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Review Article

Traditional Chinese medicine for post-viral olfactory dysfunction: A systematic review

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ABSTRACT

Background: Post-viral olfactory dysfunction (PVOD) is the common symptoms of long COVID, lacking of effective treatments. Traditional Chinese medicine (TCM) is claimed to be effective in treating olfactory dysfunction, but the evidence has not yet been critically appraised. We conducted a systematic review to evaluate the effectiveness and safety of TCM for PVOD.

Methods: We searched eight databases to identified clinical controlled studies about TCM for PVOD. The Cochrane risk of bias tools and GRADE were used to evaluate the quality of evidence. Risk ratio (RR), mean differences (MD), and 95 % confidence interval (CI), were used for effect estimation and RevMan 5.4.1 was used for data analysis.

Results: Six randomized controlled trials (RCTs) (545 participants), two non-randomized controlled trials (non-RCTs) (112 participants), and one retrospective cohort study (30 participants) were included. The overall quality of included studies was low. Acupuncture (n = 8) and acupoint injection (n = 3) were the mainly used TCM therapies. Five RCTs showed a better effect in TCM group. Four trials used acupuncture, and three trials used acupoint injection. The results of two non-RCTs and one cohort study were not statistically significant. Two trials reported mild to moderate adverse events (pain and brief syncope caused by acupuncture or acupoint injection).

Conclusions: Limited evidence focus on acupuncture and acupoint injection for PVOD and suggests that acupuncture and acupoint injection may be effective in improving PVOD. More well-designed trials should focus on acupuncture to confirm the benefit.

Protocol registration: The protocol of this review was registered at PROSPERO: CRD42022366776.

1. Introduction

Coronavirus disease 2019 (COVID-19) ravages the world, causing 765,222,932 confirmed cases and 6921,614 deaths according to the World Health Organization globally as of April 29, 2023.[1] Even after recovering from acute COVID-19 infection, some patients still have sequelae. These patients are considered to suffer from what has been termed as “chronic” or “long” COVID-19 or a form of post-acute sequelae of COVID-19.[2] Although the World Health Organization declared the end of the “COVID-19 public health emergency” on May 5, 2023, long COVID is expected to affect people’s quality of life to a large extent.[3,4] Persistent olfactory dysfunction is one of the most common symptoms

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of COVID-19 now being termed long COVID.[5] One cohort study from China showed that there was a prevalence of 11 % of olfactory dysfunction after 6 months and 4 % after 12 months in patients who had tested positive for COVID-19.[6]

Olfactory dysfunction (changed sense of smell) is a symptom of a diverse range of conditions.[7] Among them, olfactory dysfunction in long COVID belongs to upper respiratory tract virus infection. The common viruses include rhinovirus, influenza and parainfluenza viruses (type III), and respiratory syncytial viruses.[8] The olfactory dysfunction caused by virus infection was called post-viral olfactory dysfunction (PVOD).[9-11]

Olfactory training, systemic steroids, topical therapies, and a variety of heterogeneous non-steroidal oral medications are commonly used treatments for PVOD.[12] Olfactory training was the only one recommended for the treatment of PVOD by an evidence-based review with recommendations.[12] In TCM, olfactory dysfunction is considered "bu wen xiang xiu (loss of smell)", "bi long (anosmia)" caused by the disharmony of zang-fu viscera or six-excess external contraction.[13] Some clinical studies (with small effect size) have shown that herbal extracts, acupuncture and other TCM therapies are effective in treating PVOD.[12,14]

Considering that COVID-19 is an emerging infectious disease in recent years, there are few clinical studies on its sequelae. However, there are certain similarities between the pathogenesis of post-COVID-19 olfactory dysfunction and the pathogenesis of PVOD.[9,15] Therefore, we aimed to identify and analyze all kinds of design for clinical studies focusing on TCM for PVOD and investigate further possible treatments.

2. Methods

The protocol for the review was registered in PROSPERO (CRD42022366776) on October 14, 2022 (Available from: https://www.crd.york.ac.uk/PROSPERO/). The content of this review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)[16] and the details are provided in Supplement 1.

2.1. Eligibility criteria

2.1.1. Type of studies

Clinical studies included randomized controlled trials (RCTs), non-randomized controlled trials (non-RCTs, clinical controlled trials without randomization process), cohort studies, and case-control studies were included in the systematic review.

2.1.2. Type of participants

Patients diagnosed with PVOD from clinical diagnosis or defined criteria (upper respiratory tract infection history, the occurrence of anosmia must be accompanied by a viral infection, no symptom- free period between upper respiratory tract infection and olfactory dysfunction, excluding other factors caused by anosmia) were accepted.[6] There were no restrictions on age, gender, or ethnicity.

2.1.3. Type of intervention

We included all kinds of TCM therapies including: 1) Drug modalities: Chinese herbal medicines such as extracts from herbs. 2) Non-drug modalities: acupuncture (manual acupuncture), acupoint injections, tuina, taichi, wuqinxi, baduanjin, needle-knife, moxibustion, and cupping. Cointerventions (excluding TCM) were included if all arms of the randomized trial received the same co-intervention(s).

2.1.4. Type of comparisons

All control interventions should exclude all kinds of TCM. Placebo (e.g. sham acupuncture); No treatment (just observation); Western medicine (e.g. mecobalamin, prednisone); Herbs and supplements (e.g. ginkgo biloba, vitamin B12); Olfactory training were eligible.

2.1.5. Type of outcomes

Primary outcomes included: (1) Symptom disappearance rate of olfactory dysfunction; (2) The score of olfactory dysfunction symptoms, was measured by a visual analog scale (VAS), T&T olfactometer test, University of Pennsylvania smell identification test, and Sniffin'Sticks test. If there was a single score for olfactory disorders on the total symptom scale and it was stated separately in the results, the result might also be included as an olfactory disorder symptom score;

Secondary outcomes included: (1) Symptom remission rate of olfactory dysfunction; (2) Time of olfactory dysfunction symptom disappearance; (3) Time of olfactory dysfunction symptom remission. and (4) Adverse events (all forms of adverse events were included whether reported by physicians or patients.).

2.2. Search strategy

We searched the following sources for the identification of studies: five Chinese databases (China National Knowledge Infrastructure, Wanfang Database, Chinese Scientific Journal Database, SinoMed and Yiigle), and three international databases (PubMed, EMBASE and Cochrane Library). Different search strategies were applied for Chinese and international databases (Supplement 2). All the above databases were searched from the available date of inception until Feb 22, 2023. No language or publication restrictions were used. References of all related systematic reviews were searched manually to identify any missing studies.

2.3. Study selection and data extraction

The search results from Chinese and international databases were exported into NoteExpress software (V3.7.0.9258). Duplicates were removed. The titles, abstracts, and the full text were screened independently by seven reviewers (XY Zou, BX He, YL Liao, T Liu, YD Dai, SH Qi, and ZJ Sheng). Reviewers reviewed independently and worked in pairs. Disagreements on study selection were resolved by the third reviewer (XH Liu). We (XY Zou, BX He, YL Liao, T Liu, YD Dai, SH Qi, and ZJ Sheng) used Excel (2016) to extract the following items from the content of the included articles: publication, author, funding, study design, sample, participant characteristics, intervention, control/comparison groups, types of outcomes assessed, and outcome measures. Each part was extracted by two researchers independently and reviewed by each other. Differences were decided by the third reviewer (XH Liu).

Because of nonstandard explanations, the original compound outcome "Total effective rate" was transformed to "Symptom disappearance rate of olfactory dysfunction" and "Symptom remission rate of olfactory dysfunction". If the article reported that the total response rate was related to the disappearance and remission of symptoms, we divided cure, significant response, and response rate into symptom remission rate and symptom disappearance rate according to their definitions.

2.4. Quality assessment

Seven reviewers (XY Zou, BX He, YL Liao, T Liu, YD Dai, SH Qi and ZJ Sheng) worked in pairs to evaluate the risk of bias of eligible studies separately and cross-checked the findings. Disagreements were resolved by the third reviewer (XH Liu).

For RCTs, the Cochrane Collaboration "Risk of bias" assessment tool was used to assess the potential sources of bias with six parts.[17] We judged each item from three levels: "high risk", "low risk", and "unclear risk". For funding bias, trials sponsored by non-commercial funding were considered as "low risk", trials sponsored by pharmaceutical companies were considered "high risk", and no information was considered as "unclear risk". For non-RCTs, "Risk of Bias in Non-randomized Studies-of Interventions" assessment tool was used to assess the potential sources of bias with seven parts.[18] We responded to 33 signaling questions with

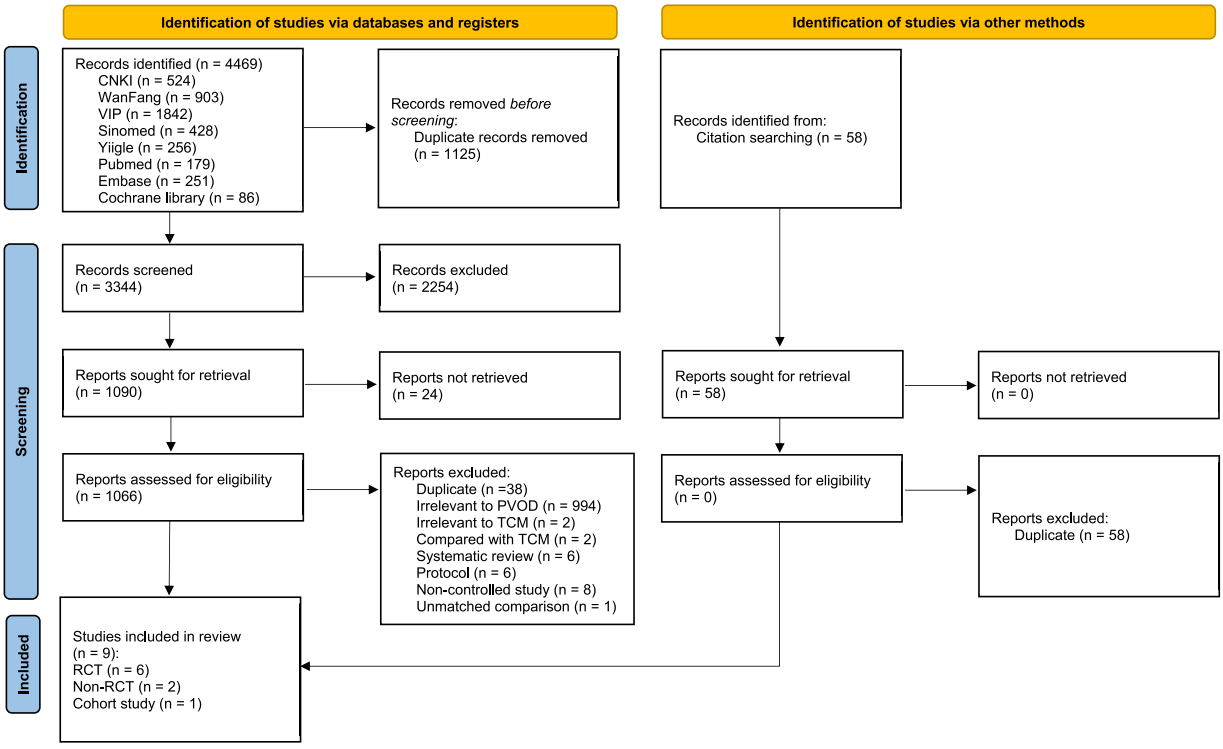

Fig. 1. Flow diagram of study selection in this review.
TCM: Traditional Chinese Medicine; PVOD: post-viral olfactory dysfunction; RCT: randomized controlled trial; Non-RCT: non-randomized controlled trial.

"Yes"; "Probably yes"; "Probably no"; "No"; and "No information". Responses to signaling questions provide the basis for domain-level judgments about the risk of bias. Then we evaluated the risk of each item: "Low risk" (If none of the answers to the signaling questions for a domain suggests a potential problem, then the risk of bias for the domain can be judged to be low), "Moderate risk", "Serious risk" and "Critical risk" and "No information". Finally, we evaluated the risk of the article with "Low risk", "Moderate risk", "Serious risk", "Critical risk" and "No information" according to the results of each item. For cohort studies and case-control studies, the "Newcastle-Ottawa Scale (NOS)" assessment tool was used to assess the potential sources of bias with eight items.[19] We scored each item according to the description under each item in the NOS scale based on the study content to get the score of case-control studies and cohort studies.

We used Grading of Recommendations, Assessment, Development and Evaluations (GRADE) scoring tool to evaluate the quality of evidence,[20] from five aspects: the risk of bias, imprecision, indirectness, inconsistency and publication bias.

2.5. Data analysis

Due to the heterogeneity of the included studies, no meta-analysis was performed in this review.We used RevMan 5.4.1 software for analysis. For the included studies, weighted mean difference (MD) with 95 % Confidence Intervals (CI) were used for continuous data, and risk ratio (RR) with its 95 % CI was used for dichotomous data. Due to the wide variety of TCM therapies which had inconsistent dosage forms, frequency, and method of administration, we used the random effect model.

3. Results

3.1. Description of included studies

We identified 4469 records and included nine studies[21-29] with 687 patients, including six RCTs, two non-RCTs, and one retrospective cohort study (Table 1). The specific screening process is shown in Fig. 1. Three studies were published in English, and six studies were in Chinese. The sample size of these studies ranged from 30 to 116. No follow-up, registration, sample size estimation and virus types were reported. The TCM therapies in nine studies[21-29] were acupuncture, acupoint injection, and the non-TCM therapies were western medicine, olfactory training, and supplements. The main western medicine used were Prednisone acetate tablets, mometasone furoate nasal spray. The main supplements used were mecobalamin tablets, ginkgo biloba extract tablets, and vitamin B. And they mainly tested the effect of two TCM therapies: acupuncture alone[21,22,25-29] or acupoint injection alone.[22,24] Only one study tested the combined efficacy of both interventions.[23] More specific treatment measures are presented in Table 2.

3.2. Quality assessment

The specific risk of bias assessment results of included studies are shown in Supplement 3. Most of the included studies are considered with a high risk of bias.

For RCTs, the "Unclear" of Random sequence generation was for only reporting random without details. Two trials reported the random allocation by random numbers.[24,28] No study reported allocation concealment and blinding methods. Four trials reported no dropout.[21,23,28,29] The other two trials analyzed data by per-protocol and reported the data of available participants.[21,23] Five trials were considered low risk,[21,23,24,28,29] and only one trial was considered high risk due to excessive dropout.[22] Four trials reported non-commercial funding,[21,22,28,29] one trial claimed no funding,[23] and another trial didn't report any funding information.[24]

For non-RCTs, two trials were considered with a serious risk of bias because the participants were grouped according to their own treatment preferences.[25,26] Another trial was considered with a serious risk of bias due to deviations from intended interventions and bias due to missing data (23 cases of withdrawals without any explanations).[26] Two trials used different olfactory tests for outcome measures.[25,26] The person

Table 1
Characteristics of included studies on TCM for PVOD participants.

First author (Year)	Study design Country	Total sample size/Sex (MF) Age	Comparisons	Outcomes	Results	Treatment time	Adverse event
Draws (2022)[21]	RCT Germany	60 anosmia type A: 30(NR); B: 30 (NR) A: 63.0; B:66.3	(A) Verum acupuncture (B) Sham acupuncture	1) Symptom remission rate	1) RR: 2.00 [0.55, 7.27]	12 times 2 sessions per week	No
Pang (2016)[22]	RCT NR	85 anosmia or hyposmia type A: 25 (11/14); B: 30(8/22); C:30 (6/24) A:55.2; B: 50.2; C:47.1	(A)Acupuncture (B)Yingxiang acupoint injection (Vt. B12, lidocaine) (C) No treatment (observation)	1) Symptom remission rate (A/C) 2) Symptom remission rate (B/C)	1) RR: 3.30 [1.20, 9.10] 2) RR: 3.50 [1.30, 9.41]	3 months	NR
Ma (2020)[23]	RCT China	90 anosmia or hyposmia type A: 45 (24/21); B: 45(25/20) A: 41.1; B: 40.8	(A) Acupuncture + acupoint injection (Vt. B12), plus (B) (B) Olfactory training + mecobalamin + prednisone acetate + ginkgo biloba extract	1) Symptom disappearance rate 2) The score of OD symptom (QOD-P) 3) The score of OD symptom (QOD-VAS) 4) Symptom remission rate	1) RR: 1.43 [0.83, 2.46] 2) MD: −1.73 [−2.40, −1.06] 3) MD: −4.54 [−5.46, −3.62] 4) RR: 1.14 [0.97, 1.33]	3 months	NR
Wang (2020)[24]	RCT China	90 anosmia or hyposmia type A: 30(9/21); B: 30(14/16); C: 30(10/20) A: 49.8; B: 49.7; C: 49.3	(A) Yingxiang acupoint injection (Vt. B12, lidocaine), plus C (B) Tiantu acupoint injection (vitamin B12, lidocaine), plus C (C) Prednisone + mecobalamin + ginkgo biloba extract	1) Symptom remission rate (A/C) 2) Symptom remission rate (B/C)	1) RR: 2.57 [1.26, 5.24] 2) RR: 2.14 [1.02, 4.49]	3 months	brief syncope (A:2) for acupuncture; pain (A:2); oral prednisone stomach discomfort (A:1; B:2; C:2)
Ding (2022a)[28]	RCT China	116 anosmia or hyposmia type A:58 (20/38); B: 58 (19/39) A: 46.4; B: 46.7	(A) Acupuncture (B) Mometasone furoate nasal spray	1) Symptom disappearance rate 2) Symptom remission rate	1) RR: 1.50 [0.89, 2.52] 2) RR: 1.34 [1.02, 1.77]	2 weeks	No
Ding (2022b)[29]	RCT China	104 anosmia or hyposmia type A: 52(16/36); B: 52(19/33) A: 44.1; B: 40.8	(A) Acupuncture, plus B (B) Conventional nasal hormone momeasone furoate nasal spray	1) The score of OD symptom (T&T olfactometer test) 2) The score of OD symptom (TDI score)	1) MD: 2.74 [2.17, 3.31] 2) MD: −0.46 [−0.93, 0.01]	4 weeks	NR
Dai (2016)[25]	Non-RCT China	50 hyposmia type A: 25(11/14); B: 25(5/20) A: 54.2; B: 49.1	(A) Acupuncture (B) No treatment (observation)	1) The score of OD symptom (UPSIT score) 2) Symptom remission rate	1) MD: 3.44 [−1.36, 8.24] 2) RR: 2.75 [1.01, 7.48]	3 months	No
Zhang(2018)[26]	Non-RCT China	62 anosmia or hyposmia type A: 33(12/21); B: 29(10/19) A: 40.5; B: 41.3	(A) Acupuncture, plus B (B) Olfactory training + prednisone + mecobalamin + ginkgo biloba extract	1) Symptom disappearance rate 2) The score of OD symptom (T&T olfactometer test) 3) Symptom remission rate	1) RR: 1.41 [0.52, 3.82] 2) MD: −0.11 [−1.05, 0.83] 3) RR: 1.06 [0.69, 1.61]	30–90day	NR
Vent (2010)[27]	Cohort Germany	30 anosmia or hyposmia type A: 15(8/7); B: 15(8/7) A: 48–73; B: 42–75	(A) Acupuncture (B) Oral vitamin B complex	1) Symptom disappearance rate 2) The score of OD symptom (Sniffin'Sticks Test) 3) Symptom remission rate	1) Not estimable* 2) MD: 2.10 [−1.99, 6.19] 3) RR: 4.00 [1.01, 15.81]	A: 9 weeks B: over 12 weeks	No

MD: mean difference; NR: not report; non-RCT: non-randomized controlled clinical studies; OD: olfactory dysfunction; PVOD: post-viral olfactory dysfunction; QOD-QOL: Questionnaire of Olfactory Disorders-Quality of life; QOD-P: Questionnaire of Olfactory Disorders-Paroxmia statements; QOD-VAS: Questionnaire of Olfactory Disorders-Visual simulation; RCT: randomized controlled trials; RR: risk ratio; TCM: Traditional Chinese Medicine; TDI: threshold discrimination identification; UPSIT: University of Pennsylvania smell identification test; *: none of the participants' symptom disappear.

Table 2
Description of treatment and control group therapies.

Study ID	Treatment group	Control group	Add-on*
Draws (2022)[21]	**Verum acupuncture**: routinely disinfected; points: meichong Bl3, shangxing GV23, yingxiang LI20, jinjin EX-HN12, ear16, lieque LU7, hegu LI4, sanyinjiao SP6, neiting ST44; 12 times with approximately 2 sessions per week	**Sham acupuncture**: routinely disinfected; points: deltoideus, upper arm, Thigh1, Thigh 2, Back1, Back2	No
Pang (2016)[22]	**Acupuncture**: routinely disinfected; huatuo acupuncture at yingxiang LI20 (double), shangyingxiang EX-HN8 (double) and biqiu (double); The needles were retained for 20 min after getting qi and were performed twice; one course of treatment was 10 times, 3 times a week, and the interval of treatment was 3–5 days; 3 months **Acupoint injection**: Extracted 0.1–0.2 ml lidocaine and vitamin B12 1 ml into the needle, slowly injected the drug into the skin of bilateral Yingxiang point. One course of treatment was 10 times, 3 times a week, and the interval of treatment was 3–5 days; 3 months	No treatment	No
Ma (2020)[23]	**Acupuncture**: routinely disinfected bilateral yingxiang LI20, Bitong EX-HN8 and yintang EX-HN3. The needle direction of yingxiang point is oblique upward along the nasolabial fold, the needle depth is 10–15 mm, the bitong point is slightly oblique upward into 10–15 mm, and the yintang point is horizontally pierced about 20 mm from top to bottom, reaching the root of the nose; The needle was kept for 30 min after the qi was obtained by the injection. During this period, the needle was administered twice; 3 times a week; 3 months **Acupoint injection**: 0.5 mg vitamin B12 was extracted from yingxiang point LI20 on both sides with a disposable skin test syringe, and the skin around yingxiang point was routinely disinfected and vertically pierced. After drawing back without blood, vitamin B12 solution was injected slowly; 2 days once, 10 times as a course of treatment with an interval of 3–5 days; 3 months	**Western medicine**: mecobalamin tablets orally, 0.5 mg/ time, tid; prednisone acetate tablets 30 mg/time, the dose was reduced by 5 mg per 5 days, and the tablets were taken orally in the morning, qd; 3 months **Supplements:** ginkgo biloba extract tablet was taken orally, 40 mg/time, tid; 3 months **Olfactory training**: select vinegar, alcohol, perfume, essence of wind Oil, sesame oil for smelling, bid; 3 months	Yes
Wang (2020)[24]	**Acupoint injection 1**: The skin at yingxiang point LI20 was routinely disinfected, 1 ml vitamin B12 injection + 0.2 ml 2 % lidocaine injection was extracted with a 2 ml syringe. The needle was vertically inserted into bilateral yingxiang point, and the needle was lifted and inserted and twisted until the acid anesthesia was heavy and swollen, and the blood was not returned after suction. The drug was slowly injected into bilateral yingxiang point, 0.5 ml of drug was injected into each side; twice a week, 8 times for a course of treatment; 3 months **Acupoint injection 2:** Routinely disinfect the skin at tiantu point RN22 (The same as above)	**Western medicine**: prednisone tablets were taken orally in the morning, the initial dose was 30 mg, and the dose was reduced to 10 mg every 5 days, qd, 15 days as a course; mecobalamin tablets 0.5 mg, orally, tid, 30 days as a course; 3 months **Supplements:** ginkgo biloba extract tablet 40 mg, orally, tid, 30 days as a course; 3 months	Yes
Ding (2022a)[28]	**Acupuncture:** Intranasal acupuncture was used under the nasal endoscope. 3-inch sterile acupuncture needle was used for bilateral neiyingxiang point (EX-HN9) and biqiu point, smooth reinforcement and diarrhea, without using special techniques, and the needles were retained for 30 min, qd, 2 weeks.	**Western medicine:** mometasone furoate nasal spray (50μg*60 presto) was used as external nasal spray, qd, 2 weeks.	No
Ding (2022b)[29]	**Acupuncture:** Intranasal acupuncture was used under the nasal endoscope at the bilateral neiyingxiang point (EX-HN9) and at the biqiu point, reinforcing and purging, without using special techniques, and leaving the needle for 30 min, qd, 4 weeks.	**Western medicine:** conventional nasal hormone momeasone furoate nasal spray (50 $\mu g \times 60$), qd, 4 weeks.	Yes
Dai (2016)[25]	**Acupuncture**: yingxiang LI20, shangyingxiang EX-HN8, and biqiu (located anterior to the middle turbinate). The needle may be turned clockwise upon insertion for tonification or counterclockwise for a more sedating effect on the points and energy centers. The needles were left in place for 20 min.; 3 times a week, 10 times per course. After each course, the patients rested for 3–5 days; 3 months	No treatment	No
Zhang (2018)[26]	**Acupuncture**: routinely disinfected, bilateral yingxiang point LI20 (tip along nasolabial sulcus upward inclined stab around 10–15 mm), bilateral bitong EX-HN8 (tip slightly inward inclined stab around 10–15 mm) and bilateral cuanzhu BL2 (about 15–20 mm from the top-down flat spines or so), 30 min after gas retaining needle, needle middle row 2 times, flat or level of skill; 3 times a week, 30days per course; 30–90 days	**Western medicine**: prednisone acetate tablets were given orally in the morning, the initial dose was 30 mg, and the dose was reduced by 5 mg every day, qd; mecobalamin tablets 0.5 mg, orally, tid; 30–90 days **Supplements:** ginkgo biloba extract tablet 40 mg, orally, tid; 30 days per course; 30–90 days **Olfactory training**: wind-oil essence, vinegar, sesame oil, alcohol and rose perfume, smell 10 s per time for each of the five odors, and then to smell another round after 10 min rest; bid, 30 days a cycle; 30–90 days	Yes
Vent (2010)[27]	**Acupuncture:** points: fengfu GV16, baihui GV20, yingxiang LI20, lieque LU7, taiyuan LU9, zusanli ST36, Ni3. The needles were left in place for 30 min. and the acupuncture sessions were repeated weekly for 10 weeks. There were 9 insertion points of acupuncture needles per session and patient; once a week; 10 weeks	**Oral vitamin B complex:** B1=thiamine, B6=pyridoxine, B12=cobalamine; over 12 weeks	no

*Whether the treatment groups also combined with the treatment of the control groups.

who completed these tests was not reported, therefore considered with a moderate risk of bias in the measurement of outcomes.

For the cohort study,[27] the exposed cohort showed somewhat representative of the average in the community. However, the non-exposed cohort was from the same community. This made the study less universal to the whole world. A standardized questionnaire was used to determine the exposure factors. At the start of the study, participants had PVOD. The study considered multiple factors such as age, sex, initial olfactory presentation, and the causes of olfactory impairment to determine comparability between the two groups. The study used olfactory tests to assess outcomes but did not report any follow-up.[27] Overall, the study scored a total of 6.

The quality of evidence assessed by GRADE mainly was low or very low (Supplement 4).

3.3. Effects of interventions

3.3.1. Symptom disappearance rate

Four studies with 298 participants reported the symptom disappearance rate.[23,26-28] Two RCTs and one non-RCT with 268 participants showed no difference. Though they were not at a significant level, acupuncture compared with western medicine (mometasone furoate nasal spray) in one RCT,[28] acupuncture, acupoint injection plus western medicine (prednisone acetate) with supplements (mecobal-

amin + ginkgo biloba extract) with olfactory training compared with the same western medicine and supplements plus olfactory training in one RCT,[23] one non-RCT[26] showed more symptom disappearance than the western medicine (prednisone) with supplements (mecobalamin + ginkgo biloba extract) plus olfactory training groups. In one cohort study (acupuncture compared with oral vitamin B complex),[27] nobody showed symptom disappearance by the end of the study (Table 1).

3.3.2. The score of olfactory dysfunction symptom

Five studies reported the score of olfactory dysfunction symptoms.[23,25-27,29] One RCT comparing acupuncture plus western medicine (conventional nasal hormone momeasone furoate nasal spray) with the same western medicine used two measurement: 1) used Sniffin'Sticks test showed beneficial result, however, 2) used T&T olfactory test did not show statistical significance.[29] Another RCT (acupuncture + acupoint injection + olfactory training + western medicine (prednisone acetate) with supplements (mecobalamin + ginkgo biloba extract) compared with olfactory training + the same western medicine and supplements) showed improvement in score of olfactory dysfunction symptoms.[23] A trial showed no difference between acupuncture and no treatment.[25] The cohort study showed no difference between acupuncture and supplement (oral vitamin B complex).[27] One non-RCT also showed no difference between acupuncture plus western medicine (prednisone acetate) and supplements (mecobalamin + ginkgo biloba extract) with olfactory training and the same western medicine and supplements with olfactory training.[24] All intervention groups failed to show significant effects on olfactory dysfunction symptoms than the control groups.

3.3.3. Symptom remission rate

Eight studies reported the symptom remission rate.[21-28] In symptom remission rate, acupuncture alone or acupoint injection was better than no treatment in one RCT[22] Acupuncture alone compared with western medicine (mometasone furoate nasal spray) showed beneficial results in one RCT,[28] and one RCT also showed better results for acupoint injection added on western medicine (prednisone acetate) and supplements (mecobalamin + ginkgo biloba extract) .[24] Two trials showed borderline statistical significance (one non-RCT[25] compared acupuncture with no treatment, one cohort study[27] compared acupuncture with oral vitamin B complex). Three trials showed no significant difference in acupuncture compared with placebo, acupuncture plus acupoint injection, western medicine, supplements, and olfactory training compared with western medicine (prednisone acetate) and supplements (mecobalamin + ginkgo biloba extract) plus olfactory training.[21,23,26] Five studies failed to show symptom remission improvement compared to the control groups.[21,23,25-27]

3.3.4. Adverse events

Only five trials (55.56 %) reported adverse events.[21,24,25,27,28] (Table 1). Among them, four trials reported no adverse events,[21,25,27,28] while one trial reported that a total of nine participants experienced adverse effects.[24]

3.3.5. Additional analysis

We were not able to conduct a meaningful funnel plot analysis to identify possible publication bias because it was less than ten included trials in each comparison.

4. Discussion

4.1. Summary of findings

Generally, we included six RCTs, two non-RCTs, and one retrospective cohort study in this systematic review. We observed that the integration of acupuncture or acupoint injection with western medicine or olfactory training exhibited a relatively discernible efficacy in alleviating olfactory dysfunction. Yingxiang LI20 and Tiantu RN22 were the most commonly used acupoints. Vitamin B12 and lidocaine were the commonly used acupoint injection agent. The two TCM therapies had a high level of safety, with only nine individuals experiencing adverse reactions and no reports of serious adverse events.

4.2. Theoretical inquiry

Although the underlying mechanism of PVOD is still unclear,[9] there were two potential types of PVOD: 1) is transitory or short-term dysfunction, which mainly occurred by the blockage of inspired air, sensorineural dysfunction, or central (olfactory bulbs and brain) dysfunction; 2) is chronic or permanent dysfunction, which caused by the loss of olfactory epithelium, or disruption of central olfactory processing networks.[30] A study showed that acupuncture may play a therapeutic role in olfactory disorders by promoting the regeneration of olfactory neurons and improving ventilation.[31]

4.3. Potential limitations

First of all, the small sample size, low quality (especially no placebo and no blinding) of included studies, and these studies sites mainly concentrated in China, may affect the reliability and the global applicability of results. Second, the included studies lacked some relatively important information, such as duration of follow-up, whether the participants had been vaccinated, and the type of OD. It prevents us from ruling out these confounding factors which could affect the accuracy of results. Third, the study did not report the specific virus type of infection, the current pathogenesis of PVOD was unclear,[9] so the lack of information regarding the virus types might affect the analysis of the targeted treatment of PVOD, which is also not conducive to the study of subsequent mechanisms. The study lacks direct evidence for COVID-19, so the applicability of our results to long COVID is questionable. Fourth, the types of TCM therapies used were single (only acupuncture and acupoint injection were used), no information about the effectiveness of other TCM therapies was reported in this review. What's more, due to the lack of placebo in the included studies, the influence of no blinding on the results cannot be ruled out.

4.4. Comparison with previous studies

Two systematic reviews reported the recommendation degrees of various treatments for PVOD (Recommendation level: No recommendation),[12,32] of which acupuncture is the only treatment associated with TCM. However, they both only referred to two clinical studies on acupuncture treatment of PVOD, without systematic retrieval and analysis. One systematic review was in line with our review which only included six trials.[33] They did not included other controlled studies. In addition, they ignored the potential high heterogeneity of the included studies for meta-analysis, and did not make subgroup analysis of different TCM therapies. They found that TCM was not significant in improving the effectiveness of PVOD treatment, but our more detailed results showed that acupuncture and acupoint injection may have positive effects.[31]

4.5. Implications for research

Well designed, multi-center, double-blind placebo-controlled trials with sufficient power should be designed in future and should be reported according to the Consolidated Standards for Reporting Trials (CONSORT) Statement and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).[34,35] Additionally, the rigorous use of scales during treatment helped improve the accuracy of diagnosis and efficacy assessment. As the wide use of coronavirus vaccine and the continuous of COVID-19 strains continue mutating, it is important to classify different types of olfactory dysfunction, specify the virus

types and explore the impact of vaccination. In addition, olfactory dysfunction often co-occurred with gustatory dysfunctions,[36] so we should record and analyze this in the treatment process.

4.6. Conclusions

This systematic review suggested that TCM (acupuncture) showed a few positive effects for PVOD in symptom remission. However, considering the generally low methodological quality of the included trials, more well-designed and high-quality trials are needed to confirm the benefit and explore safety further.

Authors' contributions

Conceptualization: JPL, XHL. Methodology: JPL, XHL, CLL, XYJ. Software: XHL, XYZ. Validation: XHL. Formal analysis: XYZ. Investigation: XYZ, BXH, LYL, TL, DYD, SHQ, ZJS. Writing – Original Draft: XYZ, XHL. Writing – Review & Editing: JPL, XHL, XYJ, CLL, GYY, TS, ZFY. Supervision: JPL, XHL. Project administration: XHL. Funding acquisition: JPL, XHL.

Declaration of competing interests

The author JPL is senior editorial board member of the journal, but none of the authors has any conflict of interest regarding this study.

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Ethical statement

Not applicable.

Data availability

All data used and/or analyzed during this review are included in public databases.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2024.101045.

Supplement 1. PRISMA 2020 checklist.

Supplement 2. Search strategy.

Supplement 3. Risk of bias of included studies.

Supplement 4. Summary of findings by GRADE.

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