LIANHUA

RECOMMENDATION

We recommend against the use of Lianhua as treatment among patients with COVID-19 infection. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues

The Consensus Panel considered the evidence from the presented trials to be of very low certainty, with only marginal benefit in terms of rate of recovery and time to symptom recovery and inconclusive evidence for harm due to imprecise confidence intervals. The accessibility issue and potential harm the drug might cause should be considered. Lianhua is currently a drug regulated by the Philippine Food and Drug Administration as it contains ephedra, a controlled substance. As a result, Lianhua could not be sold over-the-counter and may only be prescribed by physicians holding an S2 license. The ephedra content of Lianhua was reported by some physicians to be potentially harmful especially in patients with cardiovascular disease.

EVIDENCE SUMMARY

Should Lianhua be used in the treatment of patients with COVID-19 infection?

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Key Findings

Limited evidence from 3 studies with very low methodological quality shows that using Lianhua offers no clear benefit in improving the clinical status of patients with COVID-19. None of the studies provided effect estimates for the outcomes of mortality, development of ARDS, length of hospitalization, and the need for mechanical ventilation.

Introduction

Since COVID-19 was declared a pandemic in early March 2020, various potential pharmacologic therapies including traditional Chinese medicine (TCM) have been extensively explored. Lianhua Qingwen (LHQW), a classical Chinese medical preparation officially recorded in the 2015 edition of the *Chinese Pharmacopoeia*, has been used in the SARS outbreak of 2002-2003 in China [1]. Recent *in vitro* studies have shown its effectiveness against SARS-CoV-2 through inhibition of replication, modification of viral morphology, and exertion of anti-inflammatory activity [2]. Specifically, a network pharmacologic analysis has shown that it regulates TFs or miRNAs of ACE2 [3].

A systematic review and meta-analysis of five studies on the use of lianhua against COVID-19 pneumonia showed benefit in terms of improvement of flu-like symptoms, shortness of breath, and pulmonary imaging, shorter healing period, and lesser conversion to severe cases [4]. This review presents clinical studies on the efficacy and safety of Lianhua against COVID-19.

Review Methods

Databases including PubMed, Cochrane Library, Cochrane COVID-19 Study Register[1], ChinaXiv.org, MedRxiv.org, BioRxiv.org[2], clinicaltrials.gov[3], ChiCTR[4], WHO Clinical Trials Registry[5], the COVID-19 Open Living Evidence Synthesis[6], and the WHO Therapeutics and COVID-19 Living Guideline were searched for studies up to January 2, 2021. For PubMed, in addition to the general search strategy, the following search query was used: (((lianhua qingwen) OR (lianhua)) OR (lianhua qingwen capsules)) OR (lianhua capsules). For Cochrane Library, the following search strategy was used: ((“COVID-19") OR ("severe acute respiratory syndrome coronavirus 2") OR ("2019-nCoV") OR ("SARS-CoV-2") OR ("corona virus disease 2019”)) AND ((lianhua) OR (lianhua qingwen) OR (lianhua capsule) OR (lianhua qingwen capsule)). Only randomized controlled trials and retrospective studies published in any language were included. The reference list of systematic reviews, meta-analyses, and clinical practice guidelines were reviewed for possible additional studies. Review articles and other study designs were excluded.

The two reviewers independently screened the titles and abstract of identified articles for eligibility based on population, intervention, comparators, and outcomes. Full texts of potentially relevant articles were retrieved and reviewed for inclusion in the review.

The methodological quality of included studies were independently assessed based on the Cochrane Risk of Bias Tool and Newcastle-Ottawa Quality Assessment Scale . The following study characteristics were extracted: month and year of study, study site, inclusion and exclusion criteria, interventions, and outcomes.

Quality of evidence was rated using Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The interpretation of the evidence was based on the five GRADE considerations: risk of bias or study limitations, imprecision, inconsistency, indirectness and publication bias. The evidence was downgraded by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of the evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

[1] "lianhua"
[2] “COVID-19” and “lianhua”
[3] “COVID-19” and “lianhua”
[4] Target disease: COVID-19; Intervention: lianhua
[5] "lianhua"
[6] "lianhua, filter “EPI, Other, Comment, editorial…,unclassified”

Results

Characteristics of included studies

Fifteen studies were assessed for full-text review after a systematic search of electronic databases. Only 3 studies were finally included in this review, while 12 were excluded because they were either protocols of ongoing studies, mixed method review, studies mixing other traditional medicine and lianhua in the same treatment group, studies without standard of care alone as treatment group, or articles in Chinese that were untranslatable. The characteristics of included studies are summarized in Appendix 1.

The 2 RCTs and 1 retrospective non-randomized controlled study included a total of 514 patients more than 18 years of age without severe systemic diseases. The standard of care among the studies was based on the recommendations on the “Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)”, which included antivirals, oxygen therapy, and/or symptomatic treatments. One pack or bag of Lianhua Qingwen granules were used in the studies that specified the dose. Outcomes common among the studies were rates of symptom recovery, time to symptom recovery, improvement of clinical symptoms, and rate of conversion to severe cases.

Overall quality of evidence

Overall, risk of bias was rated very serious across studies because of the lack of blinding of participants, personnel, and outcome assessors in the RCTs. Evidence quality was downgraded by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of the evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Outcomes

Only data for clinical deterioration were pooled; others could not be pooled due to heterogeneity of outcomes. In 1 RCT with very low methodological quality, the group treated with Lianhua showed significantly faster rate of symptom recovery at Day 14 of illness [mean difference (MD) 9.2, 95% CI 1.3-17.1, $p = 0.022$]. It also showed that Lianhua was associated with a shorter median time to symptom recovery [Hazard ratio (HR) 1.7, 95% CI 1.3-2.2, $p < 0.01$]. Overall, the rate of clinical recovery was higher in the treatment group (MD 12.7, 95% CI 2.3-22.7, $p < 0.05$) with a significantly higher disappearance rate of symptoms of fever, cough, expectoration, and shortness of breath [5]. On the other hand, there was no significant difference in the improvement of other clinical symptoms such as headache and muscle between Lianhua and standard of care ($p > 0.05$) and duration of fever in days [(4.6 ± 3.2) vs.(6.1 ± 3.1), $p = 0.218$] in the another RCT [6]. Similar findings were reported by another study [7]. Pooled estimate of rate of conversion to severe cases (i.e. clinical deterioration) of 2 studies showed no significant difference (OR 0.63, 95% CI 0.25-1.57) [5,6].

There was no significant difference in the conversion rate of SARS-CoV-2 viral assay (MD 5.6, 95% CI -4.6-15.7, p = 0.279) and median viral assay conversion time (HR 1.2, 95% CI 0.9-1.6, p = 0.151). However, the rate of recovery of chest CT manifestations was significantly higher in the treatment group (MD 19.7, 95% CI 9.6-29.4, p < 0.001) [5].

The risk of adverse events between the two groups (45.8% control vs 54.2% Lianhua) was not significantly different (p > 0.05) (RR 0.8, 95% CI 0.7 to 1.1). The adverse events reported were abnormal liver function, renal dysfunction, headache, nausea, vomiting, diarrhea, and loss of appetite [5].

Recommendations from Other Groups

In the latest version of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the National Health Commission & State Administration of Traditional Chinese Medicine, lianhua qingwen capsules are recommended for the treatment of fatigue and fever [8].

Research Gaps

A larger sample size is warranted to support the effectiveness of Lianhua in alleviating the symptoms associated with COVID-19. Other important outcomes such as mortality, length of hospitalization, and need for mechanical ventilation should also be explored in future studies. The optimal dosing and duration of Lianhua can also be determined along with its potential use to prevent infection and transmission of COVID-19.

There are currently 5 ongoing studies including 2 systematic reviews and meta-analysis (PROSPERO registration numbers: CRD42020180877 and CRD42020190757), 2 randomized controlled trials (clinicaltrials.gov identifier number NCT04433013, ChiCTR2000029433), and 1 retrospective study (ChiCTR2000035046). All of them explore the therapeutic effects of Lianhua against COVID-19.

References

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Appendix 1: Characteristics of Included Studies

	Study design	Population (n)	Inclusion criteria	Exclusion criteria	Intervention	Outcomes
Hu K et al, 2020	multicenter, randomized controlled, open-label	Patients more than 18 y.o. with COVID-19 (n = 284)	Laboratory-confirmed cases with Covid-19; being symptomatic (either having fever, coughing, or fatigue) plus radiologic abnormalities consistent with pneumonia; patients aged 18 years or greater of either sex.	respiratory tract bacterial infections due to primary or secondary immunodeficiency, congenital respiratory malformation, congenital heart disease, gastroesophageal reflux, and lung malformation; asthma or other chronic airway diseases needing maintenance therapy, acute respiratory tract bacterial infection (i.e., bronchiectasis, tonsillitis, bronchitis, rhinosinusitis, otitis media), severe pulmonary interstitial diseases; severe pneumonia needing mechanical ventilation; severe systemic diseases (i.e., malignancy, autoimmune diseases, liver or renal diseases) or surgeries (splenectomy, organ transplantation) that in the judgement of the investigators could affect the assessment of efficacy; women during pregnancy or lactation; participation in clinical trials within 3 months; known allergies to the investigational medications; other conditions judged by the investigators.	routine treatment; Lianhua plus routine treatment (oxygen therapy, antiviral medications, symptomatic therapies)	primary endpoint: rate of symptom recovery secondary endpoint: time to symptom recovery, rate of and time to recovery of individual symptoms, proportion of patients with improvement on chest CT, proportion of patients with clinical cure, timing and rate of conversion of SARS-CoV-2 RNA assay, adverse events

Yao, Liu, Huang & Cai, 2020	retrospective analysis of clinical records	Patients who were more than 18 y.o. confirmed as novel coronavirus-infected pneumonia (NCIP) by positive nucleic acid test of sputum, throat swab, and secretion of lower respiratory tracts (n = 42)	Common inpatients aged over 18 years and met the diagnostic criteria of ordinary NCIP	severe and critically severe NCIP patients; acute respiratory diseases not caused by 2019-nCoV; any other chronic respiratory diseases, respiratory bacterial infections such as suppurative tonsillitis, acute tracheal-bronchitis, sinusitis, otitis media and other respiratory diseases that affect clinical trial evaluation; asthma patients requiring daily treatment with serious pulmonary interstitial lesions, bronchiectasis and other basic pulmonary diseases confirmed by chest x-ray and computed tomography; accompanied by basic diseases such as serious primary immunodeficiency disease, acquired immunodeficiency syndrome, congenital respiratory tract malformation, congenital heart disease, lung dysplasia and so on.	basic treatment [recommended treatment of Prevention and Control Plan of the Pneumonia Caused by the Novel Coronavirus (Trial) issued by National Health Commission of China]; basic treatment + lianhua qingwen granules (1 packet thrice a day)	disappearance rate of main symptoms (fever, asthenia and cough); disappearance time of fever; disappearance rate of other individual symptoms between the treatment group and the control group
Xiao et al, 2020	single site, randomized, controlled, non-blinded	Diagnosed cases of COVID-19 (n = 182)	diagnosed cases of COVID-19 meeting the diagnostic criteria; 18–85 years old, regardless of sex; provided informed consent.	clear evidence of bacterial infection; severe primary diseases, such as heart, kidney, lung, endocrine, blood, metabolism, or gastrointestinal tract diseases, which may affect the patient's participation in the trial or affect the outcome of the study; family history of mental illness or previous mental illness; allergies or multiple drug allergies; pregnant or lactating women	one bag of Lianhua Qingwen granules thrice a day + Western medicine; one bag of Huoxiang Zhengqi dropping pills twice a day + one bag of Lianhua Qingwen granules thrice a day + Western medicine; Western medicine	main outcome measure: clinical symptom improvement and disappearance rates after 14 days of treatment secondary outcome: proportion of patients who progressed to severe status

Appendix 2: GRADE Evidence Profile

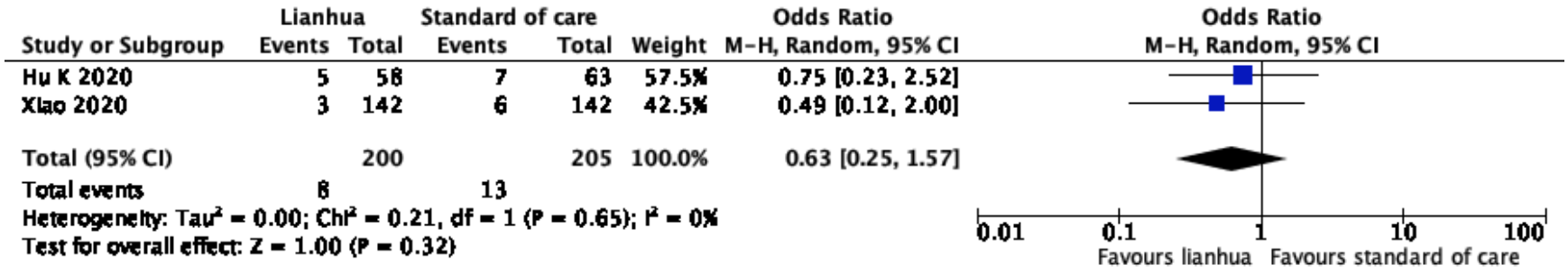
Summary of findings					Quality of evidence (GRADE)				
Outcome	**Number of patients**		**Relative effect (95% CI)**	**Number of participants (studies)**					
	Placebo or standard of care	**Lianhua and standard of care**			**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
Mortality	Not reported	Not reported	-	-	-	-	-	-	-
Development of ARDS	Not reported	Not reported	-	-	-	-	-	-	-
Length of hospitalization	Not reported	Not reported	-	-	-	-	-	-	-
Need for mechanical ventilation	Not reported	Not reported	-	-	-	-	-	-	-
Clinical deterioration	13/205	8/200	0.63 (0.25 to 1.57)	405 (2 RCTs)	Very serious[a]	Not assessed	Not serious	Very serious[d]	Very low
Rate of symptom recovery at Day 14	117/142	130/142	MD 9.2 (1.3 to 17.1)	284 (1 RCT)	Very serious[a]	Not assessed	Not serious	Not serious	Low
Time to symptom recovery [median, (IQR)]	10 (9-11)	7 (6.0-8.0)	HR 1.7 (1.3 to 2.2)	284 (1 RCT)	Very serious[a]	Not assessed	Not serious	Not serious	Low
Time to recovery for individual symptoms [median, (IQR)]									
Fever	3 (2-3)	2 (1-2)	HR 1.4 (1.0 to 1.9)	284 (1 RCT)	Very serious[a]	Not assessed	Not serious	Serious[c]	Very low
Fatigue	6 (4-8)	3 (3-5)	HR 1.8 (1.3 to 2.5)	284 (1 RCT)	Very serious[a]	Not assessed	Not serious	Not serious	Low
Cough	10 (9-11)	7 (5-7)	HR 1.7 (1.3 to 2.2)	284 (1 RCT)	Very serious[a]	Not assessed	Not serious	Not serious	Low
Rate of clinical recovery	94/142	112/142	MD 12.7 (2.3 to 22.7)	284 (1 RCT)	Very serious[a]	Not assessed	Not serious	Very serious[b]	Very low

Rate of improvement/disappearance of symptom at Day 14									
Fever	18/18[d] 12/21[e]	24/24[d] 18/21[e]	RR 1.00 RR 0.67 (0.44-1.00)	182 (1 RCT) 42 (1 non-RCT)	Very serious[a] Very serious[a]	Not assessed Not assessed	Not serious Not serious	? ?	Low
Diarrhea	8/8[d] 2/3[e]	8/8[d] 3/5[e]	RR 1.00 RR 1.11	182 (RCT) 42 (1 non-RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Nausea	6/6[d] 2/4[e]	14/15[d] 2/3[e]	RR 0.94 (0.84-1.06) RR 0.75 (0.21-2.66)	182 (1 RCT) 42 (1 non-RCT)	Very serious[a] Very serious[a]	Not assessed Not assessed	Not serious Not serious	? ?	Low
Loss of appetite	15/17[d] 2/12[e]	20/21[d] 4/11[e]	RR 1.08 RR 0.46	182 (1 RCT) 42 (1 non-RCT)	Very serious[a] Very serious[a]	Not assessed Not assessed	Not serious Not serious	? ?	Low
Tiredness	24/30[d] 4/13[e]	27/32[d] 5/12[e]	RR 1.04 RR 0.74	182 (1 RCT) 42 (1 non-RCT)	Very serious[a] Very serious[a]	Not assessed Not assessed	Not serious Not serious	? ?	Low
Sore limbs	12/14[d]	18/18[d]	RR 1.01 (0.83-1.23)	182 (1 RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Chest tightness and shortness of breath	18/23[d]	25/33[d]	RR 0.96	182 (1 RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Cough	31/34[d] 1/18[e]	25/32[d] 7/15[e]	RR 0.95 RR 0.12	182 (1 RCT) 42 (1 non-RCT)	Very serious[a] Very serious[a]	Not assessed Not assessed	Not serious Not serious	? ?	Low
Muscle pain	2/7[e]	4/6[e]	RR 0.43	42 (1 non-RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Expectoration	1/11[e]	9/14[e]	RR 0.14	42 (1 non-RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Rhinobyon	0/0[e]	1/3[e]	NA	42 (1 non-RCT)	Very serious[a]	Not assessed	Not serious	?	Low

Running nose	0/0[e]	1/3[e]	NA	42 (1 non-RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Pharyngalgia	1/3[e]	1/3[e]	RR 1.00	42 (1 non-RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Anhelation	0/5[e]	7/9[e]	NA	42 (1 non-RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Chest distress	2/9[e]	5/7[e]	RR 0.31	42 (1 non-RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Dyspnea	1/2[e]	1/2[e]	RR 1.00	42 (1 non-RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Headache	0/1[e]	2/4[e]	NA	42 (1 non-RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Vomiting	0/0[e]	3/4[e]	NA	42 (1 non-RCT)	Very serious[a]	Not assessed	Not serious	?	Low
Rate of recovery of chest CT manifestations	91/142	119/142	MD 19.7 (9.6 to 29.4)	284 (1 RCT)	Very serious[a]	Not assessed	Not serious	Serious[b]	Very low
Conversion rate of viral assay	101/142	109/142	MD 5.6 (-4.6 to 15.7)	284 (1 RCT)	Very serious[a]	Not assessed	Not serious	Very serious[d]	Very low
Timing to viral assay conversion [median, (IQR)]	12 (10-13)	11 (8-12)	HR 1.2 (0.9 to 1.6)	284 (1 RCT)	Very serious[a]	Not assessed	Not serious	Serious[c]	Very low
Adverse events	65/142	77/142	RR 0.84 (0.67- to 1.07)	284 (1 RCT)	Very serious[a]	Not assessed	Not serious	Serious[c]	Low

[a]downgraded for unclear allocation concealment, unblinded participants and investigators
[b]downgraded for wide CI
[c]downgraded for crossing line of null effect
[d]after 14 days
[e]duration of follow up not reported
[f]downgraded for wide CI, crossing line of null effect

Appendix 3: Forest Plots



Appendix 4: Characteristics of Ongoing Studies

Study authors (year)	Study design	Population	Intervention	Control	Outcome
Zhang et al. (2020)	systematic review and meta-analysis	Patients diagnosed with COVID-19 of any age, gender, and racial group; randomized controlled trials	lianhua qingwen capsule or granule	external treatment, placebo, no intervention or other pharmacological intervention	primary outcome: severe type conversion rate secondary outcome: proportion of participants with fever, proportion of participants with 1 or more adverse events, health-related quality of life.
Liu et al. (2020)	systematic review and meta-analysis	Participants with COVID-19 without life-threatening manifestations; randomized trials, randomized controlled, or prospective controlled clinical trials	lianhua (capsules, granules, or other types) alone or paired with other routine western medicine	placebo or routine western medicine therapy	primary outcomes: total efficacy, primary clinical symptoms (fever, cough, fatigue), and number of patients who had any adverse events at the end of treatment and the end of follow-up secondary outcomes: chest computed tomography manifestations, rate of conversion to severe cases, and secondary clinical symptoms (expectoration, chest tightness, loss of

					appetite, and shortness of breath) from baseline to endpoint
Yan et al. (2020)	randomized controlled trial	lab-confirmed, mild COVID-19 patients, 21 y.o. and older	lianhua qingwen capsules, 4 capsules, 3 times a day	placebo capsules, 4 capsules, 3 times a day	primary outcome: seroconversion rate secondary outcome: time taken for relief of clinical symptoms , proportion of participants progressing to moderate or severe illness, proportion of participants who test positive for COVID-19 with Ct value > 30
Shuolong et al. (2020)	randomized controlled trial	suspected and diagnosed non-severe COVID-19 patients, 18 y.o. and older	lianhua qingwen capsules/granules, 4 capsules/time or 1 bag/time, 3 times a day	routine treatment	primary outcome: clinical symptoms (fever, weakness, cough) recovery rate and recovery time, secondary outcomes: single symptom disappearance rate and main symptom disappearance time, proportion of aggravation during treatment (in line with the definition of

					severe or critical illness in the treatment scheme), rate of CT improvement, disease recovery rate, routine blood test, biochemical Indicators
Zhiyong et al. (2020)	Retrospective study	Lab-confirmed COVID-19 patients, 18 y.o. and older	lianhua qingwen capsule	usual treatment	primary outcomes: hospital discharge, death, secondary outcomes: laboratory examinations, chest CT