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Role of herbal medicines in the management of patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials

Ansul Kumar [a], Arpita Rai [b], Mohd Saif Khan [c], Amit Kumar [d], Zeya Ul Haque [a, *], Mohammad Fazil [e], Gulam Rabbani [f]

[a] Rajendra Institute of Medical Sciences (RIMS), CTVS Department, Bariatu, Ranchi, 834009, India
[b] Oral Medicine and Radiology, Dental Institute. Rajendra Institute of Medical Sciences (RIMS), Bariatu, Ranchi, 834009, India
[c] Critical Care Medicine, New Trauma Centre & Central Emergency, Rajendra Institute of Medical Sciences (RIMS), Bariatu, Ranchi, 834009, India
[d] Rajendra Institute of Medical Sciences (RIMS) Dept of Lab Medicine, Bariatu, Ranchi, 834009, India
[e] Hakim Ajmal Khan Institute of Literary and Historical Research in Unani Medicine, CCRUM, Jamia Millia Islamia Campus, New Delhi, 110025, India
[f] CHC-Karra, Khunti, Jharkhand, 835209, India

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ABSTRACT

Background and aim: The management of the worldwide spreading COVID-19 consists of amelioration of its symptoms but no cure is yet available. Herbal medicines supplemented with the Western medicine have been applied for COVID-19 treatment in India, China, Iran, and other countries. This systematic review and meta-analysis of RCTs evaluates the effect and safety of herbal intervention in the management of COVID-19.

Experimental procedure: RCTs from databases like PubMed, Cochrane Library, ScienceDirect, Google Scholar, Science Direct, CTRI, AYUSH Research Portal, India, were reviewed and the data were extracted for study sample demographics, intervention details, clinical effect, inflammatory markers and safety monitoring. Outcomes were expressed as Risk-ratio (RR) with 95% CI for dichotomous data, and Mean-Difference (MD) with 95% CI for continuous data.

Result and conclusion: From the 32 eligible studies, a total of 3177 COVID-19 patients were included in the review. Herbal intervention as an adjuvant to Western medicine causes significantly higher improvement compared to Western medicine alone [Fever (RR = 1.09 CI 1.03, 1.15), Cough (Risk-Ratio = 1.22 CI 1.08, 1.37), Fatigue (Risk-Ratio = 1.27 CI 1.11, 1.44), Chest CT Improvement (Risk-Ratio = 1.15 CI 1.08, 1.23)]. The laboratory parameters were also better in the herbal medicine group compared to standard care group only WBC (MD = 0.36 CI 0.16, 0.55), Lymphocyte percentage (MD = 5.48 CI 3.05, 7.92), Absolute lymphocyte count (MD = 0.23 CI 0.07, 0.39), CRP (MD = −5.66 CI -7.96, −3.37). However, duration of hospital stays (MD = −1.82 CI -3.84, 0.21); IL-6 (MD = −3.67 CI -8.76, 1.43), ESR Level (MD = −10.38 CI -25.96, 5.21) were statistically insignificant. No significant adverse events for herbal medications were noted in the included RCTs, during the time of the studies. (n = 665, RR 0.93; 95% CI 0.76, 1.14).

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1. Introduction

In December 2019, an incidence of a sudden outbreak of pneumonia-like illness occurred at Wuhan, Hubei Province in China, that becomes a pandemic in a very short duration. On screening, Chinese researchers isolated a novel coronavirus by January 2020 and termed it as 2019-NCoV or SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).[1] This infectious disease

* Corresponding author.
E-mail addresses: docansul@gmail.com (A. Kumar), arpita.dirims@gmail.com (A. Rai), drsaif2k2@gmail.com (M.S. Khan), amits52003@gmail.com (A. Kumar), zeya486@gmail.com (Z.U. Haque), fazildr@gmail.com (M. Fazil), rabbani120186@gmail.com (G. Rabbani).

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List of abbreviations

ADR	Adverse Drug Reaction
AEs	Adverse Events
CHM	Chinese Herbal Medicine
CI	Class Interval
CTRI	Clinical Trials Registry- India
JHQG	Jinhua Qinggan granules
KFT	Kidney Function Test
LFT	Liver Function Test
LHQW	Lianhua Qingwen granules
MD	Mean Difference
RCT	Randomized Controlled Trial
RR	Risk Ratio

has widespread symptoms that range from asymptomatic patient to normal flu symptoms such as cough, sore throat, fever, headache, body ache, dyspnea, acute respiratory distress syndrome. Some patients also reported gastrointestinal problems, abdominal pain and diarrhea. COVID-19 patients may present with a severe viral infection, a weakened immune status, and ultimately developed profound cytokine storms, pulmonary fibrosis lesion, and multi-organ failure; which ultimately become fatal that lead to death.[2]

Due to the severity of this outbreak and rapid outspread globally, WHO on January 31, 2020, announced it as a global health emergency.[3] In February 2020, WHO termed this as coronavirus disease 2019 (COVID-19). In March 2020, WHO declared it a pandemic situation [Fei Zhou]. As per data stated by WHO on Jan 6, 2022 about 296.4 million COVID-19 cases are reported globally, including 5.46 million deaths.[4]

Several treatment modalities have been attempted to treat COVID-19. These consist of RNA-dependent RNA polymerase inhibitors medications that include Remdesivir, Ribavirin Favipiravir; Protease inhibitors which include Lopinavir/ritonavir; endosomal acidification inhibitors (azithromycin, Chloroquine, hydroxychloroquine); Monoclonal or polyclonal antibodies; Adjunctive treatments (Tocilizumab) for decreasing IL-6 in cytokine storm, viral exocytosis inhibitors (Interferon-a 2a, Interferon-b 1b); convalescent plasma transfusion therapy; herbal medications based on historical documents and evidence of the SARS Association.[3,5]

1.1. Pharmacological agents for COVID-19 management

Preliminary research suggests that some medications may be effective in preventing and improving core symptoms of COVID-19**.** Although Remdesivir has shown certain beneficial effects in patients with severe COVID-19, is reported for various adverse events like increased hepatic enzymes, diarrhea, rash, hypotension, renal impairment, multiple organ dysfunction syndrome, and septic shock.[6] Apart from that, various health organizations among the globe including WHO have changed their guidelines regularly to include pharmacological agents which have some evidence to demonstrate effectiveness in COVID-19 management and exclude those which have not been supported by the current body of evidence. For instance, Lopinavir, ritonavir, umifenovir, hydroxychloroquine, interferon-beta etc., failed to show high quality evidences for beneficial effect in viral clearance, and disease progression.[7] It is not yet known whether remdesivir, ivermectin, and other drugs will bring significant benefits to patients. However, corticosteroids and IL-6 inhibitors demonstrated significant and consistent clinical benefits in severe COVID-19 patients.[8]

Herbal intervention is defined as a phytopharmaceutical preparation derived exclusively from a whole plant or parts of the plant (flower, leaves, bark, stem, rhizome, root) or its exudates (resins, latex, gums) It is used either in a crude form or as a purified pharmaceutical formulation such as extracts, juice, dried powder, decoction etc., following the procedures of distillation, extraction, filtration, and so on. These are rich source active metabolites, alkaloids and flavonoids responsible for its pharmacological activity.[9]

Pharmacological action of the herbal formulations or drugs are due to their active phytochemical constituents such as alkaloids, flavonoids, terpenoids, phenols, polyphenols, tannins, saponins, polysaccharides, proteins, lipids and peptides. The used herbal drugs have antipyretic, anti-inflammatory, expectorant, anti-asthmatic, antitussive, and antiviral properties that holds numerous functions against invasion, penetration, reproduction and expression of the virus. For example, *Allium cepa*, *Aloe vera*, *Azadirachta indica, Cannabis sativa, Curcuma longa, Glycyrrhiza glabra, Nyctanthes arbortristis, Ocimum sanctum, Withania sominifera, Zingiber officinale* are potential inhibitors of SARS-CoV-2 proteases.[10]

Herbal drug formulations are prepared by standardized process provided in herbal drug pharmacopoeia managed by the government agency. The GMP (Good Manufacture Practice) regulations are followed to ensure the quality of these drugs.[11]

Herbal medicines have been actively used as complementary medicine treatments of COVID-19. Many countries have conducted clinical trials and research studies on COVID-19 to find a cure as quickly as possible. A major part of these studies also included herbal medicine as an adjuvant along with Western medicine or alone and reported somewhat better results. In India, more than half of the COVID-19 related studies registered are from herbal medications.[12]

The traditional system of medicine in China, India, and Iran recommends certain herbal formulation for the prevention, management, and recovery from certain diseases, including the COVID-19.[3,10]

It is estimated that about four billion people (80% of the world's total population) in developing countries depend on herbal medicines as primary health care.[9] About 25,000 herbal formulas and extracts have been used in traditional medicines in the South Asian subcontinent.[10] In China, approximately 40% of total healthcare services relies on herbal drug. Acceptance and use of herbal medicines are expanding at much faster rate in developed countries like, UK and other European nations, North America and Australia.[11]

Several COVID-19 Guideline's versions for Diagnosis and Treatment (COVID-19 GDT) were issued by the National Health Commission of China. In its 3rd issue, it is recommended to use Chinese herbal decoctions to treat COVID-19. Subsequently, few patent Chinese herbal medicines such as Jinhua Qinggan granules (JHQG), Lianhua Qingwen granules (LHQW), have also been suggested for COVID-19 management.[13] Qingfei Paidu Decoction is another herbal formula used in China to treat patients with COVID-19. Dried Ginger, Hegan Mahuang Decoction and Qingfei Touxie Fuzheng Decoction can effectively treat SARS-CoV-2 as per trial results in China.[3]

Recently, the Ministry of AYUSH, India (Ayurveda, Yoga, Unani, Siddha, and Homeopathy) recommended using the herbal decoction so-called Kadha as an immune booster and relieve the symptoms caused during the COVID-19 pandemic.[3] Molecular binding studies have shown that several phytochemicals found in traditional Ayurvedic kadha can have high affinity (lower binding energy) for a variety of macromolecular and viral targets, host mediators, including different SARS-CoV-2 viral proteins and human ACE2 and Furin proteins.[14]

The common mechanism of action of plant extracts is thought to be inhibition of viral replication, but some studies have shown that common plant extracts can bind important viral proteins associated

with viral pathogenicity. Plant extracts and other active components of Rheum officinale, Polygonum multiflorum inhibit the bindings of SARS-CoV (S) spike protein with angiotensin-converting enzyme 2 (ACE2). Similarly, Methanolic extract of Dioscorea batatas and Cibotium barometz reported SARS-CoV 3CLpro inhibition activity.[3]

From the beginning of COVID-19 infection, a large number of clinical studies have reported and highlighted the benefits of herbal remedies for COVID-19 management. Also, numerous systematic reviews have been conducted to evaluate the efficacy of herbs in the treatment of COVID-19, including evidence from various case reports, case series, and observational studies. However, randomized controlled trials deliver the uppermost level of evidence in the case of clinical trials. This review focused on the assessment of the efficacy and side effects of herbal medicine supplementation with Western medicine in the treatment of COVID-19, through screening of available randomized controlled trials (RCT). We included study from India, Iran and China for this assessment. Also, multiple herbal formulations in the management of COVID-19 patients were evaluated for effectiveness and safety.

2. Methods

2.1. Study registration

The protocol of this review was first registered with the International prospective register of systematic reviews (PROSPERO) with the Registration number CRD42021244675 available at https://www.crd.york.ac.uk/prospero. The review was conducted according to the PRISMA guidelines.

2.2. Search strategy

Database: The search was performed in the following electronic database specified below. PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase and Allied and Complementary Medicine Database (AMED). We had also manually searched the National Institute of Health and Clinical Trials Database (http://www.ClinicalTrials.gov/), WHO's International Clinical Trials Registry Platform (https://www.who.int/ictrp/en/), Clinical Trials Registry - India (http://www.ctri.nic.in), Science Direct, AYUSH Research Portal (http://www.ayushportal.nic.in) and Google Scholar for any ongoing clinical trials. Search terms were reviewed constantly to ensure that they reflect any terminology changes in the topic area or the databases. The timeframe considered was January 1, 2020 to April 30, 2021.

Language: English only.

Searching Terms utilized: (“COVID-19″ OR “SARS-CoV-2″ OR “NCOV” OR ″2019 NCOV” OR “Severe Acute Respiratory Syndrome Coronavirus 2″ OR “Coronavirus disease 2019”) AND (“herbal medicine” OR “herbal” OR “alternative medicine” OR “traditional medicine” OR “complementary medicine " OR “Unani” OR “Ayurveda”)

2.3. Eligibility criteria

2.3.1. Inclusion criteria

Only RCTs and quasi-RCTs articles that reported the effect of herbal interventions on COVID-19 disease were selected.

2.3.2. Exclusion criteria

Observational, cohort, crossover trials, case reports, case series, non-RCT, preclinical studies such as in-vitro trials and studies on animal models and experimental studies, in silico drugs trials were excluded.

2.3.3. Participants/population

Participants of all ages with diagnosed COVID-19 disease confirmed through Reverse transcription-polymerase chain reaction (RT-PCR) testing. There were no restrictions for gender, age or ethnicity.

2.3.4. Intervention(s)

Clinical Trial studies with the intervention of any forms of herbal medications were included. There was no limitation for the type of herbal medications, the dosage, and duration of treatment. Studies with non-herbal medicine interventions were excluded. Non-clinical studies/reports like reviews, letters, opinions and comments were omitted.

2.3.5. Comparison

There was no restriction for the type of comparators. Included comparator groups were included: herbal intervention versus no intervention, herbal medicine versus placebo, herbal medicine versus conventional medicine/routine treatment, herbal medicine plus conventional medicine/routine treatment versus conventional medicine/routine treatment. Trials that compare herbal medicine with other forms of herbal interventions were excluded.

2.3.6. Outcome

The primary outcome was the COVID-19 symptom disappearance rate and duration for RT-PCR negativity. There were no restrictions in secondary or additional outcomes. Clinical outcomes included were effect on fever, cough, sore throat, chest pain, fatigue, length of hospital stay. Biochemical and laboratory outcomes included changes in Blood test values, e.g., WBC counts, Lymphocyte cell counts, Lymphocyte percentage, CRP level, ESR-level, IL-6 levels. Radiological outcomes include changes on chest CT scan.[15] Any side effects or adverse event reported in RCTs were also assessed.

2.4. Literature screening and data extraction

An in-depth search was done as per the search strategy described above. A simultaneous search of related trials and reviews was performed for other eligible RCTs. All the irrelevant, ineligible, or duplicate articles were removed from the analysis.

2.4.1. Data extraction

All the data from the eligible studies were extracted in a Microsoft Excel sheet by the two authors autonomously (AR, ZH) and revised by the two authors (AK, MSK). The data which was extracted were following: first author's name, year of publication, country, design, sample population and sample size, patient's age, and sex, intervention and control details (forms, dosage, and duration), outcome characteristics, safety monitoring with the reporting of adverse events. All evaluations were carried out autonomously by the authors (AK, ZH), and any discrepancies if occurred were resolved through discussions with another author (AR).

2.5. Assessment of risk of Bias

The risk of bias of the RCTs included in the review was assessed by the Cochrane Risk of Bias Tool for Randomized Controlled Trials. The risk of bias assessment includes the following areas: random sequence preparation, allocation concealment, participants blinding, blinding of outcome assessor, incomplete outcome data, and selective reporting. The results were obtained using RevMan v5.4.1 software.

2.6. Data analysis

Meta-analysis for the extracted data was performed using Review Manager (RevMan) software v 5.4.1 (Nordic Cochrane Centre, Cochrane Collaboration, Denmark).

For assessment of treatment effect, the mean difference (MD) values with 95% CIs were evaluated for outcomes having continuous data (e.g., symptom scores, Lab investigation values). The risk ratios (RR) values with 95% confidence intervals (CIs) were evaluated for outcomes with dichotomous data (e.g., symptom disappearance rate and effective rate). For pooling the data, the random-effects model was used as the variability between the included studies was taken into consideration. No subgroup analysis was performed in this review.

Assessment of heterogeneity levels of the RCTs included in the review was done applying chi^2 test of heterogeneity with the significance level set at $p < 0.10$ and applied the I^2 statistic after setting significance level $\geq$50%.

3. Results

3.1. Literature search

A total of 455 RCT articles for herbal intervention on COVID-19 were recovered after the databases search, with the search words described above in Search Strategy headings. Additional 21 RCTs were identified through other article references. After duplicate removal, 391 were selected for screening. Of these studies, 208 were either not valid RCTs, prophylactic study, pharmacological studies, in-silico studies, acupuncture, exercise, online health guide programs, healthy control participants, suspected COVID-19 patients, and therefore excluded from the review. Another 136 articles were abstracts-only articles, incomplete or unpublished articles, and therefore excluded. In the remaining 47 studies on COVID-19, 15 studies have inappropriate result data presentation or healthy/suspected participants included/retrospective and therefore these all are excluded. Thus, the current systematic review and meta-analysis include a total of thirty-two RCTs. [Fig. 1].

3.2. Description of included studies

Total 32 RCTs were included in the review that were published in the year 2020 and 2021. The majority of these trials (25 studies) were conducted in China, while the five studies were from India and two from Iran. All included studies have used herbal plus Standard care (Western medicine) or herbal alone as an intervention which was compared with placebo plus Standard care (Western medicine) or only placebo. The sample sizes ranged from 30 to 517, with a total of 3177 COVID-19 patients. The treatment duration varied from 5 to 30 days. Out of 32 studies, 4 studies have not mentioned gender characteristics of the sample.[16–19] Overall, there were 56.96% male and 43.03% female patients. The basic characteristics of the RCTs included in the review are mentioned in Table 1.

The standard treatment or control used in the included RCTs were antiviral drugs, antibiotics, oxygen support, and symptomatic supportive medicines. Ritonavir/Lopinavir, Arbidol, Chloroquine Phosphate, Ambroxol Hydrochloride, quinolone (Moxifloxacin) and cephalosporin, Interferon-α injections, and Ribavirin injections, methylprednisolone was the chief medications used as the Standard care medications. Herbal Intervention used in the studies included were in the form of granules, decoction, tablets/pills, nasal drops and herbal injections and were described in separate table. [See Supplementary Table 1].

3.3. Risk of Bias assessment

These assessment were done using the Cochrane risk of bias tool for randomized controlled trials, which includes adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete

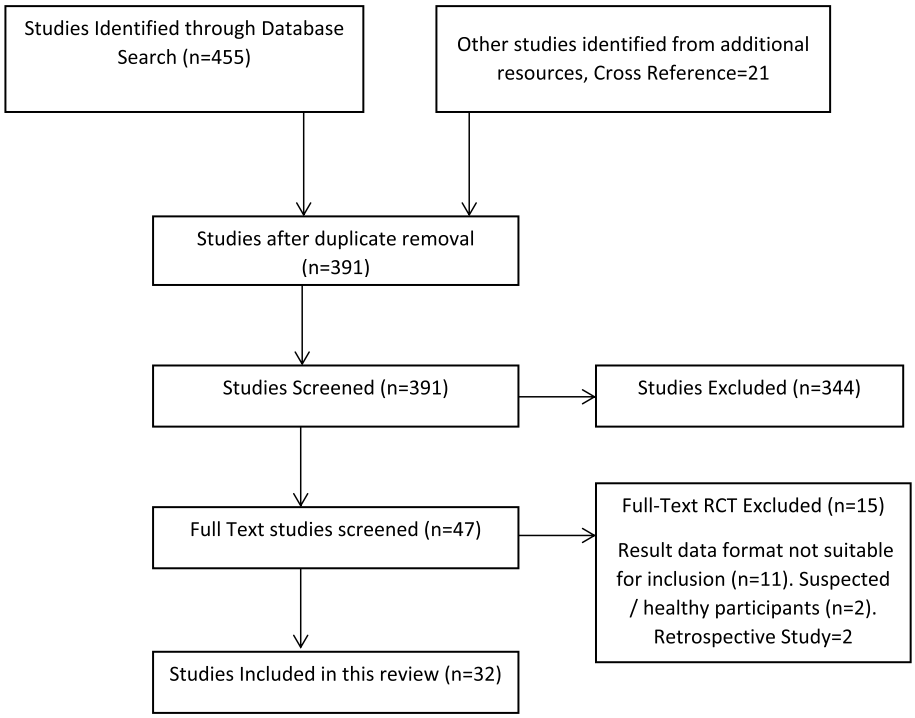

Fig. 1. PRISMA Flow diagram for study selection.

Table 1
Characteristics of included RCTs.

Author	Country, Year	Treatment Duration (Days)	Disease Stage	Sample Size	Male/ Female	Age (Mean ± SD) (I=Intervention, C=Control Group)	Intervention	Control	Outcome Measures	Safety Monitoring & Adverse Event Reporting
Ai XY et al.[45]	China, 2020		Moderate	67	40/27	I:52.33 ± 14.9 C:49.56 ± 16.3	FeiyanYihao Chinese Medicine granules one packet BD plus Standard Care	Standard Care	Disappearance rate of clinical outcomes: Fever, Cough, Fatigue.	Reported No Adverse Events.
Alireza Hashemi Shiri[26]	Iran, 2021	7	Mild, Moderate	72	36/36	I:41.03 ± 15.6 C:43.47 ± 11.3	black myrobalan and mastic and sugarcane (3 g) BD with Standard treatment	Standard Care plus Placebo	Duration of Hospital Stay.	AST, ALT, BUN, Creatinine
Anup Thakar[30]	India, 2020	14	Mild, Moderate	80	53/27	I:40 ± 12.9 C:35.31 ± 11.7	AyUSH-64 and Standard care	Standard Care	Mean Diff. for CRP, ESR Hospital Stay.	Yes (LFT, KFT)
Ding XJ et al.[44]	China, 2020	10	Mild, moderate, severe	100	78/22	I:54.7 ± 21.3 C:50.8 ± 23.25	Qingfei Touxie Fuzheng recipe one packet 2 times a day plus Standard Care	Anti-viral medicine (α-interferon atomization inhalation BD, ribavirin 500 mg BD); cephalosporin, quinolone.	Effect Rate (RR); Disappearance rate of clinical outcomes: Fever, Cough, Fatigue; Chest CT Improvement (RR); Mean Diff. for CRP, IL-6, ESR.	Reported Adverse event
Duan Can et al.[39]	China, 2020	5	Mild	123	62/67	I:51.99 ± 13.88 C:50.29 ± 13.17	Jinhua Qinggan granules, 2 packets TDS for 5 days plus Standard Care	Standard Care medicines (Chloroquine Phosphate 500 mg tablets, Lopinavir/ Ritonavir 200 mg + α interferon, ribavirin injection BD + Arbidol 500 mg tablet TDS)	Disappearance rate of clinical outcomes: Fever, Cough, Fatigue, Sore Throat.	Reported Adverse event
Fu Xiaoxia et al.[42]	China, 2020	10	Mild, Moderate	65	36/29		Toujie Quwen granules, 1 packet BD plus Standard Care	Arbidol 200 mg Tablets + Moxifloxacin 400 mg tablets OD + Ambroxol 30 mg Tablets TDS	Effect Rate (RR); Mean Diff. for duration of Fever, Cough; Chest CT Improvement (RR); Mean Diff. for WBC, Lymphocyte Count, Lymphocyte %, CRP.	Reported No Adverse Events.
Fu Xiaoxia et al. (b)[43]	China, 2020	15	Moderate	73	38/35	I:45.26 ± 7.25 C:44.68 ± 7.45	Toujie Quwen granules, 1 packet BD plus Control Drug	Arbidol HCl 200 mg Tablets + Ambroxol HCl 30 mg Tablets TDS.	Effect Rate (RR); Mean Diff. for WBC, Lymphocyte Count, Lymphocyte %, CRP.	Reported No Adverse Events.
Gang Wang[16]	China, 2020	7	Mild, Moderate	42		I:57.1 ± 14 C:62.4 ± 12.3	Xuanfei Baidu Decoction (XBD) (200 ml BD) for 7 days	Standard Care	Disappearance rate of clinical outcomes: Fever, Cough, Fatigue, Chest pain	Reported No Adverse Events. .
Ganpat Devpura[22]	India, 2021	7	Asymptomatic, Mild	95	77/18	I:33.4 ± 9 C:35.4 ± 10.4	1 g of Giloy Ghanvati, 2 g of Swasari Ras, and 0.5 g each of Ashwagandha and Tulsi Ghanvati; orally BD for 7 days. 4 drops of Anu taila (nasal drop) OD for 7 days	Placebo	RT-PCR (Risk Ratio)	Reported No Adverse Events. .
Govind Ready[24]	India, 2021	30	Asymptomatic, mild	52	36/16	I:43.86 ± 9.97 C:35.22 ± 11.8	AYUSH-64 and Standard care	Standard care	RT-PCR, Clinical Cure Rate, Fever, Cough, Sore throat, Chest pain; Mean diff. for WBC, Lymphocyte %, IL-6, ESR	Yes (LFT, KFT)
Huang H[31]	China, 2020	10	Moderate, Severe	68	30/36	I:60.42 ± 12.84 C:61.16 ± 13.58	CHM plus Standard Care	Standard medicine with antiviral medication (ribavirin, lopinavir/ ritonavir, Arbidol, α-	Disappearance rate of clinical outcomes: Fever; Chest CT	Reported Adverse event

(*continued on next page*)

Table 1 (*continued*)

Author	Country, Year	Treatment Duration (Days)	Disease Stage	Sample Size	Male/ Female	Age (Mean ± SD) (I=Intervention, C=Control Group)	Intervention	Control	Outcome Measures	Safety Monitoring & Adverse Event Reporting
								interferon), antitussive, expectorant, anti-asthmatic drugs (Doxofylline, Ambroxol), moxifloxacin, with symptomatic treatment medicine.	Improvement (RR). RT-PCR (RR); Mean Diff. for WBC, Lymphocyte Count, CRP.	
Jayesh Dutt[17]	India, 2021	7	Mild, Moderate	60		I:33.87 ± 1.94 C:36.67 ± 1.81	Aayudh Advance plus standard Care	Standard care	Hospital Stay, Mean diff. for CRP	Reported No Adverse Events. .
Jin W et al.[21]	China,2020	21	Mild, Moderate	38	20/18		Compound Yin Chai granule + Qingqiao detoxification granule (15 g qid) plus Standard Care	Standard care medicine including antiviral, antibiotics, and symptomatic medicine.	Disappearance rate of clinical outcomes: Fever, Cough, Fatigue; Mean diff. for WBC.	NO
Ke Hu[29]	China, 2021	14	Mild, Moderate	284	150/ 134	I:50.4 ± 15.2 C:51.8 ± 14.8	Lianhuaqingwen capsules plus Standard Care	Standard Care	Effect Rate, Chest CT (RR), RT-PCR (RR); Mean Diff. for duration of Fever, Cough, Fatigue.	Elevated ALT, AST
Liao GR et al.[37]	China, 2020		Mild, moderate, severe	70	37/33	I:60.25 ± 10.39 C:63.16 ± 9.55	Herbal Decoction	Standard Care	Disappearance rate of clinical outcomes: Fever, Cough, Fatigue; Chest CT Improvement (RR).	Reported Adverse event
Liu XG et al.[20]	China, 2020	9	Moderate, Severe	517	288/ 229	I:48.44 ± 2.31 C:48.27 ± 2.45	CHM plus Standard Care	Standard care medicine including antibiotics, antiviral (Ritonavir, lopinavir)	Effect Rate (RR); Mean Diff. for CRP	NO
Qiu M[32]	China, 2020	10		50	27/23	I:53.35 ± 18.35 C:51.32 ± 14.62	CHM plus Standard Care	Standard medicine including Ritonavir, interferon-α, lopinavir.	Chest CT Improvement (RR); Mean Diff. for duration of Fever, Cough.	NO
Qu XK et al.[48]	China, 2020	10	NA	70	41/29	I:40.65 ± 8.23 C:39.82 ± 6.4	Capsule Shufeng Jiedu (2.08 g, TDS) plus Standard Care	Standard care drugs including antiviral medicine (Arbidol), antibiotics (moxifloxacin), expectorant, with symptomatic treatment.	RT-PCR (RR); Mean Diff. for duration of Fever, Cough, Fatigue.	Reported Adverse event
Saeed Sardari[23]	Iran, 2020	7	Not mentioned	83	35/48	I:43 ± 19.3 C:58 ± 17.7	thyme essential oil plus conventional medicine drugs for 7 days	Standard care	Rate of disappearance for clinical outcomes: Cough, Fever, Fatigue, Chest pain, Sore Throat; Mean Diff. for WBC, Lymphocytes %	Yes (KFT)
Shi J et al.[33]	China, 2020	6	Mild, moderate, Severe	67	36/31	I:47.94 ± 14.46 C:46.72 ± 17.4	CHM plus Standard Care	Antiviral medicine (recombinant interferon α-2b, interferon K lopinavir/ ritonavir, darunavir corbita, Arbidol, HCQs), immune-modulatory, γ-globulin, anti-inflammatory drugs, with symptomatic and supportive drugs.	Chest CT Improvement (RR); Mean Diff. for duration of Hospital Stay.	NO
Sun Huimin et al.[38]	China, 2020	14	Mild, Moderate	57	28/29	I:45.4 ± 14.1 C:42 ± 11.7	Lianhua Qingke granules, 1 packet TDS plus Standard Care	Standard Care (Lopinavir/Ritonavir + Alpha interferon injection	Disappearance rate of clinical outcomes: Fever, Cough, Fatigue, Sore Throat, Chest CT Improvement (RR).	NO

Table 1 (*continued*)

Author	Country, Year	Treatment Duration (Days)	Disease Stage	Sample Size	Male/ Female	Age (Mean ± SD) (I=Intervention, C=Control Group)	Intervention	Control	Outcome Measures	Safety Monitoring & Adverse Event Reporting
Umesh Shukla[27]	India, 2020	10	Asymptomatic, Mild, Moderate	30	23/7	I:30.27 ± 8.83 C:32.27 ± 7.35	Guduchighan Vati 500 mg BD	Hydroxychloroquine FOR 5 Days	Disappearance rate of clinical outcomes: Fever, Cough, Sore Throat Time to negative RT-PCR; Mean Diff. for WBC, Lymphocyte %, ESR, IL-6	Yes (LFT, KFT)
WANG Jia-bo[25]	China, 2020	14	Mild, Moderate	47	26/21	I:46.8 ± 14.4 C:51.4 ± 17.6	Keguan-1 plus Standard Care	Standard care	Time Period for Fever; Mean diff. for WBC.	Yes (LFT, KFT)
Xia WG et al.[34]	China, 2020	10	Moderate, Severe, Critical	52	23/29	I:54.18 ± 13.08 C:53.67 ± 12.7	CHM plus Standard Care	Standard care medicine including antiviral medicines (lopinavir/ ritonavir, Arbidol, ribavirin, oseltamivir, α-interferon), antibiotics (levofloxacin, moxifloxacin, penicillin, azithromycin, cephalosporins), with supportive treatment (γ- globulin, methylprednisolone etc.)	Effect Rate (RR); Chest CT Improvement (RR); Mean Diff. for duration of Fever, Hospital Stay.	Reported No Adverse Events.
Xiao Qi et al.[40]	China, 2020	14	Mild, Moderate	200	130/70		Shufeng Jiedu capsule, 4 capsules TDS plus Standard Care	Standard Care (Arbidol Hydrochloride tablets, 200 mg TDS)	Effect Rate (RR); Mean Diff. for duration of Fever, Cough, Fatigue; Chest CT Improvement (RR); Mean Diff. for WBC, Lymphocyte %.	Reported Adverse event
Yang MB[35]	China, 2020	7	Moderate	49	25/24	I:50.35 ± 13.37 C:47.17 ± 16.57	Reyanning mixture formulation (20 ml, BD/QID) plus Standard Care	Standard care medicine including antivirals (ribavirin, lopinavir/ ritonavir, α-interferon, Arbidol)	Chest CT Improvement (RR). RT-PCR (RR); Mean Diff. for Lymphocyte Count, CRP.	NO
Yong-an Ye[28]	China, 2020	7	Mild, Moderate	42	6/35	I:62.5 ± 11.5 C:57.66 ± 14.8	Chinese herbal medicine (CHM)	Standard Care	Mean Diff. for WBC, Lymphocyte Count, CRP, ESR.	Yes (LFT, KFT)
Yu Ping et al.[41]	China, 2020	7	Mild, Moderate	295	171/ 124	I:48.27 ± 9.56 C:47.25 ± 8.67	Lianhua Qingwen granules, 1 packet BD plus Control Drug	Arbidol 200 mg Tablets + Ambroxol 30 mg Tablets TDS + Moxifloxacin 400 mg tablets OD	Effect Rate (RR); Mean Diff. for duration of Fever, Cough; Chest CT Improvement (RR); Mean Diff. for WBC, Lymphocyte Count, CRP.	Reported No Adverse Events.
Zhang CT et al.[19]	China, 2020		Moderate	45			Jiaweidayuan (JW) granules granules, TDS for 7 days plus Standard Care	Standard Care	Chest CT Improvement (RR); Mean Diff. for duration of Fever, Cough, Fatigue; Mean Diff. for WBC, Lymphocyte %, CRP.	Reported No Adverse Events. .
Zhang YL et al.[46]	China, 2020	10	Moderate	120	80/40	I:53.4 ± 13.7 C:52 ± 14.1	Jinyinhua oral liquid 60 mL TDS plus Standard Care,	Anti-viral (lopinavir/ ritonavir 2 capsules BD, α-interferon (5 million Unit) BD, supportive treatment	Effect Rate (RR); Disappearance rate of clinical outcomes: Fever, Cough, Fatigue.	Reported Adverse event
Zhijian Luo[18]	China, 2021	14	Severe	60		I:60.26 ± 15.6 C:56.35 ± 18.3	Xuebijing (XBJ) Herbal IV injection plus Standard Care	Standard Care	Mean Diff. for duration of Fever, Cough, Fatigue, Hosp Stay, Mean	Yes (LFT, KFT)

(*continued on next page*)

Table 1 (*continued*)

Author	Country, Year	Treatment Duration (Days)	Disease Stage	Sample Size	Male/ Female	Age (Mean ± SD) (I=Intervention, C=Control Group)	Intervention	Control	Outcome Measures	Safety Monitoring & Adverse Event Reporting
Zhou WM et al.[36]	China, 2020	14	Moderate	104	60/44	I:52.47 ± 10.99 C:51.11 ± 9.87	enteric-coated herbal capsules containing 150 mg of Diammonium glycyrrhizinate, TDS plus Standard Care	Antiviral drugs (ritonavir/lopinavir) 0.5 g BD	Diff. for WBC, Lymphocyte Count, IL-6, CRP. Effect Rate (RR).	Reported Adverse event

Abbreviations Used in Table.
BD = Twice a day; C= Control Group; CHM= Chinese Herbal Medicine; I= Intervention Group; KFT=Kidney function test; LFT = Liver function test; OD=Once a day; QID = Four times per day; RR = Risk-Ratio; TDS; Thrice a day.

outcome data, and selective reporting.[47] Out of 32 studies, only 20 studies have reported adequate random sequence generation. Seven studies have clearly reported valid allocation concealment.[18,25,26,28,29,39,44] In the remaining 25 studies, two RCTs have high risk because of odd-even number used in allocating groups,[16,22] rest 23 have an unclear risk for allocation concealment. Only three RCTs reported proper blinding.[18,22,26] Improper blinding of the patients and research-staffs were reported in three studies.[19,29,38] The performance bias for 26 studies was unclear. Proper blinding of outcome assessors was reported only in four studies.[18,22,29,39] One study is at high risk,[38] while the other 27 were at unclear risk due to inadequate information on blinding. Risk of bias for incomplete outcome data is unclear for seven studies.[19,21,36,37,43,45,46] On the grounds of having no dropouts and intention-to-treat analysis were performed, other 25 studies have a low risk for attrition bias. The risk of selective reporting was unclear for all studies, due to the lack of evidence for the judgment, and absence of the study protocol for most of the included studies [See Fig. 2 & Fig. 3].

3.4. *Effect of herbal intervention on COVID-19*

3.4.1. *Effect of herbal intervention on RT-PCR negativity*

Seven studies have evaluated the effect of herbal intervention on RT-PCR negativity.[22,24,27,29,31,35,48] The combined treatment with herbal medications and Western medicine showed likely a good effect regarding RT-PCR negativity with effect rate but statistically insignificant (n = 591, RR 1.22, 95% CI 1.00 to 1.44). [See Supplementary Fig. 1.].

3.4.2. *Effect of herbal intervention on clinical symptoms of the COVID-19*

In the present review article, the effect of herbal medication on foremost symptoms like fever, cough, fatigue, chest pain, sore throat, hospital stay of COVID-19 were assessed.

3.4.2.1. Effect on fever. A total of 24 RCTs have evaluated effect of Herbal medicine on cough relief. Twelve studies reported the effect of herbal intervention on fever as the number of patients with decreased body temperature during the protocol treatment period, represented as Risk Ratio.[16,21,23,24,27,31,37–39,44–46] The combination of herbal intervention and Western medicine showed a significant effect with the overall effect rate (n = 850, RR 1.09, 95% CI 1.03 to 1.15). [See Fig. 4 A.]. Eight studies showed the effect of herbal intervention on fever as the number of days to recover from fever[18,19,25,29,32,34,40,48] represented as MD + CI. The combined herbal intervention showed a significant effect with the effect rate (n = 850, MD -1.39, 95% CI -1.76 to −1.03). [See supplement Fig 2].

3.4.2.2. Effect on the cough. Total of seventeen studies have reported the effect on cough. Eleven RCTs[16,21,23,24,27,37–39,44–46] have shown the effect as the number of patients get relief from cough, and the data reported a significant effect as Risk Ratio. (n = 782, RR 1.22 [95% CI 1.08−1.37]; I^2 = 23.5%; p = 0.227) [See Fig. 4B]. Six studies[18,19,29,32,40,48] reported time for relief from cough and the effect is represented as MD + CI. (n = 706, MD -2.00, 95% CI -3.33 to −0.68) [See supplement Fig 3].

3.4.2.3. Effect on chest pain. Three studies[16,23,24] have reported the effect as the number of patients without chest pain after treatment

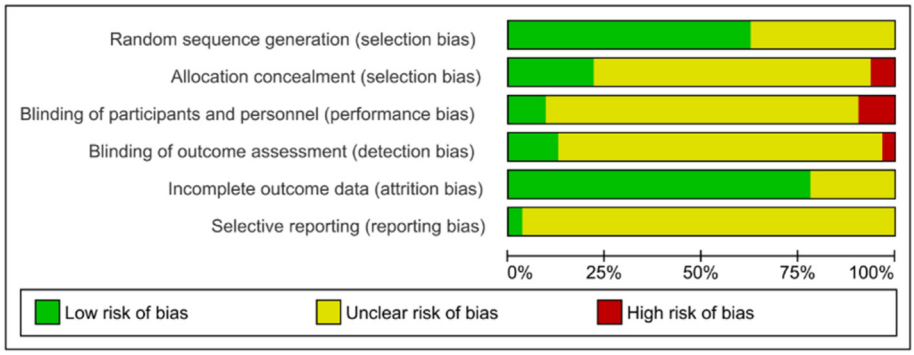

Fig. 2. Risk of bias - Graph.

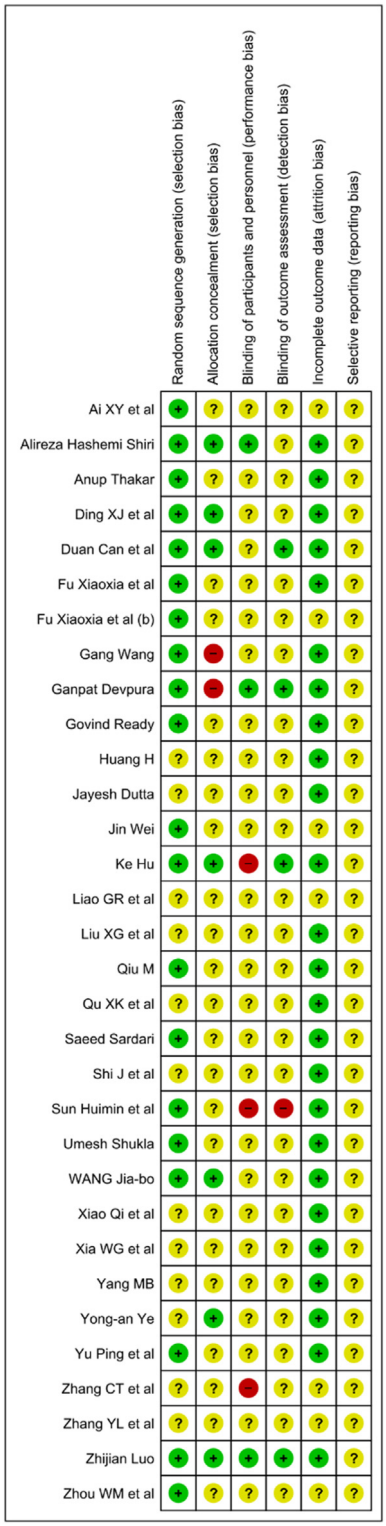

Fig. 3. Risk of bias - Summary.

and were represented with the effect rate (n = 177, RR 1.12 95% CI 0.75–1.48) [See Fig. 4C].

3.4.2.4. Effect on sore throat. Six studies[16,23,24,27,38,39] have analyzed the effect as the number of patients without sore throat after treatment (n = 387, RR 1.09 [95% CI 0.99–1.19]; I^2 = 22.1%; p = 0.268). [See Supplementary Fig. 4].

3.4.2.5. Effect on fatigue. A total of fourteen studies reported the effect of herbal intervention on fatigue. Nine studies[16,21,23,37–39,44–46] have represented the number of patients without fatigue after treatment. and showed a significant effect with the effect rate (n = 700, RR 1.27 [95% CI 1.11–1.44]; I^2 = 19.6%; p = 0.269. Other five RCTs[18,19,29,40,48] have reported the effect as the duration (in days) for relief from fatigue. The net result showed a significant effect with the effect rate represented as MD + CI (n = 656, MD -2.07; 95% CI -3.35, −0.78). [See Supplementary Fig. 5].

3.4.2.6. Effect on chest CT improvement. A total of thirteen studies[19,29,31–35,37,38,40–42,44] have evaluated the effect of herbal intervention as the number of patients having chest CT improvement after treatment. The overall combined effect was significant and represented by Risk Ratio (n = 1402, RR 1.15 [95% CI 1.08–1.23]; I^2 = 29.9%; p = 0.145). [See Supplementary Fig. 6].

3.4.2.7. Effect on the duration of hospital stay. Six studies[17,18,26,30,33,34] have reported the effect of herbal intervention on improvement in number of days for hospital stay. The overall combined effect rate is represented by MD + CI (n = 388, MD -1.82; 95% CI -3.84, 0.21). [See Supplementary Fig. 7A].

3.4.2.8. Effect on the clinical effect rate. Ten studies[20,29,34,36,40–44,46] have evaluated the clinical effect of herbal intervention as the number of patients with improved effect rate. The overall combined effect rate is significant and is represented by Risk Ratio (n = 1810, RR 1.13; 95% CI 1.08, 1.17) [See Supplementary Fig. 7B].

3.4.3. Effect on lab parameters of COVID-19 patients

Several RCTs have evaluated the effect of herbal medicine on different laboratory parameters (e.g., WBC count, Lymphocyte percentage, Absolute Lymphocyte count, CRP, IL-6, and ESR level) in COVID-19 patients.

3.4.3.1. Effect on WBC count. 12 studies[19,21,23–25,27,28,31,40–43] have evaluated the effect of herbal intervention on improvement of WBC as mean increase in WBC count. The net effect is a significant increase shown by MD + CI (n = 1036, MD 0.36; 95% CI 0.16, 0.55) [See Fig. 5A].

3.4.3.2. Effect on absolute lymphocyte count. Seven studies[18,28,31,35,41–43] have evaluated the effect of herbal intervention on absolute lymphocyte count represented as Mean ± SD. The net effect is a significant improvement shown by MD + CI (n = 647, MD 0.23; 95% CI 0.07, 0.39) [See Fig. 5B].

3.4.3.3. Effect on lymphocyte percentage. Seven studies[19,23,24,27,40,42,43] have evaluated the effect of herbal intervention on lymphocyte percentage and the result was represented as a change in Lymphocyte percentage (Mean ± SD). The net effect is a significant improvement shown by MD + CI (n = 548, MD 5.48; 95% CI 3.05, 7.92) [See Fig. 5C].

3.4.3.4. Effect on C- reactive protein. 12 studies[17–20,28,30,31,35,41–44] have reported the effect of herbal intervention on CRP level as Mean ± SD. The net effect is a significant decrease in CRP level after treatment shown by MD + CI (n = 1423, MD -5.66; 95% CI -7.96, −3.37) [See Supplementary Fig. 8].

3.4.3.5. Effect on IL-6 level. Four studies[18,24,27,44] have reported the effect of herbal intervention on IL-6 as Mean ± SD. The net effect was decrease in IL-6 level after treatment but statistically insignificant, showed by MD + CI (n = 239, MD -3.67; 95% CI -8.76, 1.43) [See Supplementary Fig. 9].

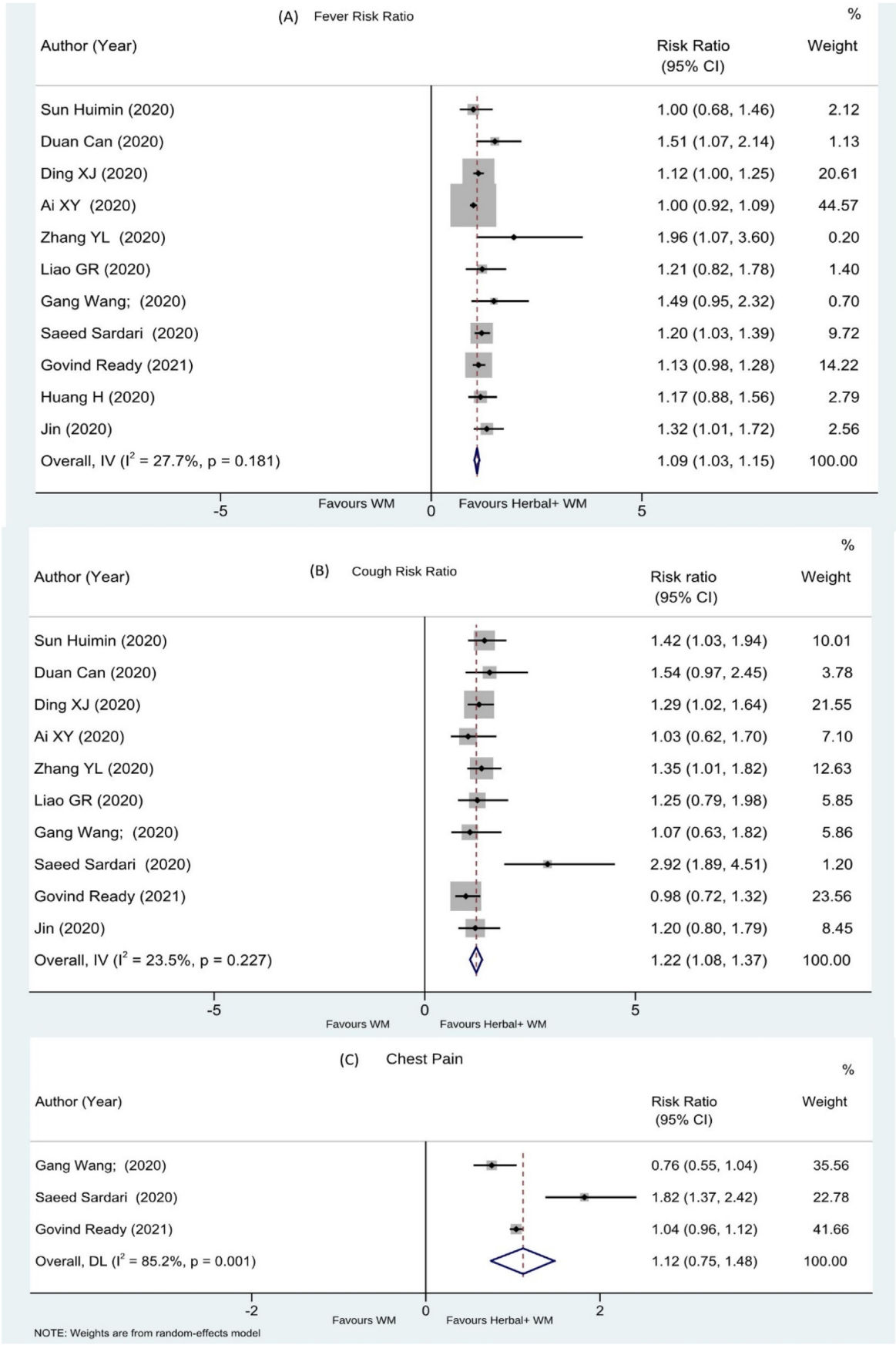

Fig. 4. (A)Fever, (B) cough, (C) chest pain.

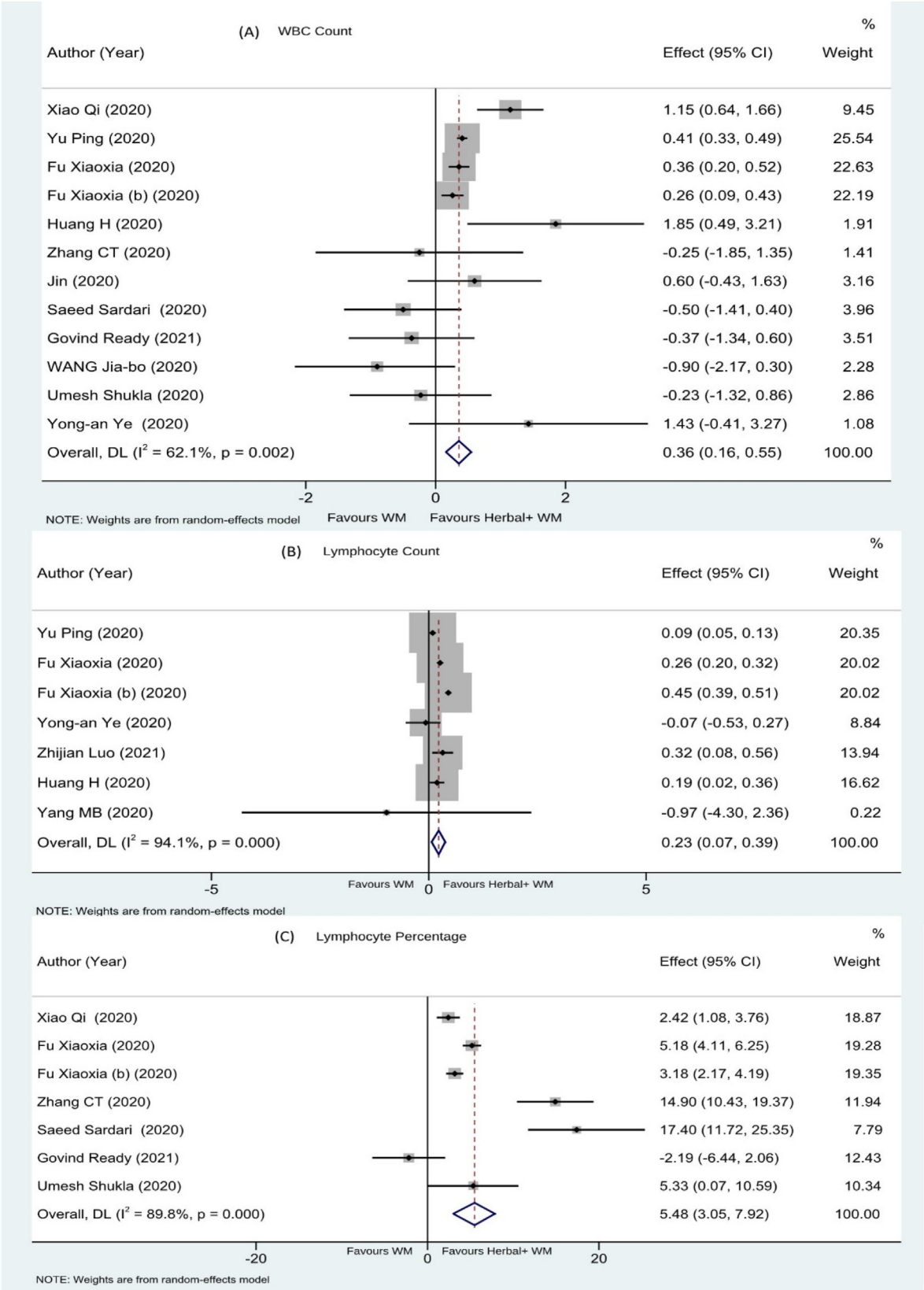

Fig. 5. Effect on (A) WBC, (B) Lymphocyte Count & (C) Lymphocyte percentage.

3.4.3.6. Effect on ESR level. Five studies[24,27,28,30,44] have evaluated the effect of herbal intervention on ESR values represented as mean ± SD. The net effect is a decrease in ESR after treatment but statistically insignificant shown by MD + CI (n = 304, MD -10.38; 95% CI -25.96, 5.21) [See Supplementary Fig. 10].

3.4.3.7. Effect on recovery time. Herbal interventions have shown better effectiveness in shortening the recovery period through early resolution of the main symptoms of COVID-19 like fever, cough, fatigue and hospital stay period as described above in section 3.4.2 of this article.

Thus, the overall result can be summarized as herbal medicine as an adjuvant with the Western medicine have better recovery rate for COVID-19 symptoms like fever, cough, fatigue, chest CT improvement. Also, the laboratory parameters like WBC count, Absolute Lymphocyte count, Lymphocyte percentage, and CRP levels were also better in the herbal medicine group compared to standard care group only. Effect on the duration of hospital stay (MD = −1.82 CI -3.84, 0.21); IL-6 (MD = −3.67 CI -8.76, 1.43), ESR Level (MD = −10.38 CI -25.96, 5.21), and adverse events for herbal medications during the time of the studies (n = 665, RR 0.93; 95% CI 0.76, 1.14) were statistically insignificant.

3.4.4. Assessment of adverse effects

Out of 32 studies, 14 studies[18,29,31,34,36,37,39–44,46,48] have provided data on adverse effects as the number of events in the treatment groups. (n = 665, RR 0.93; 95% CI 0.76, 1.14). (See Supplementary Fig. 11). Another six studies[20,21,32,33,35,38] did not described about the adverse effects of herbal intervention. Six studies[23–25,27,28,30] have reported no significant adverse effect of herbal intervention and also provided laboratory values of LFT, KFT [See Supplementary Table 2]. The remaining RCTs have reported insignificant adverse events in treatment groups but didn't provide any data relevant to that context. The most common occurring ADRs reported in different RCTs were diarrhea, anorexia, nausea, abdominal pain, rashes, deranged LFT and KFT values.

4. Discussion

4.1. Summary of evidence

The current review includes an assessment of thirty-two RCTs involving 3177 patients that reported the effect of the herbal interventions for the COVID-19 management (See Table 1). We have analyzed the effect of herbal intervention on RT-PCR negativity (Supplementary Fig. 1), reduction of clinical symptoms, biochemical and laboratory parameters, radiological changes (chest CT improvement), associated adverse events in COVID-19 patients. This meta-analysis showed a beneficial effect of herbal medicine supplementation with Western medicine in early resolution of fever in COVID-19 patients (Fig. 4A) and the number of cases got relieved from cough (Fig. 4B). Also, fatigue reduction time, total effect rate, WBC count (Fig. 5A), lymphocyte percentage (Fig. 5B), absolute lymphocyte count (Fig. 5C), and CRP level were also better in herbal medicine supplementation group. The various herbal intervention used for management is mentioned in Table 1. The treatment duration for herbal drugs varied from 5 to 30 days which was also a point of consideration. Whether herbal medicine can produce a significant effect in such a short time duration is a subject of concern. If the herbal medications were introduced during early onset of symptoms, or if used prophylactically, the management could be more expeditious by reducing clinical symptoms duration. As a result, in most of the cases, COVID-19 can be efficiently stopped in advancing from mild to a critical stage, thus decreasing duration of hospital stays, and mortality rate.

Regarding the side effects, six studies reported no adverse effects during the treatment period. Fourteen studies[18,29,31,34,36,37,39–44,46,48] reported some adverse events like diarrhea, anorexia, nausea, abdominal pain, rashes, deranged LFT and KFT values but statistically insignificant in the herbal group during the time of studies, which varies from 5 to 30 days for most of the included studies. Another six studies[23–25,27,28,30] have reported no significant adverse effect of herbal intervention and also provided laboratory values of LFT, KFT [See Supplementary Table 2]. No follow ups were done or mentioned in included RCTs for assessment of secondary side effects. The results in the present study suggest that herbal interventions were relatively safe for the management against COVID-19. However, due to the lack of adverse event reporting in some studies, the safety of herbal medications should be recognized and included in more comprehensive evidence.

4.2. Advancement from the preceding systematic reviews

The preceding systematic reviews included studies from case reports, case-control studies, and cohort studies.[49] Some reviews were focused only on case reports and case series,[50] a few reviews reported only single herbal medicine or formulation,[52,54,55] certain reviews focused only on Ayurvedic medicine.[53] Several reviews focused only on Chinese herbal medicine.[2,3,13,51,56–59] In this review, we included RCTs from China, India, and Iran which assessed the effect of different herbal formulations in the COVID-19 patients.

4.3. Limitations of this review

The current systematic review possesses some limitations. First, the RCTs included weren't of superior quality following the Cochrane Review Manual. Out of 32, only 20 studies have reported adequate random sequence generation, 7 studies have reported valid allocation concealment and only 3 RCTs reported proper blinding. Second, this review included articles from the English language only that may enhance the publication bias risk. Third, different studies have reported an event as a different parameter, therefore, there is a variation in assessing the overall effect for an event. Fourth, different herbal formulations were used as the intervention in the included RCTs, and therefore, it is not easy to isolate the specific constituent/formulations which may be the main source of the efficiency of herbal formulations. Fifth, even in the outcomes like the effect on WBC, Lymphocyte count, we have different data for effect assessment such as, mean increase in WBC level, and the number of patients with increased WBC. This may affect the assessment of overall effect of the intervention in studies. Sixth, this review does not explain the pharmacological mechanism of effect of drugs separately.

4.4. Clinical implications

Based on the evidence summarized here, we have noticed more favorable effect in reducing the duration of COVID-19 symptoms (e.g., fever, cough, fatigue), improvement in the effect rate, WBC count, absolute lymphocyte count, lymphocyte percentage, C-Reactive protein level in the patients treated with herbal plus Standard care compared to the patients treated with standard care (Western medication) alone. This signifies that herbal intervention has a good supporting effect in reducing COVID-19 symptoms. Herbal medicines supplemented in combination with Western medicine improves symptoms of COVID-19 earlier than standard care alone. The sooner the symptoms disappear, the less time it will take to recover from the disease. Therefore, it could be an important substitute for better management of COVID-19 disease and reduction of the overall treatment duration.

As per observation in included RCTs, favorable response in COVID-19 management have been reported by use of Maxing Xuanfei Jiedu decoction, Shufeng Jiedu capsule, Jiaweidayuan granules, Lianhua Qingwen granules, Thyme essential oils, Xuebijing (XBJ) Herbal IV injection, Jinhua-Qinggan formulation, Lianhua-Qingke granules, AYUSH-64, Formulation for Pneumonia No. 1, Formulation for Pneumonia No. 2.

The most used single drug in these formulations are Ephedra Herb, Thorowax (Bupleuri) Root, Baical Skullcap (Scutellariae Baicalensis), Liquoric (Glycyrrhizae) Root, Forsythiae Suspensae fruit, Giant Knotweed (Polygoni Cuspidati), Caoguo (Tsaoko) Fruit, Armeniacae Amarum seed, Bitter Apricot (Armeniacae Amarum) seed, Pinellia (Pinelliae Tematae) Rhizome, Root-Rhubarb (Rhei), Honeysuckle (Lonicerae), Balloon Flower (Platycodi), Trichosanthis Fructus, Turmeric (Curcumae Longae) rhizome, Atrina Glass (Patriniae) herb.

4.5. Research implications

Further clinical trials of superior quality (study with an adequate method for random allocation to minimize selection bias, proper blinding of the participants, investigators, statisticians, outcome and result analysts to eliminate detection bias with performance bias) including a large sample of participants are needed to provide stronger evidence of the benefits of herbal intervention along with Western medicine. Additionally, the trial investigators should assess for the core outcome sets development, e.g., COS-COVID-like parameter.[60] This will be enormously helpful in the standard assessment of the effect of herbal medicine. Next, the clinical trial investigating the effects of herbal medications on COVID-19 disease with varying severity of symptoms should be considered; because as the severity varies, the effect will also be quite different. Third, all clinical trials should have assessed the safety and adverse events in detail in the case of herbal interventions. Fourth, it usually requires a long duration of treatment for the effect being produced using herbal medicine; however, the treatment duration reported in the current review was 5–30 days. Therefore, trials with longer treatment courses are recommended to carry out along with extensive follow-up of the participants after the end of the treatment protocol period.

5. Conclusions

The result in this systematic review suggests that the herbal medications as an adjuvant with Western Medicine treatment have add-on beneficial effect and is likely to help in improvement of the core symptoms of COVID-19 disease like (e.g., fever, cough, fatigue), in a relatively shorter period. Improvement in the effect rate, chest CT images, WBC count, absolute lymphocyte count, lymphocyte percentage, C-Reactive protein level are also better. However, due to the lack of high-quality clinical trials and the high grade of heterogeneity in the included studies, a more definite conclusion on the effects of herbal interventions on lowering body temperature and adverse effects could not be assessed at this time. There are some variations between different herbal interventions in the obtained therapeutic effects for the same outcome of COVID-19 disease. The conclusion of this review should be further assessed by thoroughly designed, good sample-sized randomized clinical trials.

Author contributions

AK, AR, and ZH planned the study and designed the PICOs, and initiated screening of the studies. MSK, MF, GR helped in searching, screening, and selection of studies. AR, AK, and ZH has done a statistical analysis, interpreted the study results, and estimated the methodological quality of included clinical studies. AR, ZH drafted the manuscript and produced the tables, figures. AK, MSK, and AK critically revised and finalized the manuscript. The final manuscript has been read, revised, and approved for submission by all authors.

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Author disclosure statement

There is no any competing financial interest.

Declaration of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcme.2022.01.002.

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