promotes the development potential of TCM drugs and provides research ideas for the modernization and internationalization of TCM.

Competing interests

The authors declare all financial and non-financial competing interests.

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