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Comparative clinical trial of Langenlianqiao oral liquid and Lianhuaqingwen capsule in the treatment of mild cases of coronavirus disease 2019 (COVID-19)

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Abstract

Objective To evaluate the clinical efficacy of Langenlianqiao (LGLQ) oral liquid treatment and provide a reference basis for the clincal treatment of coronavirus disease 2019 (COVID-19).

Design An experimental clinical study was conducted on three groups with confirmed diagnoses of COVID-19.

Site This study was conducted at Changde Hospital.

Participants A total of 253 patients were enrolled in this study.

Methods The patients were divided into the LGLQ treatment group (100 cases), the Lianhuaqingwen (LHQW) treatment group (100 cases) and the placebo control group (53 cases), according to the treatment each group received. The occurrence of major clinical symptoms, the duration of symptom disappearance, the number of days in hospitalisation and the duration of infection were compared among the three groups.

Results Compared with the placebo control group (10.0 [1.2] d, 9.4 [1.3] d), the duration of infection and hospitalisation effectively decreased in the LGLQ group (6.8 [0.6] d, 7.4 [0.8] d) and the LHQW group (6.8 [1.0] d, 7.3 [1.0] d). Furthermore, the incidence of fatigue in the LGLQ group (4.0%) was lower compared to the LHQW group (14.0%) and the placebo control group (15.1%), but this difference was not statistically significant ($P=0.580$ for LGLQ vs. LHQW, $P=0.246$ for LGLQ vs. placebo). In the treatment of cough, the LGLQ group showed a significantly different effect compared to both the LHQW group ($P=0.014$) and the placebo group ($P=0.016$). Additionally, for dry cough specifically, LHQW was effective in reducing its incidence compared to the placebo control group ($P<0.05$), while LGLQ showed no statistically significant difference from either LHQW ($P=0.39$) or the placebo group ($P=0.14$). However, neither the LGLQ group nor the LHQW group showed a reduction in the duration of symptom disappearance in patients with pre-existing symptoms ($P>0.05$).

Conclusions Compared with the placebo control group, the LGLQ group showed an improvement in the clinical symptoms of COVID-19 and a decrease in the duration of hospitalisation and infection, which confirmed that the

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LGLQ treatment had the same antiviral effect as the LHQW treatment. This may provide in-depth insights for antiviral therapy research.

Keywords COVID-19, Effectiveness of antiviral treatment, Chinese medicine oral liquid, Symptom improvement, Treatment effect

Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by the novel coronavirus (SARS-CoV-2), with droplet transmission and contact transmission being the main routes of spread [1]. Patients often present symptoms such as fever, fatigue, and dry cough, while severe patients may also exhibit difficulty in breathing and respiratory system failure. Since the outbreak in December 2019, COVID-19 has quickly attracted domestic and international attention due to its high infectivity, long incubation period, and fast transmission speed, and was listed as a "Public Health Emergency of International Concern" by the World Health Organization (WHO) on January 30, 2020 [2]. Antiviral, anti-inflammatory, and anticoagulant drugs have been rapidly tested in randomized controlled trials (RCTs) [3–7]. However, these treatments do not always have the same efficacy in all patients, which means that more research on antiviral drugs is required.

Herbal formulas have unique efficacy and mechanism in the treatment of these infectious diseases, and they have been used to treat a wide range of viral infections [8–10]. During the recent COVID-19 pandemic, the National Health Commission of the People's Republic of China announced that 92% of new confirmed cases of post covid pneumonia were treated with a combination of traditional Chinese and Western medicines. Moreover, more than 90% of the treatment cases were either effective or showed significant improvement [11]. For patients with mild-to-moderate illnesses, early intervention with traditional Chinese medicine (TCM) proved to be effective in preventing the transition of the disease to a severe and critical state. In severe cases, TCM helped stabilise the condition and extend the treatment window [12]. Increasing evidence suggests that the early use of TCM in patients with COVID-19 is important for improving recovery rate, shortening the disease duration, delaying disease progression and reducing mortality, the use of TCM to prevent epidemics of infectious diseases was traced back to ancient Chinese practice cited in Huangdi's Internal Classic (Huang Di Nei Jing) where preventive effects were recorded [13, 14]. There were 3 studies using TCM for prevention of Severe acute respiratory syndrome coronavirus (SARS) and 4 studies for H1N1 influenza. None of the participants who took TCM contracted SARS in the 3 studies. The infection rate of H1N1 influenza in the TCM group was significantly lower than the non-TCM group (relative risk 0.36, 95% confidence interval 0.24–0.52; $n=4$) [15].

Langenlianqiao (LGLQ) oral liquid is a common Chinese patent medicine, which is mainly extracted from isatidis root, forsythia and other Chinese herbs [16]. In China, LGLQ oral liquid is widely used for the treatment of fever, cough, sore throat, headache and other symptoms caused by colds and the flu; it can clear away heat and has detoxifying, antiviral and antibacterial effects [17, 18]. Lianhuaqingwen (LHQW) Capsules are an innovative traditional Chinese medicine compound developed under the guidance of traditional Chinese medicine theory on collateral diseases. The formulation is based on the "Ma Xing Shi Gan Tang" from the Han Dynasty by Zhang Zhongjing and the "Yin Qiao San" from the Qing Dynasty by Wu Jutong [19]. It also integrates the characteristics of using rhubarb to treat epidemics from the Ming Dynasty by Wu Youke, and draws on the experiences of many Chinese medical practitioners in treating externally contracted diseases. It is prepared from 13 traditional Chinese medicinal ingredients, including forsythia, honeysuckle, fried Ephedra, stir-fried bitter apricot kernel, gypsum, isatis root, eucalyptus, asarum, Houttuynia cordata, broad wormwood, rhubarb, Rhodiola, menthol, and licorice [19]. It possesses the effects of clearing pestilence and detoxifying, as well as promoting lung qi and releasing heat. Clinically, it is used to treat influenza with symptoms of heat-toxicity invading the lungs, including fever or high fever, chills, muscle aches, nasal congestion and rhinorrhea, cough, headache, dry throat and painful throat, red tongue with yellow or greasy fur, etc. In recent years, LHQW Capsules have gradually become a representative traditional Chinese medicine for dealing with respiratory system public health events and have been included in national guidelines for the prevention and control of respiratory infectious diseases, including the guidelines for the 2009 H1N1 influenza and COVID-19 [2, 19]. This study aims to evaluate the clinical efficacy of LGLQ oral liquid in the treatment of COVID-19 and provide a reference for clinical treatment by comparing it with LHQW capsules and general supportive treatment.

Materials and methods

Research participants

The data of 253 patients with COVID-19 who were hospitalised between November and December 2022 in Changde Hospital were enrolled in this study. The

patients were divided into the LGLQ treatment group (100 cases), the LHQW treatment group (100 cases) and the placebo control group (53 cases), according to the treatment each group received. The inclusion criteria were as follows: ① the diagnosis of COVID-19 infection confirmed by quantitative polymerase chain reaction (qPCR) test; ② patients aged 18 years or older; ③ patients who had received more than two doses of the COVID-19 vaccine; and ④ asymptomatic patients or patients with mild symptoms at the time of hospitalisation.

The exclusion criteria were as follows: ① patients with malignant, autoimmune, liver, kidney, blood, neurological and endocrine diseases, as well as other serious diseases that may affect the patient's participation in the trial or affect the results of the study; ② pregnant women, lactating mothers and allergic patients; ③ patients allergic to the known components of the drug; ④ patients vaccinated with less than one shot; and ⑤ patients who did not agree to participate in this study. This study was approved by the hospital's research ethics committee, and informed consent was obtained from all the patients (ethics approval number: YX-2023-119-01). The clinical trial is registered with the number: NCT06355193.

Clinical classification

According to the Diagnosis and Treatment Program for Novel Coronavirus Infections (Trial Ninth Edition) issued by the National Health and Wellness Commission [20], patients were categorised into four types: asymptomatic, mild, common and heavy. Asymptomatic infections were defined as confirmed cases without clinical symptoms. Mild infections were defined as upper respiratory tract infections as the main manifestations, such as sore throat, cough and fever.

Treatment programme

All patients were isolated in accordance with the Diagnostic and Treatment Program for Novel Coronavirus Pneumonia (Trial Ninth Edition) issued by the National Health and Wellness Commission [21].

Langenlianqiao oral liquid was produced in accordance with the Hunan Provincial Medical Institutions Preparation Specification (2016 Edition), and its main ingredients were Mohanlian, Japanese ardisia herb, radix rehmanniae recens, Indigowoad root and forsythia (produced by Hunan Xinhui Pharmaceutical Co., Ltd). The prescription process of 1 L of LGLQ oral liquid was as follows: Mohanlian (500 g), Japanese ardisia herb (500 g), radix rehmanniae recens (300 g), Indigowoad root (500 g), forsythia (300 g), which is decocted twice, each time for 2 h. Following this, the decoction is combined and filtered before the filtrate is concentrated to a thick paste with a relative density of 1.20–1.25 (60℃); and 90% ethanol to 52% alcohol is added, stirred well and allowed to stand for 48 h before being filtered. Ethanol is then recovered from the filtrate to the extract with a relative density of 1.15 C, and 170 g sucrose is added. Water is then added, and the mixture is stirred, filtered, filled and sterilised. After isolating the patients, the LGLQ group took the treatment (Batch No. 220701; 10 ml/branch, 1 branch per time, three times a day) orally for 7 days.

LHQW capsules were manufactured in accordance with the Pharmacopoeia of the People's Republic of China (2020 Edition). Its main ingredients were honeysuckle, forsythia, rhubarb, Panax quinquefolium, Chinese ephedra, patchouli, crude scaly fern, urtica dioica, rhodiola rosea, mountain plum, fritillaria and gypsum. In the LHQW group, after isolating the patients, the treatment was administered orally (batch number: A2204058H; 0.35 g/capsule, four capsules per time, three times daily) for 7 days (Fig. 1).

The placebo control group did not receive any drug treatment.

Observation of symptoms and laboratory tests

The observation indexes for patients included qPCR results monitoring and clinical observation indexes. During hospitalisation, the results of the qPCR were recorded. In terms of qPCR data, specimens were collected with pharyngeal swabs on admission and from the 5th day after admission, and primer pairs targeting 2019-NCoV-N and 2019-nCoV-ORF1ab were judged to be converted if they were both >35. The clinical symptoms of the patients during hospitalisation, the duration and proportion of clinical symptoms were also observed.

Statistical analysis

The data were analysed using SPSS 27 statistical software. The Cochran formula was utilized to meticulously estimate the required sample size. This calculation was based on our assessment of the anticipated differences in the primary outcome measures between groups, while ensuring that the study had a statistical power of 80% and a significance level of 0.05 to detect actual clinical differences between groups. The randomisation was performed using a computer-generated random number table, and the allocation was concealed using sealed envelopes. The sample size was 253, with 100 patients in each of the two intervention groups and 53 patients in the placebo group. The allocation of a larger sample size to the two intervention groups, as opposed to the control group, was a deliberate decision influenced by considerations of resource optimization and cost-effectiveness. The measurement data were expressed as median (interquartile range), and comparisons between the groups were made using the Kruskal–Wallis test. Furthermore, the count data were expressed as cases (frequency/percentage) and statistically analysed using two-tailed test. All statistical

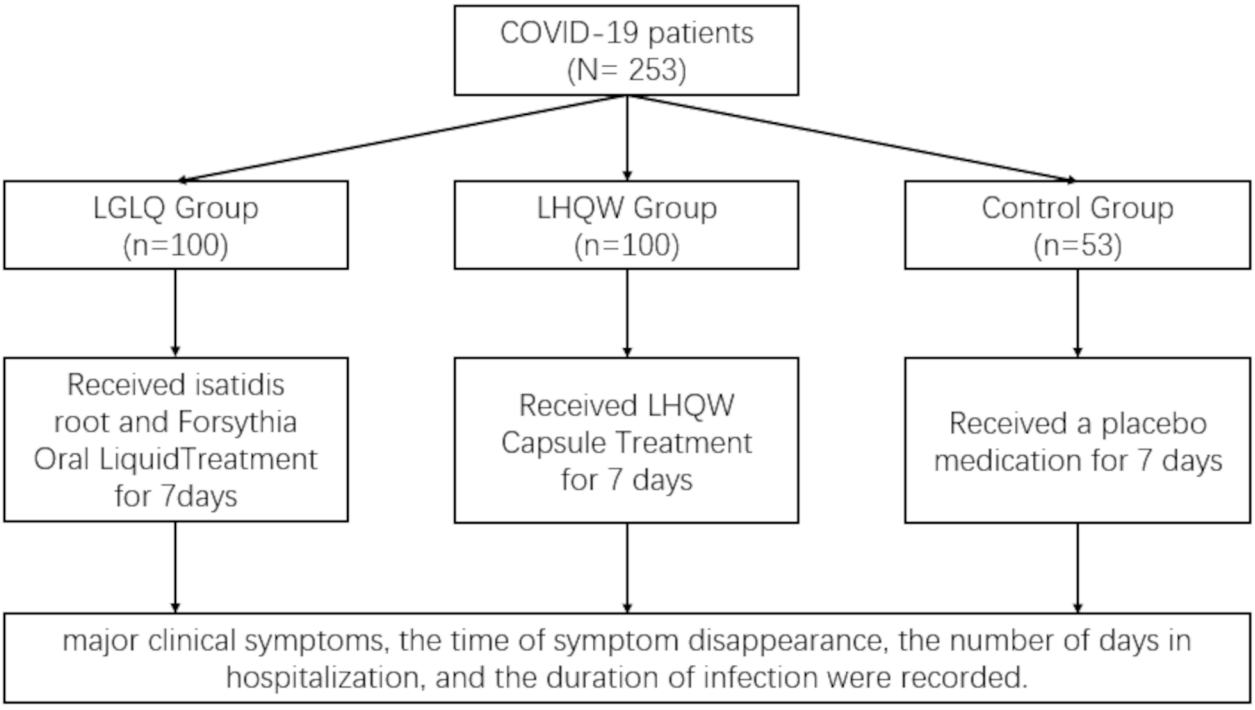

Fig. 1 Flowchart of the present study

Table 1 General information about the patient

		LGLQ	LHQW	Placebo	*P* value
Sex	Male	59 (59%)	63 (63%)	28 (53%)	0.476
	Female	41 (41%)	37 (37%)	25(47%)	
Age		45.4 (12.0)	45.2 (12.5)	44.6 (11.1)	0.535
Number of vaccinations		2.9(0.3)	2.8 (0.4)	2.85 (0.4)	2.586
Weight		63.9 (10.9)	66.1 (10.2)	65.0 (11.2)	0.266

Note Data are expressed as mean (standard deviation) or number (percentage). LGLQ, langenlianqiao; LHQW, LianhuaQingWen

analyses were based on the two-tailed hypothesis test, with $\alpha = 0.05$ as the test level; $P < 0.05$ was considered statistically significant.

Results

General information about the participants

A total of 253 patients were enrolled in this study, of which 100 were allocated to the LGLQ group, 100 to the LHQW group and 53 to the placebo control group. The percentage of men in the three groups was 59.3%, the average age was 45.1 (12.0) years, the mean number of COVID-19 vaccinations was 2.8 (0.4) times and the mean body weight was 65.0 (10.7) kg. The maximum and minimum ages of patients in the LGLQ group were 57.4 and 33.4, while these were 57.7 and 32.7 in the LHQW group, and 55.7 and 33.5 in the placebo group. There were no statistically significant differences in sex, age, number of vaccinations and body weight between the three groups ($P > 0.05$) (Table 1).

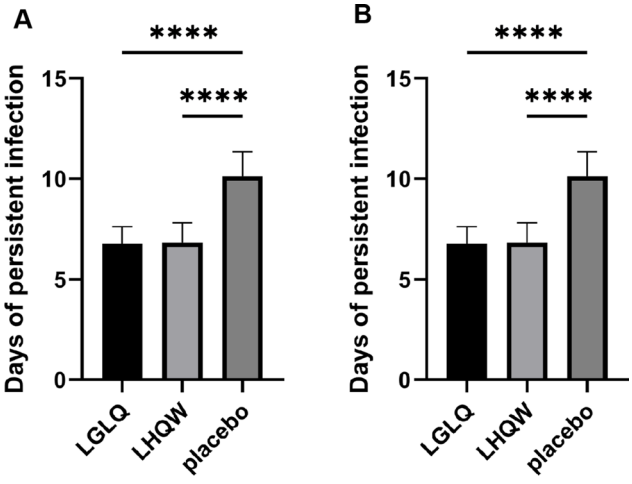

Fig. 2 Days of hospitalization and persistent infection after receiving treatment. (**A**) Days of hospitalization. (**B**) Days of persistent infection. *Note* LGLQ, langenlianqiao; LHQW, LianhuaQingWen; ****, $P < 0.0001$

Treatment and symptomatic improvement effects of Langenlianqiao

The results of this study showed that the duration of infection was 6.8 (0.6) days in the LGLQ group, 6.8 (1.0) days in the LHQW group and 10.0 (1.2) days in the placebo group. Moreover, the LGLQ and LHQW treatments significantly reduced the duration of novel COVID-19 infections (Fig. 2). In addition, it was found that LGLQ was effective in reducing the incidence of malaise, which was statistically different from that of the LHQW and

placebo groups ($P<0.05$). Furthermore, LHQW was effective in reducing the incidence of dry cough, which was statistically different from that of the placebo control group ($P<0.05$) (Table 2). Moreover, LGLQ also reduced the incidence of dry cough in patients, with no statistically significant difference from both the LHQW and placebo control groups ($P=0.39$, $P=0.14$). However, the LGLQ and LHQW groups did not differ from the placebo control group in reducing the incidence of total symptoms, fever, nasal congestion, runny nose, sore throat, myalgia and diarrhoea ($P>0.05$). The LGLQ and LHQW also did not reduce the duration of symptom improvement in patients with existing symptoms ($P>0.05$) (Fig. 3).

Discussion

Chinese herbs such as forsythia, scutellaria baicalensis, honeysuckle are widely used in the clinical treatment of viral diseases and have good therapeutic effects. With its long history, long-term clinical experience and rich chemical composition, TCM has unique advantages in the treatment of some difficult and miscellaneous diseases. Compared with Western medicine, the use of TCM can effectively shorten the patient's disease duration and reduce the occurrence of complications through the interactions of multi-targets, multi-pathways and multi-links [22]. This study investigated the therapeutic effect and symptom improvement of LGLQ in neo-coronavirus and compared it with LHQW clinically. It was found that LGLQ has good antiviral effects in the anti-infection treatment of novel COVID-19. Here, LGLQ was found to significantly reduce the time to nucleic acid conversion and effectively improve the symptoms of malaise in patients. Although the global pandemic of COVID-19 and its effects have gradually receded, public health is still facing the threat of viral infections like influenza and pandemic influenza. This study may provide more options for the selection of antiviral drugs.

Studies have shown that LHQW has better broad-spectrum antiviral, antibacterial, antipyretic, anti-inflammatory, antitussive, phlegmatic and immune-regulating effects, and that it can be used in the treatment of respiratory viral diseases [23, 24]. Furthermore, LHQW preparation has broad-spectrum antiviral effects against influenza A viruses (H1N1, H3N2), influenza B viruses, avian influenza viruses (H5N1, H9N2, H7N9), COVID-19 and a variety of cold and flu viruses. It can also effectively inhibit a variety of bacteria [25]. In the treatment of COVID-19 in China, LHQW was listed as a recommended medication in the Diagnosis and Treatment Program of Pneumonia with Novel Coronavirus Infection [21]. In this study, LGLQ was recognised to have similar efficacy to LHQW and was more advantageous in treating fatigue.

In terms of composition, both LGLQ and LHQW formulations contain forsythia and honeysuckle

Table 2 Effectiveness of treatment and symptom reduction

					P value		
		LGLQ case	**LHQW case**	**Placebo case**	**LGLQ vs. LHQW**	**LGLQ vs. Placebo**	**LHQW vs. Placebo**
Fever	Yes	13	17	6	0.429	0.765	0.351
	No	87	83	47			
Dry cough	Yes	30	25	22	0.393	0.143	**0.030**
	No	70	75	31			
Cough	Yes	46	40	31	**0.014**	**0.016**	0.855
	No	54	60	22			
Fatigue	Yes	4	14	8	0.580	0.246	0.499
	No	96	86	45			
Nasal congestion	Yes	6	8	6	0.792	0.420	0.564
	No	94	92	47			
Nasal mucus	Yes	9	10	7	0.386	0.868	0.373
	No	91	90	46			
Sore throat	Yes	42	36	23	0.093	0.079	0.774
	No	58	64	30			
Myalgia	Yes	9	17	10	0.651	0.514	0.798
	No	91	83	43			
Constipation	Yes	2	2	2	0.418	0.249	0.074
	No	98	98	51			
Clinical symptom	Yes	77	72	45	0.429	0.765	0.351
	No	23	28	8			

Note LGLQ, langenlianqiao; LHQW, LianhuaQingWen

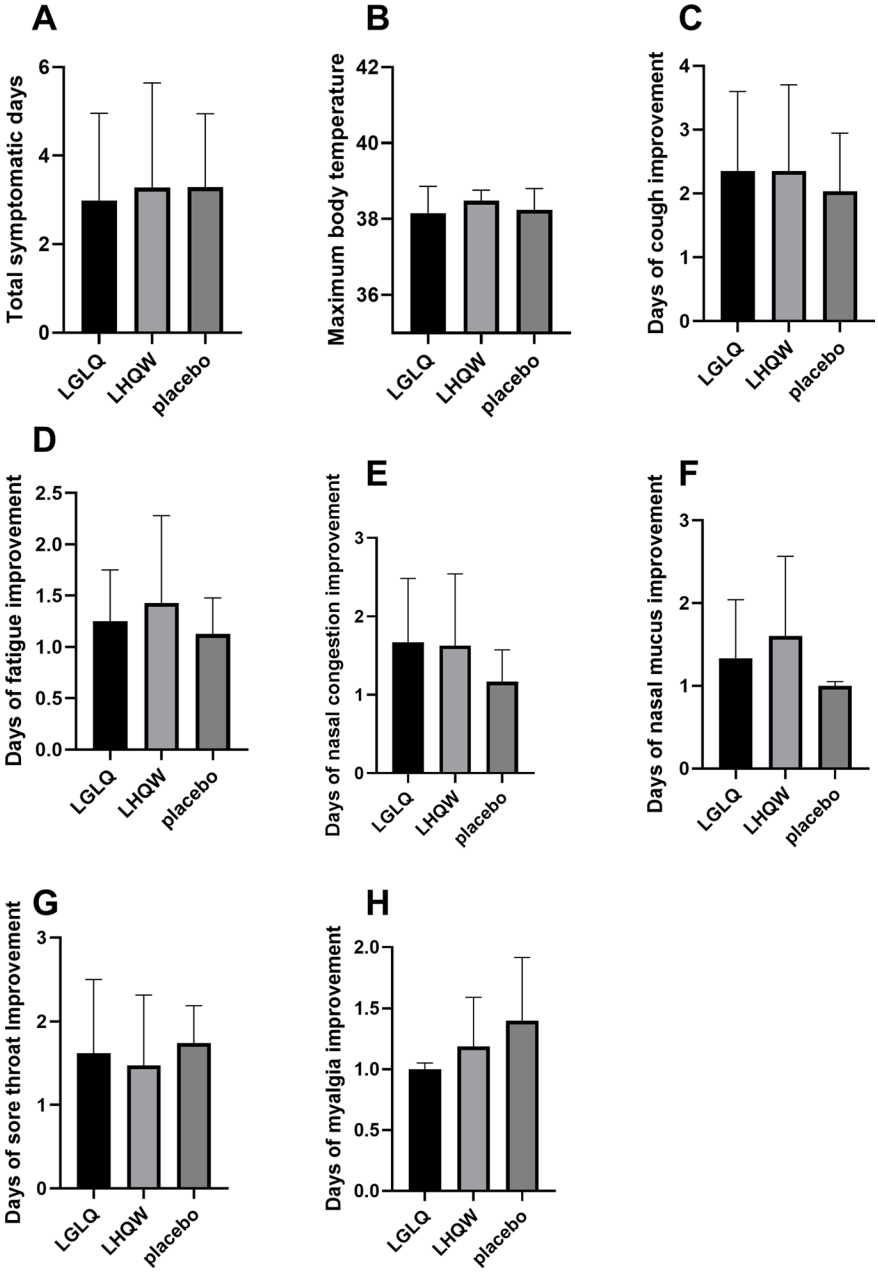

Fig. 3 Days of symptomatic improvement after receiving treatment. (**A**) Total symptom. (**B**) Maximum body temperature. (**C**) Cough. (**D**) Fatigue. (**E**)Nasal congestion. (**F**)Nasal mucus. (**G**)Sore throat. (**H**) Myalgia. *Note* LGLQ, langenlianqiao; LHQW, LianhuaQingWen

components, which may be the common effective-acting substances in their antiviral effects. Many studies have found that forsythia and its active ingredients have better therapeutic effects on a variety of viral diseases. Sheng Nan et al. [26] found that mice infected with H9N2 avian influenza virus (AIV) treated with forsythiaside A (FTA) could inhibit MyD88-NF-KB gene expression levels, thereby reducing the production of the inflammatory cytokine, interleukin-1 beta (IL-1β), and attenuating AIV-induced inflammatory injury.

Based on the research method of network pharmacology, Xu Jiahui et al. [27] employed gene ontology functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis and found that the sterols and flavonoids active ingredients contained in forsythia could regulate key targets such as IL-l, IL-6, C-C motif chemokine 2, mitogen-activated protein kinase-like 1 (MAPK l), mitogen-activated protein kinase-like8 (MAPK 8), mitogen-activated protein kinase-like 14 (MAPK l4), the c-Fos proto-oncogene protein, caspase 3 and albumin. This regulates oxidative

stress injury, pulmonary fibrosis and proliferation, inflammatory response, apoptosis and other processes, thereby reducing the novel COVID-19-induced lung injury. Jia Wei et al. [28] examined the in-vivo antiviral effects of honeysuckle through influenza virus FM/1 strain-infected mice, and the honeysuckle polysaccharide group could significantly reduce the morbidity and mortality rate, prolong the survival time and alleviate the degree of lung lesions in virus-infected mice. Honeysuckle polysaccharide has good anti-influenza A virus effects. Chen Shuang et al. [29] adopted network pharmacology research and found that a LHQW preparation of forsythia and honeysuckle was the key drug for the treatment of COVID-19, which can inhibit viral replication by regulating the key targets, modulating inflammatory response, regulating apoptosis, mediating the immune response and causing changes in the shape of viral particles and inhibiting the expression of inflammatory factors of host cells. The treatment, therefore, plays a role in the anti-SARS-induced disease and inhibiting the expression of anti-SARS-induced diseases. The anti-COVID-19 effect can be achieved by regulating key targets, modulating the inflammatory response, mediating the immune response and inhibiting the replication of the virus. Ultimately, lung damage is reduced to alleviate the symptoms of the disease. The difference between the two remedies may be related to the different effects on symptom improvement.

This study has several limitations. Firstly, the relatively small sample size may limit the statistical power to detect treatment effects, particularly for secondary outcomes such as the duration of symptom improvement. The study's population composition, primarily consisting of middle-aged patients, may not fully represent the experiences of younger and older individuals, potentially restricting the ability to discern treatment efficacy across a broader age range. Secondly, the unequal distribution of samples across study groups, due to limitations in resources and costs, could introduce selection bias. The single-center design may also affect the generalizability of the results to various healthcare settings. Additionally, the qPCR technology used for monitoring viral load and infection status does not distinguish between live and non-live viruses, which might lead to an overestimation of viral activity and transmissibility. This factor should be considered when interpreting the duration of infection and other clinical outcomes. Finally, an important limitation of this study is the lack of a placebo in the control group. Although all participants received standardized symptomatic care, the absence of a placebo control may affect the study results, particularly in assessing patient expectation effects. Ideally, including a placebo control group would provide a more rigorous benchmark. However, our design ensured that all patients received equal medical interventions aside from the study drugs, allowing for a more accurate assessment of the additional effects of LGLQ and LHQW. Despite these limitations, the study provides significant insights into the potential therapeutic effects of LGLQ oral liquid and LHQW capsule in patients with mild COVID-19, contributing valuable information for future research and clinical practice. It is recommended that larger, multicenter studies with more diverse populations be conducted to further validate and expand upon these findings.

Conclusion

In the treatment of COVID-19 infection, LGLQ oral liquid has similar antiviral effects as LHQW, that is, it can shorten the duration of infection and reduce the symptoms of patients with mild disease. Moreover, compared with LHQW, LGLQ can effectively reduce patients' fatigue, and this study may provide insights and ideas for antiviral therapy research.

Author contributions

Conception and design of the research: ZM, YYM. Acquisition of data: YYM, LQX. Analysis and interpretation of the data: LQX, LYZ. Statistical analysis: YYM, LQX, LYZ, ZM. Obtaining financing: None. Writing of the manuscript: YYM, LQX. Critical revision of the manuscript for intellectual content: ZM.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Changde Hospital (ethical batch number: YX-2023-119-01), and informed consent was obtained from all participants.

Competing interests

The authors declare no competing interests.

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