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Review Article

Traditional, complementary and integrative medicine for fatigue post COVID-19 infection: A systematic review of randomized controlled trials

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ABSTRACT

Background: Chronic fatigue is a predominant symptom of post COVID-19 condition, or long COVID. We aimed to evaluate the efficacy and safety of Traditional, Complementary and Integrative Medicine (TCIM) for fatigue post COVID-19 infection.

Methods: Ten English and Chinese language databases and grey literature were searched up to 12 April 2023 for randomized controlled trials (RCTs). Cochrane "Risk of bias" (RoB) tool was applied. Evidence certainty was assessed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE). Effect estimates were presented as risk ratio (RR) or mean difference (MD) with 95% confidence interval (CI).

Results: Thirteen RCTs with 1632 participants were included. One RCT showed that Bufei Huoxue herbal capsules reduced fatigue (n=129, MD -14.90, 95%CI -24.53 to -5.27), one RCT reported that Ludangshen herbal liquid lowered fatigue (n=184, MD -1.90, 95%CI -2.38 to -1.42), and the other one RCT shown that fatigue disappearance rate was higher with Ludangshen herbal liquid (n=184, RR 4.19, 95%CI 2.06 to 8.53). Compared to traditional Chinese medicine rehabilitation (TCM-rahab) alone, one RCT showed that fatigue symptoms were lower following Qingjin Yiqi granules plus TCM-rehab (n=388, MD -0.48, 95%CI -0.50 to -0.46). Due to concerns with RoB and/or imprecision, the certainty in this evidence was low to very low. No serious adverse events was reported.

Conclusions: Limited evidence suggests that various TCIM interventions might reduce post COVID-19 fatigue. Larger, high quality RCTs of longer duration are required to confirm these preliminary findings.

Study Registration: The protocol of this review has been registered at PROSPERO: CRD42022384136.

1. Introduction

With the global coronavirus disease (COVID-19) pandemic continuing, the sequalae following acute infection are becoming apparent. Many of those who survived and recovered from COVID-19 suffer from unexpected, persistent symptoms, of which fatigue is one of the most common symptoms. An estimated 50% (95% CI: 10% to 73%) of adults infected with SARS-CoV-2 report persisting fatigue at 4 to 7 weeks from symptom onset[1] and 32% (95% CI: 27% to 37%) experience fatigue for longer than 12 weeks.[2] The real world data reveals that symptoms can last for up to 12 months.[3] However, based on evidence from survivors of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome, it may last longer, as persistent fatigue was reported by some at 18 to 40 months follow-up.[4]

Persistent fatigue after a viral infection is not a new phenomenon. Post-viral fatigue syndrome has been a public health concern for a long time.[5] It is implicated in the pathogenesis of myalgic encephalomyelitis and chronic fatigue syndrome.[6] There is, however, limited understand-

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ing of the pathogenesis of post viral fatigue, including post COVID-19.[7] Currently, a biopsychosocial approach to researching and managing the condition is recommended.[1]

Due to the paucity of high quality research, evidence-based advice on the specific treatment and management of fatigue is scarce. Clinical guidelines mostly rely on the findings of uncontrolled observational studies or apply indirect evidence from other non-COVID conditions with similar presentations such as myalgic encephalomyelitis and chronic fatigue syndrome.[8,9,10] Notably, despite the existence of several systematic reviews,[9,11-14] none of them have included non-English language databases. According to an evidence map of traditional Chinese medicine for COVID-19 prevention, treatment and rehabilitation, it is likely that relevant research was yet to be evaluated.[15]

Therefore, the purpose of this systematic review was to summarize the evidence on the efficacy and safety of traditional, complementary and integrative medicine (TCIM) for managing fatigue post COVID-19 infection.

2. Methods

2.1. Protocol and registration

This systematic review was conducted in accordance with the Cochrane Handbook[16] and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA-2020) statement.[17] The protocol of the review was registered in PROSPERO (CRD42022384136; Available from: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=384136).

2.2. Search strategies

Ten electronic databases were searched from their inception to 12 April 2023. Five were Chinese language databases: Chinese National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Sinomed, Yiigle Database, and Wanfang Database. Five were English language databases: PubMed, EMBase, Epistemonikos, the Cochrane Library, Web of Science Core Collection. The International Clinical Trials Registry Platform (ICTRP) was searched for ongoing trials. The reference lists of included articles and review articles known to the authors were also screened to retrieve potentially eligible studies. The search terms were the following MeSH terms connected with boolean operations, which were broader than respiratory post-viral fatigue syndrome as the research team is also reviewing the literature for all types and causes of pathological fatigue. The database search strategies are reported in Supplement 1.

2.3. Eligible criteria

2.3.1. Type of studies

All types of randomized controlled trials (RCTs), including cluster and cross-over trials, published in English or Chinese languages were included. Quasi-RCTs and non-randomized studies of interventions were excluded due to the importance of focusing on studies with the highest methodological quality to inform decision making.

2.3.2. Type of participants

Included were participants of any age, gender or ethnicity who were experiencing persistent fatigue beyond the acute phase (no more than two weeks) of COVID-19 infection. No restriction was placed on the duration of fatigue or other symptoms, as a consensus is yet to be reached on the required duration of persisting symptoms.[9,10,18]

2.3.3. Type of interventions and comparators

The Cochrane Complementary Medicine Field's operational definition of complementary, alternative, and integrative medicine,[19] the WHO definition of TCIM[20] and the United States National Center for Complementary and Integrative Health definition of complementary, alternative and integrative health[21] were used to decide if an intervention was a TCIM therapy. For instance, vitamins and minerals used to treat deficiencies and rehabilitation interventions designed or provided by conventional practitioners (e.g., physical therapist, physiotherapist, occupational therapist, psychologist, exercise physiologist, personal trainer, health coach etc.) were classified as conventional unless the intervention was clearly a traditional or complementary therapy (e.g. herbal medicines, mind-body therapies). No restrictions were placed on the comparison and administration route or mode of delivery, dose, frequency or settings.

2.3.4. Type of outcomes

Primary outcome measures were: (1) fatigue symptom disappearance rate; (2) fatigue symptom disappearance time; Secondary outcome measures were: (1)fatigue symptom(s) severity evaluated using a single-item or multi-item patient reported outcome measure, including subscales from quality of life measurement tools and investigator - defined tools; (2)fatigue symptom remission rate, where remission is defined as >50% improvement in fatigue severity; and (3) fatigue remission time. (4) adverse events.

2.4. Study selection and data extraction

Title and abstract screening had two phases. First, records were screened for RCTs and SRs evaluating fatigue post respiratory virus infections. These were then rescreened to identify RCTs pertaining to fatigue post COVID-19. Titles, abstracts, and full texts were screened by four authors in pairs independently (XYC, YYZ and JYL, JLW). Any conflicts were resolved through discussion and consultation with the third author (JPL). The extraction data included: (1) basic characteristics of the study, participant, sample size, and interventions; (2) primary and secondary outcomes and (3) methodological characteristics of the studies.

Two authors independently extracted data from all eligible articles into a pre-designed data extraction sheet. Any conflicts were resolved through discussion and consultation with the third author (JPL).

2.5. Assessment of evidence quality and certainty

The quality of included RCTs were assessed independently by two authors (CYW, NCH) using the Cochrane Collaboration's "Risk of bias (RoB) 1.0" tool.[19] The RoB comprises seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (e.g. funding bias) that are rated as "low risk", "high risk", or "unclear risk". Given the fatigue outcomes were evaluated and reported subjectively, a high risk of bias was assigned unless there was adequate blinding of participants and assessors. Bias referring to conflict of interest was judged as high risk if the study was industry led, or fully or partially industry funded, and no statements were made about their role. For commercially manufactured interventions, it was judged as unclear risk if no information was reported about who supported the trials. Any disagreement between the two authors was resolved by discussing with the third author (CLL).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was selected for the certainty assessment of the primary outcomes only.[22] Estimates of effect were rated as high, moderate, low, or very low certainty evidence based on RoB, inconsistency, indirectness, imprecision, and publication bias. To aid consistency and transparency, a rubric was developed and agreed upon between the authors (see footnotes in Supplement 9). Single authors (CLL, XYJ, XYC, QYW, XRP, JH) made an initial rating that was verified by at least one senior reviewer. Any disagreements were resolved by discussing with other authors.

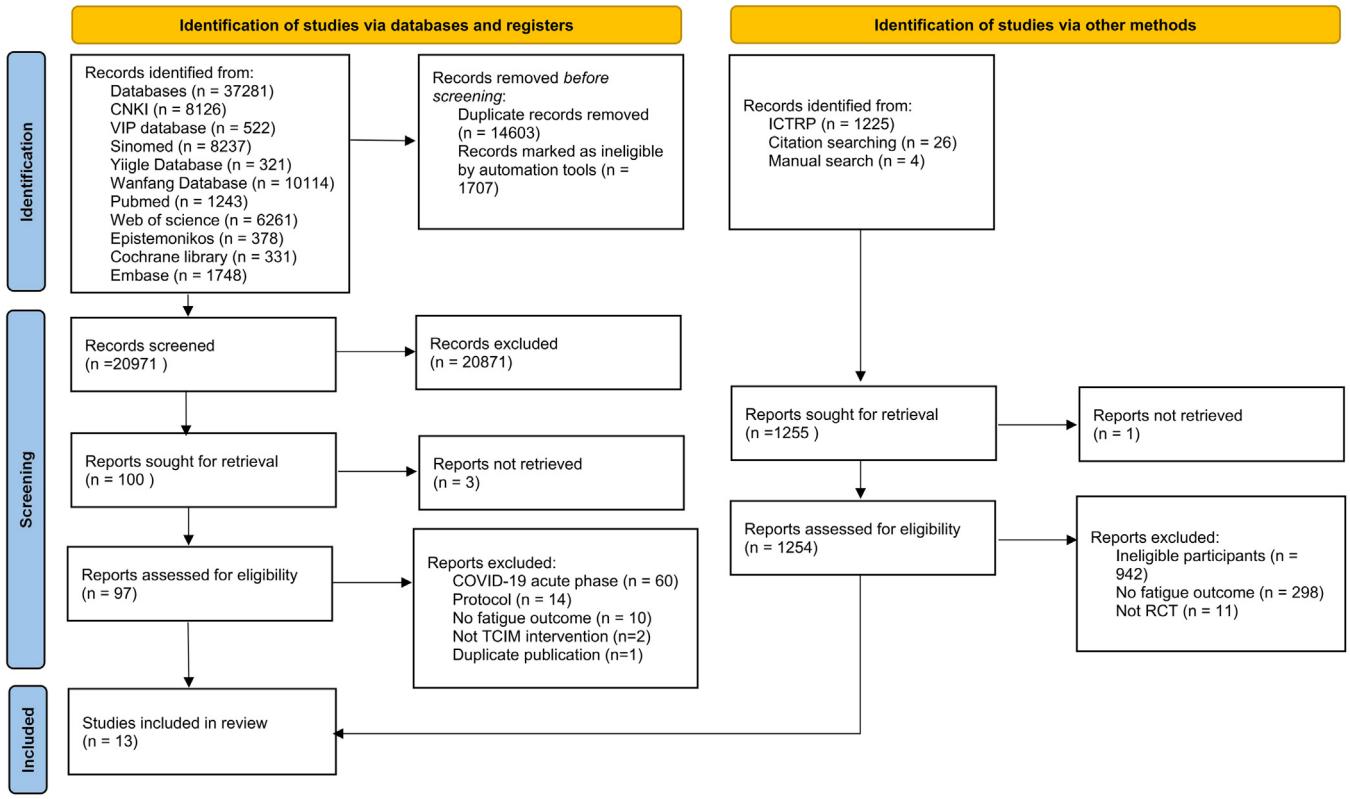

Fig. 1. PRISMA flow diagram.

2.6. Data analysis and synthesis

We planned to pool data for meta-analyses if the study design, participants, interventions, control, and outcome measures were similar. As this was not the case, results from the individual studies are presented separately in text and tabular form. If the study reported multiple post-intervention and follow-up scores, the last follow-up score is presented. For the reported outcome in different analysis sets, we chose the full intention-to-treat set in preference to other sets and the other set were then used to evaluate the robustness of the results. For dichotomous outcomes, risk ratios (RR) and risk differences (RD) with relevant 95% confidence intervals (CI) are presented. For continuous outcomes, the mean difference (MD) and standardized mean difference (SMD) and standardized mean differences (SMD) with relevant 95% CI are presented. Cochrane RevMan 5.4 software was used to calculate these estimates.

Minimal clinically important differences (MCID) were set *post hoc* according to accepted standards. A RR ≤ 0.75 or ≥ 1.25 or RD ≤ 0.01 or ≥ 0.01 of was deemed to be clinically important.[23] As a MCID is yet to be established for any of the fatigue measurement tools for this population, SMD were used to estimate effect sizes for continuous outcomes. A SMD of 0.20, 0.50, and 0.80 were considered minimally important (i.e., small effect size), important (i.e., medium effect size) and important (i.e., large effect size) differences, respectively.[24]

3. Results

3.1. Study selection

Thirteen RCTs[25-37] with 1632 participants of searched 37,281 records were included (Fig 1). Details of the 87 articles excluded at full-text screen with reasons are reported in Supplement 2.

3.2. Study characteristics

3.2.1. Characteristics of included studies

The characteristics of the thirteen RCTs are summarized in Table 1. Further details are reported in Supplement 4. Participants from eight RCTs conducted in China[25-28,33,34,36,37] and were diagnosed as convalescent COVID-19 according to "The Diagnosis and Treatment Scheme of COVID-19" released by the National Health Commission of the People's Republic of China.[38,39] Four of these studies also specified a traditional Chinese medicine syndrome diagnosis for the inclusion criteria.[26,28,36,37] The average or median time since discharge from medical isolation ranged from 2 to 11 weeks. Further details about participant characteristics are reported in Table 1 and Supplement 5.

Eight RCTs evaluated different oral Chinese herbal medicine formulas.[25-28,33,34,36,37] One preparation contained only one single Chinese herb,[27] and the other preparations were Chinese herbal compound consisting of multiple herbal ingredients. In four of these trials, the herbal treatments were combined with TCM-rehab therapies, which encompassed qigong and breathing exercises.[33,34,36,37] Further details of the interventions are presented in Table 2.

There was also substantial heterogeneity in the fatigue outcome measurements and endpoints. Further details of the outcome measures are reported in Table 1 and Supplement 6. We identified 23 registered protocols for RCTs focusing on fatigue post COVID-19 infection, two[26,28] of which were completed, published, and thus included in this review (Supplement 3).

3.3. Effects of interventions

The summary of findings is presented in Table 1. Further details of the estimates of effect for the primary and secondary outcomes, including per protocol analyses when available are presented in Supplement 7.

Table 1
Characteristics of included parallel RCTs on TCIM for fatigue post COVID-19 infection*.

First author (year) [ref]	Country Setting (No. sites)	Sample size (M/F) Age	Interventions (Duration)	Outcomes Timepoints †	Results	Certainty of evidence	Adverse Event
Ai (2020)[25]	China Hospital (1 site)	67 (40/27) 16-17 y	E: CHM formula + various conventional drugs C: Conventional drugs (12 days)	1) Fatigue disappearance rate 2) Adverse events Week 4	1) RR 2.16 [1.07, 4.35], *P*=0.03 2) E: rate 0 per 100 C: NI	Low	None
An (2022)[26]	China Hospital (3 sites)	199 (61/136) 18-70 y	E: CHM Ludangshen oral liquid C: Placebo (14 days)	1) Fatigue symptom severity (10cmVAS) 2) Fatigue disappearance rate 3) Fatigue remission rate 4) Adverse events Day 7, 14	1) MD -1.90 [-2.38, -1.42], *P*<0.001 2) RR 4.19 [2.06, 8.53], *P*<0.001 3) RR 2.04 [1.58, 2.63], *P*<0.001 4) RR 0.99 [0.61, 5.85], *P*=0.99	1) Low [d] 2) Low [d] 3) Low [d] 4) Low [d]	Nose bleeding (E:1) Headache (C:1)
Chen (2020)[27]	China Hospital (1 site)	70 (35/35) 21-65 y	E: CHM + Interferon α-2b C: Arbidol + Interferon α-2b (15 days)	Fatigue severity score 2) Chest CT imaging evaluation Day 15	MD 0.62 [0.26, 0.98], *P*=0.007 RR 1.36 [1.02, 1.82], *P*=0.04	Very low [b,d] Very low [b,d]	NI
Chen (2022)[28]	China (5 sites)	E:64 C:65 (E:64 C:65) ≥18 y	E: CHM C: Placebo (90 days)	Fatigue Assessment Inventory Improvement rate of chest CT imaging evaluation Month 3	MD -14.90 [-24.53, -5.27], *P*=0.02 RR 2.03 [0.64, 6.41], *P*=0.23	Low [d] Low [d]	Abnormal liver function (E:4;C:2); liver injury (E:1); diarrhea (E:1); excessive menstruation (C:1)
Hajibashi (2023)[29]	Iran (1 site)	E:29 C:29 (E:26 C:26) 18-65 y	E: Progressive muscle relaxation + Pulmonary telerehabilitation (PTR) C: PTR (6 weeks)	Fatigue Severity Scale (FSS) Week 2, 6	MD -0.92 [-1.55, -0.29], *P*=0.007	Very low [a,d]	NI
Hausswirth (2023)[30]	France (1 site)	E:17 C1:17 C2‡:15 (E:17 C1:17 C2‡:15) ≥18 y	E: Neuro-meditation Rebalance® Program C1: blank C2‡: blank (5 weeks)	Chalder Fatigue Scale (CFQ) - physical fatigue Chalder Fatigue Scale (CFQ) - mental fatigue Week 5	MD -13.00 [-15.21, -10.79], *P*< 0.001 MD -7.90 [-9.58, -6.22], *P*< 0.001	Very low [a,d] Very low [a,d]	NI
Hawkins (2022)[31]	USA (1 site)	E: 22 C: 21 (E: 20 C: 20) 19-49 y	E: Aromatherapy C: Placebo (2 weeks)	Multidimensional Fatigue Symptom Inventory (MFSI) Adverse event Day 14	MD -11.71 [-20.72, -2.70], *P*=0.01 RR 2.87 [0.12, 66.75], *P*=0.45	Low [a,c] Low [a,c]	Headache (E:1)

(*continued on next page*)

Table 1 (*continued*)

First author (year) [ref]	Country Setting (No. sites)	Sample size (M/F) Age	Interventions (Duration)	Outcomes Timepoints †	Results	Certainty of evidence	Adverse Event
Karosanidze (2022)[32]	Georgia (1 site)	E:50 C:50 (E:49 C:50) ≥18 y,	E: Chisan®/ ADAPT-232 herbal formula C: Placebo (14 days)	Fatigue disappearance time (days) Adverse event Day 14, 21	MD -1.02 [-2.40, 0.36],*P*=0.15 RR 0.34 [0.01, 8.15], *P*=0.51	Low [d] Low [d]	Allergic conjunctivitis (C:1)
Li (2021)[33]	China (1 site)	E:60 C:58 (E:48 C:46) 18-80 y	E: CHM + moxibustion therapy + TCM rehabilitation therapy C: TCM rehabilitation therapy (2 weeks)	Fatigue disappearance rate Day 28	RR 1.75 [0.53,5.76], *P*=0.36	Very low [b,e]	NI
Pang (2022)[34]	China (2 sites)	E:194 C:194 (E:194 C:194) 18-75 y	E: CHM + TCM rehabilitation treatments C: TCM rehabilitation treatments (14 days)	Fatigue Borg scale Adverse event Day 7,14	MD -0.48 [-0.50, -0.46], *P*<0.001 RR 0.72 [0.36, 1.43], *P*=0.35	Low [b] Low [b]	ALT abnormality (E:9; C:10); AST abnormality (E:4; C:8)
Rathi (2021)[35]	India (3 sites)	E:100 C:100 (E:100 C:100) 18-75 y	E: Systemic enzyme complex + Probiotic complex C: Placebo (14 days)	Fatigue disappearance rate Day 14	RR 6.07 [3.79, 9.71], *P*<0.001	Low [d]	None
Shi (2021)[36]	China (5 sites)	E1:30 E2:30 C:30 (E1:30 E2:30 C:30) 18-65 y	E1: CHM + TCM rehabilitation exercise C: blank (14 days)	Fatigue severity score Adverse event Day 14	MD -1.60 [-2.15, -1.05], *P*<0.001 E1: rate 0 per 100 E2: rate 0 per 100 C: rate 0 per 100	Very low [b,d] Very low [b,d]	None
Yang (2021)[37]	China (1 site)	E:60 C:60 (E:59 C:59) 28-69 y	E: CHM+TCM rehabilitation therapy C:Acetyl cysteine tablets+TCM rehabilitation therapy (7 days)	Fatigue severity score Adverse event Day 7	MD -0.47 [-0.73, -0.21], *P*=0.0004 RR 0.50 [0.05, 5.37], *P*=0.57	Very low [b,d] Very low [b,d]	Insomnia (E:1) Diarrhea (C:1) Nausea (C:1)

C, comparison group; CFQ, Chalder Fatigue Scale; CHM, Chinese Herbal Medicine; E, experimental group(s); FAI, Fatigue Assessment Inventory; FSS, Fatigue Severity Scale; NI, No information; TCM, Traditional Chinese Medicine; y, years.

* COVID-19 immunization status not reported for any of the included studies.

† Timepoints are for fatigue outcome measurements.

‡ The third arm was an external normative control group of healthy people.

GRADE certainty assessments:

[a] Serious concerns with risk of bias.

[b] Very serious concerns with risk of bias.

[c] Serious concerns with imprecision.

[d] Very serious concerns with imprecision.

[e] Extremely serious concerns with imprecision.

Table 2
Detailed description of interventions for fatigue post COVID-19 infection.

Study ID	Intervention (Administration route)	Dose Frequency Duration	Description and Indications
Ai (2020)[25]	CHM formula granules (oral)	2 x day 12 days	Ingredients: Huangqi (*Astmgali Radix*), Dangshen (*Codonopsis Radix*), Chuanbei (*Fritillariae Cirrhosae Bulbus*), Ziwan (*Tatarian Aster Root*), Quanxie (*Scorpio*), Dilong (*Pheretima*), Jiangcan (*Bombyx Batryticatus*), Shenqu (*Medicated Leaven*), Jineijin (*Galli Gigerii Endothelium Corneum*), Sangye (*FoLium Mori*), Muli (*Concha ostreae*), Fuling (*Poria Cocos Sclerotium*). NI: dose, standardization or manufacturer for each herbal ingredient. Efficacy: Release the exterior and promote skin eruption, clear heat and detoxify, resolve phlegm and disperse nodules.
	Conventional therapy	NA	Oxygen therapy, antiviral, anti-inflammatory and symptomatic treatment.
An (2022)[26]	Ludangshen liquid (oral)	10 ml 2 x day 2 weeks	Ingredients: Dangshen (*Codonopsis pilosula*). NI: dose, extraction method, standardization of herbal ingredient. Manufacturer: Shanxi Zhenglai Pharmaceutical Co., Ltd., Shanxi, China, production batch No. 2003305. Efficacy: Reinforce the spleen and tonify the stomach, strengthen the spleen and benefiting the lungs, nourish and fortify, enhance the body's immune capability.
	Placebo liquid (oral)	10 ml 2 x day 2 weeks	Ingredients: NI Matched for flavor, taste, and appearance, color and packaging. NI: matched for smell. Manufacturer: Shanxi Zhenglai Pharmaceutical Co., Ltd., Shanxi, China.
Chen (2020)[27]	Lianhua Qingwen capsule (oral)	1.4g 2 x day 15 days	Ingredients: Lianqiao (*Forsythiae fructus*), Mahuang (*Ephedrae herba (honey-fried)*), Jinyinhua (*Lonicerae japonicae flos*), Banlangen (*Isatidis radix*), Mianmaguanzhong (*Dryopteris crassirhizomatis rhizoma*), Bohenao (*menthol*), Shigao (*gypsum fibrosum*), Guanghuoxiang (*Pogostemonis herba*), Hongjingtian (*Rhodiolae crenulata radix et rhizoma*), Yuxingcao (*Houttuyniae herba*), Dahuang (*Rhei radix et rhizoma*), Kuxingren (*Semen armeniacae amarum (stir-baked)*), Gancao (*Glycyrrhizae radix et rhizoma*), starch excipient. NI: dose, extraction, standardization for each herbal ingredient. Manufacturer: Beijing Yiling Pharmaceutical Co., LTD. Batch number: B1907008. Efficacy: Clear pestilence and detoxify, disperse lung heat and reduce fever.
	Umifenovir	0.2g 2 x day 15 days	Manufacturer Shijiazhuang SiYAO Co., LTD., Batch number: 20190913. Efficacy: antiviral agent.
	Interferon α-2b (atomized inhalation)	600,0000 U 2 x day 15 days	Manufacturer Shijiazhuang Siyao Co., LTD., Batch number: 20190913. Efficacy: antiviral, inhibiting cell proliferation and regulating immune function.
Chen (2022)[28]	Bufei Huoxue capsules (oral)	4 capsules 3 x day 90 days	Ingredients: Huangqi 0.14 g (*Astragali radix*), Chishao 0.07g (*Paeoniae radix rubra*), Buguzhi 0.14 g (*Psoraleae fructus*). NI: extraction methods or standardization for each herbal ingredient. Manufacturer: Chinese medicine Z20030063, Guangdong Lei Yun Shang Pharmaceutical Co., Ltd. (Yunfu, Guangdong Province, China); batch number 022001; specifications: 0.35 g per capsule. Efficacy: Tonify qi and circulate blood, reinforce the lung and kidney.
	Placebo capsules (oral)	4 capsules 3 x day 90 days	Ingredients: starch, caramel, and tartrazine. Matched for smell, colour, shape, and packaging Manufacturer: Guangdong Lei Yun Shang Pharmaceutical Co., Ltd.; batch number 012007; specifications: 0.35 g per capsule.
Hajibashi (2023)[29]	Progressive muscle relaxation (PMR)	2 x day 5 days/wk 42 days	A physiotherapist provided one face-to-face tuition of PMR technique, written and video instructions, and two sessions per week supervised by via video call. PMR was "based on" Bernstein's modified Jacobson's method where the 16 main muscle groups are progressively contracted during deep inhalation for 5-7s then relaxed for 30-40s[46]. Session duration was 15-20 min.
	Pulmonary telerehabilitation (PTR)	1 x day 5 days/wk 42 days	A physiotherapist provided one face-to-face tuition of PTR technique, written and video instructions, and two sessions per week supervised by via video call. PTR sessions involved breathing exercises (e.g., diaphragmatic breathing exercises, pursed lip breathing, chest expansion, deep breathing with arm movement), upper and lower limb strength training (e.g., shoulder or elbow flexion/extension with external load, squats, standing heel-rise) and aerobic exercises (e.g., walking, upper-limb exercises). Exercise intensity was progressively increased, set at the Borg scale (moderate-intensity score: 3–4). Session duration began at 10 min, increasing to 30 min as tolerated, including rest intervals.

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Table 2 (*continued*)

Study ID	Intervention (Administration route)	Dose Frequency Duration	Description and Indications
Hausswirth (2023)[30]	Neuro-meditation Rebalance® Program	30 min/ session 10 x sessions 5 weeks	Ten 30-min neuro-meditation mindfulness training sessions were spread over four weeks (i.e., two to three sessions a week). Participants would lie in the Rebalance Impulse® device in a zero gravity position where they were exposed to light stimulations (synchromotherapy® based on a real-time electro-encephalogram (EEG)), sound therapy and coach-guided meditation.
	No treatment	NA	No therapies were provided, including no "usual care".
Hawkins (2022)[31]	Aromatherapy essential oil blend (nasal inhalation)	4 drops 15 minutes 2 x day 14 days	Ingredients: Thyme *(Thymus vulgaris*) oil, Orange peel *(Citrus sinensis)* oil, Clove bud *(Eugenia caryophyllus*) oil, Frankincense *(Boswellia carterii*) oil. Self-administered, 4 drops on "tester strip" held 2 inches from nose, deep breathing. Commercially available product, provided by Young Living Essential Oils (Lehi, Utah, USA).
	Placebo oil (nasal inhalation)	4 drops 15 minutes 2 x day 14 days	Ingredients: Inert, odorless fractionated coconut oil. Self-administered as per instructions for aromatherapy intervention. Manufacturer: Young Living Essential Oils (Lehi, Utah, USA).
Karosanidze (2022)[32]	ADAPT-232 / Chisan® (oral)	30 ml 2 x day 14 days	ADAPT-232/Chisan® oral suspension (Product Registration No: 2006-2004) was manufactured according to ICH Guidelines for GMP (Swedish Herbal Institute AB, Vallberga, Sweden). One daily dose (60 mL oral solution) contained: 180 mg of soft extract of *Rhodiola rosea L.*, radix et rhizome (DER 2.5-5.0:1, extractions solvents - 70% ethanol and water) corresponding to 0.45–0.90 g of dried plant material, 600 mg of soft extract of *Schisandra chinensis* (Turcz.) Baill., fructus, (DER 2.0-5.0:1, extraction solvent-95% ethanol) corresponding to 1.2–3.0 g of dried plant material, 156 mg of soft extract of *Eleutherococcus senticosus* (Rupr. et Maxim) Maxim, radix, (DER 17-30:1, extraction solvents—70% ethanol and water) corresponding to 2.64-4.68 g of dried plant material, and inactive ingredients: dark syrup, anhydrous ethanol, glycerol, caramel aroma, polysorbate 80, methyl parahydroxybenzoate (E218), anhydrous citric acid, rosemary extract, propyl parahydroxybenzoate (E216), ginger extract, and potassium sorbate and water. Efficacy: (i) modulating innate and adaptive immunity, (ii) anti-inflammatory activity, (iii) detoxification and repair of oxidative stress-induced damage in compromised cells, (iv) direct antiviral effects of inhibiting viral docking or replication, and (v) improving quality of life during convalescence.
	Placebo (oral)	30 ml 2 x day 14 days	Placebo suspension containing the same inactive ingredients had a similar appearance, smell, and color and was organoleptically indistinguishable from serum-containing active pharmaceutical ingredients.
Li (2021)[33]	CHM decoction (oral)	3 x day 14 days	Ingredients: Shengshaishen 15 g (*Ginseng Radix Et Rhizoma*), Fuling 10 g (*Poria Cocos Sclerotium*), Baizhu 10 g (*Macrocephalae Rhizoma*), Baibiandou 15 g (*Semen Dolichoris Album*), Chenpi 10 g (*Citrus reticulata Blanco*), Lianzi 10 g (*Nelumbinis Semen),* Shanyao 15 g (*Rhizoma dioscoreae*), Yiyiren 15 g (*Semen coicis*), Sharen 5 g (*Amomi Fructus*), Jiegeng 10 g (*Radix platycodoni*), Danshen 15 g (*Radix salviae miltiorrhizae*), Dilong 10 g (*Pheretima),* Huangqi 15 g (*Astmgali Radix*), Danggui 10 g (*Angelicae Sinensis Radix*, Chuanxiong 10 g (*Rhizoma chuanxiong*), Shenqu 10 g (*Medicated Leaven*). NI: extraction method or standardization for each herbal ingredient. Manufacturer: Sichuan New Green Pharmaceutical Technology Development Co. LTD. Efficacy: Tonify qi and circulate blood.
	Moxibustion therapy	20-30 min QOD 14 days	Moxibustion box, covering Shenque (CV8, RN8), Qihai (RN6), Guanyuan (RN4), Zhongwan (RN12), Tianshu (ST25) acupoints. NI: materials used, patient posture/environment, provider.
	TCM rehabilitation therapy	14 days	Health guidance, "Turtle Breath regulating Lung exercise". NI: provider, instructions, tailoring, location, duration, adherence/fidelity.
Pang (2022)[34]	Qingjin Yiqi granules	10 g 2 x day 14 days	Qingjin Yiqi granules comprises by 16 herbals: Renshen (*Ginseng Radix Et Rhizoma*), Maidong (*Ophiopogonis Radix*), Wuweizi (*Schisandrae Chinensis Fructus*), Fuling (*Poria Cocos Sclerotium*), Banxia (*Pinelliae Rhizom*), Xuanshen (*Scrophulariae Radix*), Cangzhu (*Atractylodis Rhizoma*), Chenpi (*Citri Reticulatae Pericarpium*), Gancao (*Glycyrrhizae Radix Et Rhizoma*), Chaihu (*BupleuriRadix*), Shengma (*Cimicifugae Rhizoma*), Yiyiren (*Coicis Semen*), Huangqin (*Scutellariae Radix*), Mabiancao (*Verbenae Herba*). These herbs are initially extracted with water, followed by concentration and spray-drying to powder, after which excipients are added with the final mixture pelletized by dry granulation method. Efficacy: Norish yin and supplement qi, reinforce the spleen and tonify the stomach, clear heat and eliminate dampness.
	TCM rehabilitation treatments	3 x day 14 days	Respiratory training (Lip breathing training, 20 minutes each time, 3 times daily; abdominal breathing training was performed at a rate of 7 breaths per minute for 20 minutes, twice a day; respiratory rhythm training, 20 minutes each time, 3 times per day); and Baduanjin exercise (a traditional Chinese exercise consisting of eight gentle movements that promote physical and mental health), twice a day. NI: provider, tailoring, location, adherence/fidelity.

(*continued on next page*)

Table 2 (*continued*)

Study ID	Intervention (Administration route)	Dose Frequency Duration	Description and Indications
Rathi (2021)[35]	Systemic enzyme complex (oral)	2 capsules 2 x day 14 days	ImmunoSEB (Systemic enzyme complex, multi-enzyme formulation of Peptizyme SP, an enteric coated serratiopeptidase, bromelain, amylase, lysozyme, peptidase, catalase, papain, glucoamylase and lactoferrin, 500 mg/capsule), 4 capsules of ImmunoSEB daily (two capsules in the morning and two in the evening) on an empty stomach (1 h before or 2 h after a meal) with 1-2 cups of warm or room temperature water. NI: standardization or manufacturer for each herbal ingredient. Efficacy: These enzymes are known for their antioxidant, anti-inflammatory, and analgesic activities.
	Probiotic complex (oral)	2 capsules 1 x day 14 days	ProbioSEB CSC3 (Probiotic complex, probiotics blend of Bacillus coagulans LBSC (Lactobacillus acidophilus, Bifidobacterium bifidum, and Streptococcus thermophilus), Bacillus subtilis PLSSC (one of strains of Bacillus subtilis, 5 billion CFUs /capsule) 2 capsules of ProbioSEB CSC3 daily, to be taken with lunch. Efficacy: Supplementation with probiotics has been associated with a significant decrease in anxiety symptoms and positive modifications in well-being status, as well as inflammatory and oxidative indexes in Chronic Fatigue Syndrome (CFS) patients.
	Placebo (oral)	2 capsules 3 x day 14 days	Placebo: Maltodextrin. 4 capsules of placebo daily (two capsules in the morning and two in the evening) on an empty stomach (1 h before or 2 h after a meal) with 1–2 cups of warm or room temperature water. 2 capsules of placebo daily, to be taken with lunch.
Shi (2021)[36]	Yiqi Yangyin granules (oral)	2 x day 14 days	Yiqi Yangyin granule: Dangshen (*Radix codonopsis*), Maidong (*Raxid ophiopogonis*), Baihe (*Bulbus Lilii*), Fuling (*Poria Cocos Sclerotium*), Baizhu (*Macrocephalae Rhizoma*), Chenpi (*Citrus reticulata Blanco*), Maiya (*Fructus Hordei Germinatus*), Hehuanpi (*Cortex albiziae*), Digupi (*Coptex lyciilicorice root*), Zhigancao (*Radix glycyrrhizae preparata*). NI: dose, extraction method, or standardization for each herbal ingredient. Manufacturer: Jiangyin Tianjiang Pharmaceutical Co. LTD. Efficacy: Norish yin and supplement qi.
	Traditional Chinese rehabilitation self-massage and breathing exercises	6 min morning 15 min evening 14 days	"Tai Chi Six Qi exercise" (Taiji Liuqi Gongfa): After getting up in the morning, massage a circle around the periphery of the head and a circle with the navel as the center and 6cm as the radius, clockwise direction, and with the thumb for 6 min. "Breathing exercise" (Huxi Tuna Gongfa): Take the lying position or sitting position before going to bed, first breathe in the dantian position (three inches below the umbilicus) with the nose deep and slow to the greatest extent, and then breathe out all the turbid air in the lung with the mouth deep and slow, and practice for 15 min. NI: provider, tailoring, location, adherence/fidelity.
	No treatment	NA	No therapies were provided, including no “usual care”.
Yang (2021)[37]	Xianghuo spray (oropharyngeal)	3 spray 3 x day 7 to 14 days*	Ingredients: 2.86 mg Guanghuoxaing (*patchouli*) oil, 1.43 mg Xiangru (*Herba moslae*) oil, 1.43 mg Qinghao (*Artemisia argyi*) oil, 0.714 mg Dingxiang (*clove*) oil and 0.714 mg mint oil. Produced by Yunnan Institute of Materia Medica, Batch number: 20200303 (Research). Efficacy: transform phlegm and disperse the lung, supplement the spleen and resolve the dampness.
	Traditional Chinese rehabilitation	7 to 14 days*	Various traditional rehabilitation interventions: health education, dietary guidance, emotional counseling, breathing six-word exercise (Huxi Liuzi Jue), Baduanjin (therapeutic Qi Gong) or Tai chi, etc. NI: provider, instructions, tailoring, location, duration, adherence/fidelity.
	Acetylcysteine tablet (oral)	0.2 g (1 tablet) 3 x day 7 to 14 days*	Manufacturer: Hainan Zambang Pharmaceutical Co., LTD., batch number: 1001781. Efficacy: mucolytic agent.

CHM, Chinese Herbal Medicine; g, gram; h, hour; min, minute; mg, milligram; NA, Not Applicable; NI, No information; QOD, every other day; TCM, Traditional Chinese Medicine; wk, week; x, times; +, plus.

* The general course of treatment was 7 days, and could be extended appropriately when necessary.

There was no significant difference between the intention-to-treat and per protocol analyses.

3.3.1. Primary outcomes

Fatigue disappearance rate

Fatigue disappearance rates were significantly higher following two weeks of Ludangshen CHM liquid compared to placebo,[28] 14 days of systemic enzymes plus probiotics compared to placebo,[35] and 12 days of a CHM granules plus conventional treatment compared to conventional treatment alone.[25] However, there was no significant difference between two weeks of a CHM granules combined with moxibustion second daily and TCM rehabilation compared to TCM rehabilitation only.[33]

Fatigue disappearance time

Across the included studies, only one trial measured the fatigue disappearance time. There was no significant difference between ADAPT-232 / Chisan® herbal formula and placebo on the duration of fatigue.[32]

3.3.2. Secondary outcomes

Fatigue severity score

Nine RCTs reported fatigue severity score outcomes.[26-31,34,36,37] Compared to placebo, Ludangshen CHM oral liquid significantly reduced fatigue on VAS after 2 weeks.[26] Bufei Huoxue capsules, showed a significant improvement of fatigue on Fatigue Assessment Inventory scores at 3-month compared to placebo.[28] Progressive muscle relaxation combined with pulmonary telerehabilitation (PTR) significantly reduced fatigue on Fatigue Severity Scale compared to PTR alone.[29] Aromatherapy significantly relieved fatigue on after two weeks compared to placebo.[31]

Compared to no treatment, the neuro-meditation Rebalance® program alleviated fatigue measured by various fatigue scales.[30] Compared to no intervention, Yiqi Yangyin CHM granule with or without TCM-rehab significantly reduced the fatigue symptom score.[36]

Compared to conventional therapy, one trial found that Lianhua Qingwen capsules was significantly less effective than Umifenovir (also known as Arbidol) in reducing the fatigue symptom score.[27] Compared to TCM rehabilition therapy alone, Qingjin Yiqi CHM granules had an add-on effect in reducing fatigue on Brog scale after 2 weeks.[34] Compared to the nutritional supplements, acetylcysteine, plus TCM-rehab, Xianghuo CHM spray in combination with TCM-rehab significantly improved fatigue symptom scores.[37]

Fatigue remission rate

Only one trial[26] reported fatigue remission rate. Compared to placebo, the fatigue remission rate was significantly higher following two weeks of Ludangshen oral liquid treatment.

Adverse events

Only nine trials[25,26,28,31,32,34-37] reported adverse events. Among them, three trials[25,33,34] reported no adverse events. Two RCTs monitored liver enzymes.[28,34] Five participants (7.8%, n=64) in the Bufei Huoxue CHM capsules group developed abnormal liver function tests (LFTs), one of whom was diagnosed with liver injury and two participants (3.1%, n=65) in the placebo group also developed abnormal LFTs.[28] There were 13 participants in the Qingjin Yiqi CHM granules group and 18 participants in the control group had abnormal liver function indicators. None of the abnormalities in ALT and AST were considered to be related to the drugs by the assessment of clinical investigators.[34] The other four trials only reported one or two mild adverse events (see Supplement 8).[26,28,32,37] None of the trials reported serious adverse events. As shown in Supplement 7, there was no significant statistical difference in adverse event rates between the experimental group and control group.

3.4. Quality and certainty assessment

The summary of the RoB assessment for the thirteen RCTs is presented in Fig 2. Of the 13 primary outcomes/estimates of effect, seven were rated as low certainty and six as very low certainty evidence. This was due to serious concerns with RoB for one estimate of effect, very serious concerns with RoB for six estimates of effect, and very serious concerns with imprecision for 12 estimates of effect. There were no concerns with indirectness as all the populations and outcomes were directly relevant to the research question. Inconsistency and publication bias did not apply as each estimate was informed by a single study. Details of the GRADE certainty assessments are reported in Supplement 9.

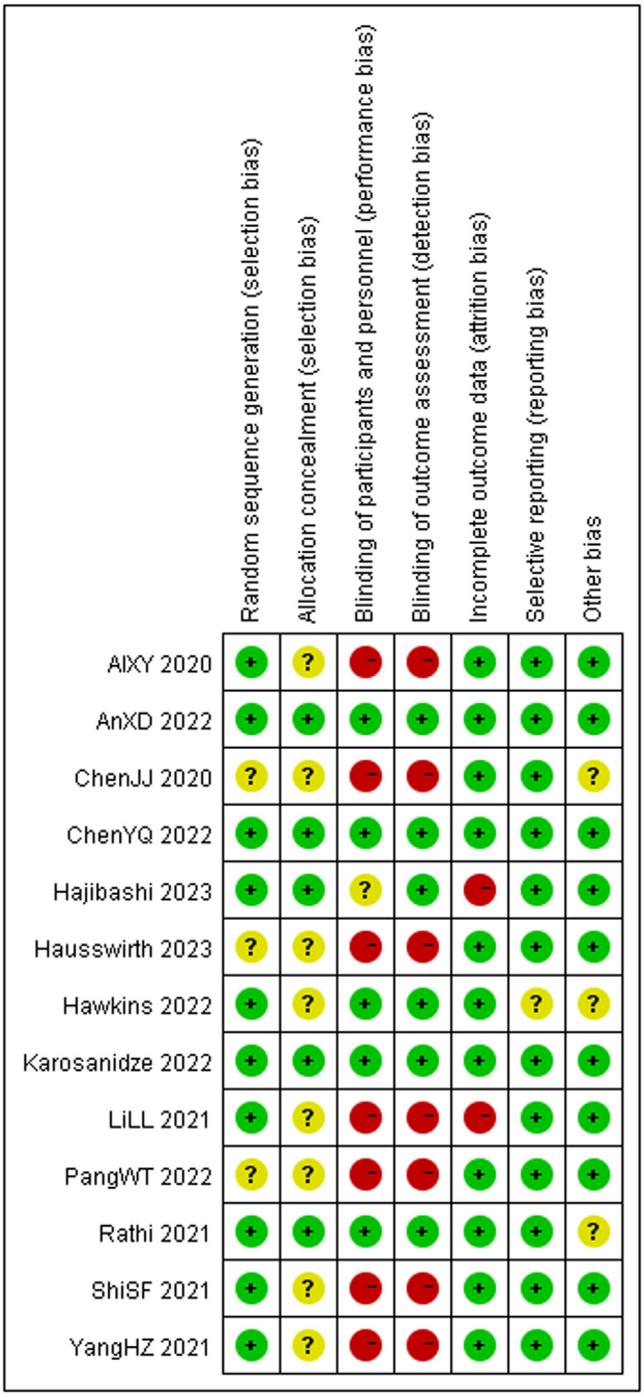

Fig. 2. Risk of bias summary.

4. Discussion

4.1. Summary of findings

This systematic review has initially identified the randomized controlled trials (RCTs) that specifically address the management of persis-

tent fatigue following COVID-19 infection, based on the available limited evidence. Low certainty evidence suggests that Ludangshen oral liquid, Bufei Huoxue capsules, Qingjin Yiqi granules added to TCM rehabilitation, systemic enzymes plus probiotics, an aromatherapy blend may help fatigue symptoms experiences by adults post COVID-19 infection. The combination of integrated Chinese herbal medicine and exercise, such as qigong, may potentially serve as a viable treatment option for individuals experiencing long-term symptoms associated with COVID-19. However, an herbal adaptogenic formula ADAPT-232 / Chisan®, may not be more effective than placebo. Due to very low certainty evidence, it is unclear if these interventions are more effective than the comparison interventions. There was no apparent increase in the incidence of adverse events, however, the findings are unreliable due to very low event rates and small sample sizes.

The hypothesized mechanisms for the pathogenesis of fatigue associated with post COVID-19 condition are wide ranging and include immune dysregulation, with or without persisting SARS-CoV-2 infection or reactivation of other viral infections; microbiota dysbiosis in the respiratory and gastrointestinal tracts, possibly accompanied by persisting SARS-CoV-2 infection; autoimmune activation; sequalae of microvascular damage to end organs; and dysfunctional neurological signaling.[7]

The herbal remedies examined in this review exemplify intricate interventions characterized by multiple components and targeting various pathways. An illustrative example is the Qingjin Yiqi granules, crafted from extracts of 16 traditional Chinese herbs. This formulation encompasses nine primary phytochemical groups and contains over 160 constituents, with at least 50 possessing potential biological activities beneficial for addressing post-COVID-19 conditions.[34]

Contrastingly, only a single study focused on the impact of an individual herbal component, Codonopsis pilosula.[26] Despite being a singular ingredient, it represents a complex intervention due to its wide array of polysaccharides, which are known for their antiviral, anti-inflammatory, antioxidant, immunomodulatory, anti-hypoxic, and prebiotic effects.[40]

According to the principles of TCM, which emphasize syndrome differentiation, tonifying herbs might offer greater advantages in the recuperation from long COVID-19, particularly in cases of fatigue, compared to herbs aimed at clearing heat and detoxifying. Future research into TCM's application for fatigue might profitably concentrate on tonifying herbs to address Qi deficiency.

4.2. Comparison with previous studies

Other systematic reviews of post COVID-19 condition have been published,[41-44] however, only two of the studies included in this review were identified,[31,35] that in part reflected English language bias. In contrast with the findings of systematic reviews evaluating conventional physical rehabilitation,[41,45] none of the studies included in this review compared TCM rehabilitation to a comparison intervention that was hypothesized to be less effective (e.g., no treatment, usual care, or education).

Moreover, this review contributes to the growing evidence on the potential benefits of various TCIM interventions for managing post-viral fatigue. It is worth noting that the interventions examined in this review, which include herbal medicines, probiotics, aromatherapy, and combined approaches, were not addressed in a recent systematic review specifically focused on post-viral fatigue.[13]

4.3. Strength and limitations

The chronic symptom of fatigue, which lacks a definitive treatment and is the most prevalent among individuals post COVID-19 infection, poses a significant challenge. There remains a dearth of effective treatments for fatigue, as well as new evidence to identify potential strategies for managing post COVID-19 symptoms. This systematic review aims to bridge this knowledge gap by providing comprehensive evidence from both English and Chinese publications. By conducting a comprehensive search across Chinese language databases and incorporating relevant publications in the Chinese language, this systematic review has identified a larger pool of studies compared to other similar reviews.[13,42] However, it is important to acknowledge the potential presence of language bias.

The findings of this review are constrained by the limited or very low certainty of evidence for most outcomes. The majority of trials exhibited a high risk of bias, primarily due to inadequate blinding. Only three studies were assessed as low risk of bias in all domains.[26,28,32] While blinding participants in studies involving movement-based interventions is inherently difficult, the incorporation of placebo controls in trials examining conventional and herbal medications could have mitigated bias risks.[25,27,33,34,36,37]

The generalizability of the review findings is limited due to the predominant focus on studies conducted in China. Crucial participant characteristics, including the duration since COVID-19 infection, vaccination status, and specific virus variants of SASR-CoV-2, were not reported across any of the included studies. Furthermore, a significant proportion of participants in these studies were infected prior to the emergence of the SARS-CoV-2 Omicron variant,[46] which currently prevails as the most widespread infection globally. Consequently, it remains uncertain whether interventions with targeted antiviral activity will also be effective against other SARS-CoV-2 variants. The aforementioned evidence can still offer potential approaches for managing fatigue and further research.

4.4. Implication of future research

Due to the limitations of the review findings, there is still a need for more high-quality studies evaluating the efficacy of TCIM for fatigue post COVID-19 infection. Further studies should clarify the dimension and duration of fatigue, as participants with fatigue immediately following acute infection may respond differently to those with longer lasting fatigue who already meet the definition of post COVID-19 condition. The characteristics of participants, such as the infected virus variants, vaccine status, and pre-existing diseases should be reported. The other recommended core outcomes for post COVID-19 condition should also be reported as baseline characteristics and as outcomes when relevant.[47] Due to the subjectivity of fatigue, placebo or sham interventions should be used in the comparison group whenever possible. If laboratory biomarkers are identified and validated for fatigue post COVID-19 infection,[7] future trials should include these objective measures as secondary outcomes, especially when participant blinding is not possible. To enable reproducibility of the findings, trialist should pay greater attention to the Consolidated Standards of Reporting Trials (CONSORT) extensions according to the TCIM intervention(s) being evaluated, such as CONSORT Extension for Chinese Herbal Medicine Formula[48] or the Template for Intervention Description and Replication (TIDieR) checklist and guide.[49] Appropriate comparison settings, such as active comparators or placebo controls, should be considered to ensure the validity and reliability of the study result. The study designs should include longer follow-up times to establish whether an intervention provides temporary symptom relief or has a curative effect.

We have made every effort to include the most current and high-quality studies into our systematic review, despite the limitations and potential biases inherent in the available evidence due to the exigency of responding to the pandemic.[50] Although the WHO has declared the termination of the COVID-19 Public Health Emergency of International Concern,[51] the enduring impact of the pandemic persists. It is crucial to sustain research efforts and address comprehensively the long-term health ramifications of COVID-19, while promptly updating our understanding in light of emerging evidence.

In conclusion, very low to low certainty evidence indicated that some herbal medicines, probiotics, mind-body therapy, and aromatherapy may be effective, either as stand-alone therapies or combined with

either TCM or conventional rehabilitation. Further investment in well-designed, high quality RCTs focusing on the efficacy and safety of TCIM in treating fatigue of post COVID-19 infection is needed.

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Author contributions

Conceptualization: JPL and CLL. Supervision: JPL and CLL. Methodology: XYC. Investigation: XYC, YYZ, JLW, JYL, CYW, NCH, BJD, QYW, and XRP. Formal Analysis: XYC. Writing - Original Draft: XYC. Writing - Review and Editing: JPL, CLL, XHL, XYJ, and JH. All authors approved the final manuscript.

Declaration of competing interest

All authors declare that they have no competing interests.

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Ethical statement

Not applicable. All data in our study came from publicly available data and our study did not recruit human subjects.

Data availability

All data in our current study came from public databases, all results were presented in this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2024.101039.

Supplement 1. Search Strategy

Supplement 6. Outcome Measurements - Additional Information

Supplement 7. Estimates of Effect for All Primary and Secondary Outcomes and Analysis Sets

Supplement 8. Details of adverse events

Supplement 9. GRADE Certainty of Evidence Assessments for Primary Outcomes

Supplement 10. PRISMA Checklist

Supplement 2. List of Excluded Studies References

Supplement 3. Characteristics of Registered Trials

Supplement 4. Characteristics of Studies - Additional Information

Supplement 5. Characteristics of Participants - Additional Information

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