

LETTER TO THE EDITOR

High-quality trials and pharmacological studies needed as translational evidence for the application of traditional Chinese medicine Lianhua Qingwen against COVID-19

Nan Huang¹  | Saichao Li²¹Cerui Consulting Firm, Shanghai, China²Department of Health Technologies, Yidu Cloud Technology (Shanghai) Inc, Shanghai, China**Correspondence**

Nan Huang, Cerui Consulting Firm, 999 West Zhongshan Rd, Shanghai 210000, China.

Email: szhuangnan@gmail.com**Abstract**

Traditional Chinese medicine (TCM) has been employed as complementary medication against COVID-19 in China since 2020. Two years since then, TCM, with Lianhua Qingwen (LHQW) as an example, has been included in every version of official clinical protocol guidelines. Recently, LHQW is even distributed to general public at risk but not yet infected. Such common application and widely claimed positive outcome among mild to moderate patients were accompanied by a number of published studies on antiviral, antiinflammatory, and immune modulatory potential using either in vitro or animal models. However, aside from retrospective understanding and open-labeled clinical trials with relatively small subject size, major gap in conclusive proof for efficacy and safety remains due to the lack of double-blind placebo-controlled studies and comprehensive pharmacodynamic and kinetic investigations. This is also supported by a recent WHO expert meeting on this subject, which acknowledged the potential benefits of TCM in mild-moderate cases, while recommended more rigorous studies to further understand effect size, application implications, and outcome determinants. Therefore, there is an urgent need to address the exact role TCM like LHQW could play in COVID-19 management from translational evidence-based perspective. High-quality clinical trials, pharmacological studies, and real-world data from recent outbreak are recommended.

KEYWORDS

clinical trial, complementary medicine, COVID-19, LHQW, Lianhua Qingwen, TCM, traditional Chinese medicine

With the recent resurgence of COVID-19 in China driven by the highly contagious Omicron BA.2 variant, exponential increase in cases impose significant pressure on the healthcare system in major cities like Shanghai. As majority of the patients were mild-to-moderate, traditional Chinese medicine (TCM) treatments were prescribed to ~98% of the patients (Goh & Liu, 2022). At the same time, over the counter TCM medication Lianhua Qingwen (LHQW) were distributed to citizens under quarantine in Shanghai (Wang, 2022).

In sharp contrast to its almost universal application among mild-to-moderate COVID-19 patients in China, translational research on TCMs' efficacy, safety, and mechanisms remained limited (Ganguly &

Bakhshi, 2020; Wang & Yang, 2021). For example, as of April 21, 2022, a search for ("traditional Chinese medicine" and COVID-19) in Pubmed rendered 1,263 hits, among which only 27 were clinical trials, together with a disproportional 65 articles as meta-analyses. Such crude breakdown of research papers on this subject clearly suggests a lack of robust validation, with overpopulated reviews based on a small number of highly heterogeneous original studies of varied quality. The larger chunk of the reports came up from the search were either in vitro screening in cell culture or network pharmacological speculations based on data from in silico and/or simple cell culture models, without much needed consideration of the complex

pharmacodynamic and pharmacokinetic (PDPK) processes after oral intake of TCM medications (Hao, Wang, & Xiao, 2022). The few clinical trials were conducted as open label without placebo, covering low number of subjects, and mainly focused on symptomatic benefits (Liang et al., 2021).

In order to elaborate on the necessity to generate more robust translational understanding of TCM's potential efficacy as well as safety in the context of COVID-19, a brief review on the present knowledge of one of the most widely used TCM medications, LHQW, is presented herein as an example. LHQW is selected because it is produced under standard pharmaceutical processes and was relatively well-studied using a plethora of *in silico*, *in vitro*, and *in vivo* approaches among all TCMs.

Like most TCM medications, LHQW is formulated as a recipe of herbal extracts, namely *Forsythia suspensa* (Forsythia), *Lonicera japonica* (Honeysuckle), plaster, *Isatis indigotica* (Radix Isatidis), *Dryopteris crassirhizoma*, *Houttuynia cordata*, *Ephedra sinica* (Ephedra), *Armeniaca sibirica* (Apricot), *Pogostemon cablin* (Patchouli), *Rhodiola rosea* (Rhodiola), *Glycyrrhiza uralensis* (Licorice), *Rheum officinale* (Rhubarb), and *Mentha haplocalyx* (Mint) (Li et al., 2020). It received approval in 2003 for flu management and recently has been recommended by the officials as a COVID-19 treatment option (National Health Commission & State Administration of Traditional Chinese Medicine, 2020).

There are over 400 bioactive constituents characterized in LHQW, including lignans, flavonoids, alkaloids, phenethanol glycosides, phenolic acids, and triterpenes among others. This complex composition inevitably makes it impossible to pinpoint pharmacophore-molecular mechanism. Alternatively, most molecular mechanistic understanding was generated based on *in silico* docking. For example, network pharmacology analyses based on known phytochemical profiles and their molecular targets has been employed to propose biological targets of LHQW, resulting in proposition of interleukin-6 (IL-6), IL-17, Akt1, and viral infection pathways in play (Chen et al., 2021; Tianyu et al., 2021; Xia et al., 2020). With that said, due to the lack of experimental insight regarding active molecules and their serum level after intake, it would be extremely challenging to validate the mechanisms *in vivo*. Drug interaction should also be considered for complementary or adjunct usage of LHQW, as it could have profound influence on eventual clinical outcome.

Chinese herbal ingredients have been extensively studied for their anti-viral potential, primarily in *in vitro* or animal models at exaggerated dosages (Wu et al., 2021). When it comes to LHQW against SARS-CoV-2, Lu et al. compared LHQW to Remdesivir head-to-head using Vero E6 cells and found the respective IC_{50} being an unimpressive 411.2 $\mu\text{g/mL}$ for LHQW, in sharp contrast to Remdesivir's 0.651 μM (Runfeng et al., 2020). The same study also found cytotoxic CC_{50} for LHQW being just over 1,000 $\mu\text{g/mL}$, suggesting an impractically impractical narrow safety margin for direct anti-SARS-CoV-2 activity. Alternatively, under more *in vivo* relevant context, Chen et al. identified rhein, forsythoside A, forsythoside I, neochlorogenic acid, and its isomers as bioactive components in the circulation after 8 doses of LHQW, with inhibitory activity against angiotensin-converting enzyme 2 (ACE2) that could facilitate blockage of viral

infection (Chen et al., 2021). Overall, current evidence does not suggest direct viral inhibition potential of LHQW at pharmacologically reasonable dosage. Instead, LHQW might impede the infection process of SARS-CoV-2 by lowering the activity of ACE2.

The presence of ephedrine in LHQW and the confirmed identification of ephedrine hydrochloride in urine after taking the medicine could partially explain the symptom alleviation effect, via adrenergic receptors (Chen et al., 2021; Liang et al., 2021). Consistent with the prediction by network pharmacology analysis, LHQW was able to drastically inhibit IL-6 production in cell culture infected with SARS-CoV-2, at reasonable 150 $\mu\text{g/mL}$ (Runfeng et al., 2020; Tianyu et al., 2021). Lan et al. focused on constituents from *Glycyrrhiza uralensis* roots in LHQW in a preliminary pharmacokinetic investigation and found representative post-absorption active metabolites with antiinflammatory potentials, namely glycyrrhetic acid and liquiritigenin, present in the plasma of 14 human volunteers at concentrations in the range of 48.5–88.2 nmol and 3.8–4.2 nmol, respectively (Lan et al., 2021). No other *in vivo* pharmacokinetic study has covered putative bioactives from the LHQW holistically, to our best knowledge. While there is yet to be any *in vivo* animal study addressed LHQW's anti-inflammatory effect against SARS-CoV-2 infection, it was investigated in H1N1 or particulate matter challenged mice and found to be able to dampen inflammation mediators including prostaglandins, tumor necrosis factor (TNF)- α , IL-1 β , IL-6, while increased antiviral interferon (IFN)- γ (L.-C. Li et al., 2020). Inflammation and immune regulation are common benefits associated with herbal phytochemical materials, ranging from foods, dietary supplements, and complementary/alternative medicines. Therefore, it is not surprising that LHQW's proposed mechanism of action involved such pathways. Further understanding of the relative effect size compared to standard antiinflammatory treatments including glucocorticoids and non-steroid antiinflammatory drugs (NSAIDs) in the context of COVID-19 management can help defining proper treatment regimen and facilitate effective yet safe application clinically (Pawar & Pal, 2020).

Given the fact that LHQW is recommended for and widely used clinically in China as emergency first line therapy against COVID-19 patients for over 2 years, it is surprising to find a lack of high-quality clinical evidence from placebo-controlled randomized clinical trials (RCTs).

Li et al. recently conducted a systematic review and meta-analyses that covered most up-to-date reports on LHQW's efficacy and safety, which eventually included 7 studies, with only 3 being randomized clinical trials while the rest being case-control observations (Li, Xiao, Liu, & Zhang, 2022). Liu et al. also have summarized clinical studies that attempted to assess COVID-19 treatment benefits of LHQW, which amounted to a similarly small number of eight records worth being included (Liu et al., 2021). Five of those studies were retrospective by nature, in which LHQW was often used as adjunct treatment together with Abidole or other medications. For instance, it was found that standard therapy + LHQW granules was associated with higher lymphocyte count and lower inflammatory biomarkers in a study of 248 cases (Shen et al., 2021). One of the higher-quality RCTs, out of a total of three, conducted in 2020 by leading respiratory

TABLE 1 Planned clinical trials on LHQW against COVID-19

Trial registration #	Site & time	Design features	Outcome parameters	Subject #
ChiCTR2200058563	Shanghai, China 2022/4–2022/6	LHQW versus no treatment among quarantined close-contact subjects	Preventive effect based on COVID-positive rate ^a	25,000 per arm
ChiCTR2200056727	China, Cambodia, Vietnam, Thailand, Singapore 2022/1–2022/12	Phase IV: Standard therapy + LHQW versus Standard therapy + placebo among mild to moderate patients	Within 14 days, median time to symptom resolution ^a , symptom improvement rate, viral nucleic acid test negative rate, imaging improvement rate, incidence of critical cases, mortality, inflammatory biomarkers	430 per arm
ChiCTR2200058079	Shanghai, China 2022/3–2022/6	LHQW only versus placebo among asymptomatic COVID-19 patients	Within the 7-day quarantine period, nucleic acid negative conversion time and rate ^a	800 per arm
ChiCTR2200058639	Shanghai, China 2022/4–2022/6	Phase IV: LHQW only versus placebo in asymptomatic and mild COVID-19 patients	Within the 7-day quarantine period, nucleic acid negative conversion time and rate ^a	20,000 for treatment and 10,000 for control
NCT05223660	United States 2022/7–2022/9	Phase I: Single dose open label and single & multiple dose double blinded LHQW (KT07) versus placebo	Pharmacokinetic profile parameters ^a , incidence, causality, and severity of adverse events	6 for open label part 1; 10 per arm for part 2
NCT05275933	Singapore 2022/9–2022/12	Phase II/III: LHQW + standard PRN medicine versus placebo + standard PRN medicine among COVID-19 Patients on Home Recovery Program	Time to become asymptomatic ^a , time to viral antigen test negativity, symptom severity score, and adverse event	150 per arm

^aIndicates primary outcome; ChiCTR numbers are under the Chinese Clinical Trial Registry.

experts compared LHQW + conventional treatment to conventional treatment, and found the former led to higher symptom recovery rate and pulmonary imaging improvement rate over the period of 14 days (Hu et al., 2021). The LHQW treated subjects on average reported resolution of fever, fatigue, and coughing 1–3 days earlier, but was not showing benefit in nucleic acid negative conversion rate or reduction in severe case incidence. In all the reported RCTs, no placebo or blinding was applied, making them subjected to placebo effect as well as observational bias. Also, LHQW as the sole medication instead of complementary adjunct therapy has not been well-studied yet.

Recently, Gong et al. reported a prospective open label trial that evaluated preventive efficacy of LHQW among close contact of confirmed patients (Gong, Yuan, Yuan, & Li, 2021). Although there was statistically significant superiority in positive rate for LHQW treatment group (0.27%) over non-treated control group (1.14%), the lack of placebo control, difference in relevant subject profiles, and most importantly the extremely low incidence of positivity (13 in a total of 1,976 subjects) warrant further studies to validate LHQW as effective and safe COVID-19 preventive agent.

Overall, there is a lack of conclusive direct evidence generated from double-blinded RCTs to support LHQW's prevention and therapy effect against COVID-19, even as adjunct treatment. With that

said, the existing data from open label RCTs and retrospective studies all suggest LHQW being effective in alleviating COVID-19 symptoms.

It should be acknowledged the challenge to evaluate phytomedicine and traditional medicine following the modern drug development process and standards (Wu et al., 2021). But to scientifically leverage the potential power of alternative and complementary medicines, it is advisable to accelerate research in TCMs like LHQW in phytochemistry, PDPK, molecular mechanisms of action, as well as clinical efficacy and safety. A recent WHO expert meeting also evaluated TCM as COVID-19 treatment as COVID-19. The experts commended the benefits reported based on existing studies and clinical practice, while also urged for more high-quality studies (World Health Organization, 2022).

It is reassuring to see a few new prospective controlled trials with good quality currently on the agenda for LHQW as either adjunct treatment or single treatment, as summarized in Table 1. Also worth noting is that one of the planned clinical studies (NCT05223660) is expected to generate pharmacokinetic insights as well. Hopefully, findings from such upcoming research could strengthen the case for LHQW, and TCM in general, as legitimate COVID-19 treatment option. Lastly, the recent outbreak in major cities like Shanghai could also help generate real-world data on the use of TCM, which can also provide valuable insights on their clinical outcome implication.

AUTHOR CONTRIBUTIONS

Nan Huang and Saichao Li were responsible for the conceptualization, literature review, and writing of this manuscript.

FUNDING INFORMATION

This manuscript is self-funded.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

There is no original data associated with this manuscript.

ORCID

Nan Huang  <https://orcid.org/0000-0002-7873-7294>

REFERENCES

- Chen, X., Wu, Y., Chen, C., Gu, Y., Zhu, C., Wang, S., ... Wu, C. (2021). Identifying potential anti-COVID-19 pharmacological components of traditional Chinese medicine Lianhuaqingwen capsule based on human exposure and ACE2 biochromatography screening. *Acta Pharmaceutica Sinica B*, 11(1), 222–236. <https://doi.org/10.1016/j.apsb.2020.10.002>
- Ganguly, S., & Bakhshi, S. (2020). Traditional and complementary medicine during COVID-19 pandemic. *Phytotherapy Research*, 34(12), 3083–3084. <https://doi.org/10.1002/ptr.6828>
- Goh, B., & Liu, R. (2022). China relies on traditional medicine to fight COVID surge in Shanghai. Reuters. <https://www.reuters.com/world/china/china-relies-traditional-medicine-fight-covid-surge-shanghai-2022-04-06/>
- Gong, X., Yuan, B., Yuan, Y., & Li, F. (2021). Efficacy and Safety of Lianhuaqingwen Capsules for the Prevention of Coronavirus Disease 2019: A Prospective Open-Label Controlled Trial. *Evidence-based Complementary and Alternative Medicine*, 2021, 1–9. <https://doi.org/10.1155/2021/7962630>
- Hao, D.-C., Wang, F., & Xiao, P.-G. (2022). Impact of Drug Metabolism/Pharmacokinetics and their Relevance Upon Traditional Medicine-based anti-COVID-19 Drug Research. *Current Drug Metabolism*, 23, 374–393. <https://doi.org/10.2174/1389200223666220418110133>
- Hu, K., Guan, W., Bi, Y., Zhang, W., Li, L., Zhang, B., ... Zhong, N. (2021). Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial. *Phytomedicine*, 85, 153242. <https://doi.org/10.1016/j.phymed.2020.153242>
- Lan, X. f., Olaleye, O. E., Lu, J. I., Yang, W., Du, F. f., Yang, J. I., ... Li, C. (2021). Pharmacokinetics-based identification of pseudoaldosterogenic compounds originating from Glycyrrhiza uralensis roots (Gancao) after dosing LianhuaQingwen capsule. *Acta Pharmaceutologica Sinica*, 42(12), 2155–2172. <https://doi.org/10.1038/s41401-021-00651-2>
- Li, L.-C., Zhang, Z.-H., Zhou, W.-C., Chen, J., Jin, H.-Q., Fang, H.-M., ... Kan, L.-D. (2020). Lianhua Qingwen prescription for Coronavirus disease 2019 (COVID-19) treatment: Advances and prospects. *Biomedicine & Pharmacotherapy*, 130, 110641. <https://doi.org/10.1016/j.biopha.2020.110641>
- Li, Y., Xiao, P., Liu, N., & Zhang, Z. (2022). Efficacy and Safety of Chinese Medicine Lianhua Qingwen for Treating COVID-19: An Updated meta-Analysis. *Frontiers in Pharmacology*, 0, 1997. <https://doi.org/10.3389/FPHAR.2022.888820>
- Liang, C., Hui, N., Liu, Y., Qiao, G., Li, J., Tian, L., ... Ren, X. (2021). Insights into forsythia honeysuckle (Lianhuaqingwen) capsules: A Chinese herbal medicine repurposed for COVID-19 pandemic. *Phytomedicine Plus*, 1(2), 100027. <https://doi.org/10.1016/j.phyplu.2021.100027>
- Liang, S.-B., Fang, M., Liang, C.-H., Lan, H.-D., Shen, C., Yan, L.-J., ... Liu, J.-P. (2021). Therapeutic effects and safety of oral Chinese patent medicine for COVID-19: A rapid systematic review and meta-analysis of randomized controlled trials. *Complementary Therapies in Medicine*, 60, 102744. <https://doi.org/10.1016/j.ctim.2021.102744>
- Liu, M., Gao, Y., Yuan, Y., Yang, K., Shi, S., Tian, J., & Zhang, J. (2021). Efficacy and safety of herbal medicine (Lianhuaqingwen) for treating COVID-19: A systematic review and meta-analysis. *Integrative Medicine Research*, 10(1), 100644. <https://doi.org/10.1016/j.imr.2020.100644>
- National Health Commission & State Administration of Traditional Chinese Medicine. (2020). *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia*.
- Pawar, A., & Pal, A. (2020). Molecular and functional resemblance of dexamethasone and quercetin: A paradigm worth exploring in dexamethasone-nonresponsive COVID -19 patients. *Phytotherapy Research*, 34(12), 3085–3088. <https://doi.org/10.1002/ptr.6886>
- Runfeng, L., Yunlong, H., Jicheng, H., Weiqi, P., Qin Hai, M., Yongxia, S., ... Zifeng, Y. (2020). Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). *Pharmacological Research*, 156, 104761. <https://doi.org/10.1016/j.phrs.2020.104761>
- Shen, P., Li, J., Tu, S., Wu, Y., Peng, Y., Chen, G., & Chen, C. (2021). Positive effects of Lianhuaqingwen granules in COVID-19 patients: A retrospective study of 248 cases. *Journal of Ethnopharmacology*, 278, 114220. <https://doi.org/10.1016/j.jep.2021.114220>
- Tianyu, Z., Xiaoli, C., Yaru, W., Min, Z., Fengli, Y., Kan, H., ... Jing, L. (2021). New tale on LianHuaQingWen: IL6R/IL6/IL6ST complex is a potential target for COVID-19 treatment. *Aging*, 13(21), 23913–23935. <https://doi.org/10.18632/aging.203666>
- Wang, M. (2022, May 9). CGTN exclusive: Zhang Boli helps thousands of asymptomatic patients with TCM treatment. <https://news.cgtn.com/news/2022-05-09/Exclusive-Zhang-Boli-helps-thousands-of-COVID-19-patients-with-TCM-19TUgxfzL1u/index.html>
- Wang, Z., & Yang, L. (2021). Chinese herbal medicine: Fighting SARS-CoV-2 infection on all fronts. *Journal of Ethnopharmacology*, 270, 113869. <https://doi.org/10.1016/j.jep.2021.113869>
- World Health Organization. (2022). WHO Expert Meeting on Evaluation of Traditional Chinese Medicine in the Treatment of COVID-19. <https://www.who.int/publications/m/item/who-expert-meeting-on-evaluation-of-traditional-chinese-medicine-in-the-treatment-of-covid-19>
- Wu, X., Li, W., Qin, Z., Xue, L., Huang, G., Luo, Z., & Chen, Y. (2021). Traditional Chinese medicine as an adjunctive therapy for mild and common COVID-19. *Medicine*, 100(40), e27372. <https://doi.org/10.1097/MD.00000000000027372>
- Xia, Q., Xun, Y., Lu, J., Lu, Y., Yang, Y., Zhou, P., ... Wang, S. (2020). Network pharmacology and molecular docking analyses on Lianhua Qingwen capsule indicate Akt1 is a potential target to treat and prevent COVID-19. *Cell Proliferation*, 53(12), e12949. <https://doi.org/10.1111/cpr.12949>

How to cite this article: Huang, N., & Li, S. (2022).

High-quality trials and pharmacological studies needed as translational evidence for the application of traditional Chinese medicine Lianhua Qingwen against COVID-19.

Phytotherapy Research, 1–4. <https://doi.org/10.1002/ptr.7574>