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Systematic Review

Comparison of herbal products with antifungal drugs in cure of oral candidiasis: A systematic review

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ABSTRACT

Background: Oral candidiasis is one of the most common fungal infections affecting the oral mucosa. It is usually managed by taking antifungal medication that might result in side effects such as toxicity and drug resistance. Therefore, consumption of herbal medicine with antifungal activity and fewer side effects has become popular. This study is a systematic review to investigate the improvement and reduction of oral candidiasis symptoms by herbal compounds compared to conventional antifungal drugs.

Materials and Methods: PubMed, Scopus, Web of Science, Cochrane, and Magiran databases were searched from 1995 to 2021 based on the keywords of the question formula – oral candidiasis (P), herbal compounds (I), antifungal drugs (C), and improvement of clinical symptoms and laboratory tests (O) – to find related randomized controlled trials (RCTs) in English and Persian languages. Related articles were extracted based on inclusion and exclusion criteria and critically appraised using the modified-CONSORT checklist. The risk of bias was also assessed using the Cochrane tool.

Results: After removing duplicates and checking the title and abstract of the articles, 98 articles from 1995 to November 2021 of 715 were reviewed. 83 RCTs were excluded due to non-relevancy and 15 remained for critical appraisal, of which 5 articles were rejected. Finally, 10 articles were included in the systematic review. Based on the risk of bias assessment, one article had low risk, 6 articles had unclear risk, and 3 articles had a high risk of bias. Herbal compounds were applied in the form of gel in 3 articles, in the form of ointment and mouthwash in 1 and 6 articles, respectively. In terms of clinical improvement and laboratory findings, herbal compound mouthwashes and ointment did not have a significant difference from conventional antifungal drugs, but the articles related to compound gels reported variable effects (better, similar, and weaker). Furthermore, herbal compounds generally had more patient satisfaction than antifungal drugs.

Conclusion: It seems that herbal compounds have clinical applications in the treatment of oral candidiasis and gained more patients' satisfaction. To achieve more valid results, it is suggested to conduct more RCTs with a low risk of bias.

Key Words: Antifungal agents, drug therapy, herbal medicine, oral candidiasis, systematic review

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INTRODUCTION

Oral candidiasis is one of the most prevalent fungal infections of the oral mucosa. *Candida albicans* – the most commonly observed species – is one of the components of normal oral microflora of 30%–50% of people. Various local and systemic factors can increase the growth of this microorganism and its pathogenicity by disrupting the balance of the microbial flora of the mouth.[1] Wearing dentures, changes in the quality and quantity of saliva, smoking, and inhalation of steroids are examples of the local factors. Systemic predisposing factors are immunodeficiency, diabetes, systemic antibiotics, hematinic deficiency, and chemotherapy.[2]

This infection is usually managed by eliminating or reducing the predisposing factors and taking antifungal drugs. Available antifungal agents for managing candidiasis belong to four drug classes: azoles, polyenes, echinocandins, and pyrimidine analogs (flucytosine). Azoles and polyenes act at the level of the fungal membrane, echinocandins on the fungal cell wall, and flucytosine impairs nucleic acid synthesis.[1] Topical antifungals such as nystatin and miconazole are at the first line of treatment.[3] However, it is not uncommon for patients to suffer from the adverse side effects of taking chemical antifungals; toxicity might occur, especially in elderly people who suffer from denture stomatitis or immunosuppressed patients who have to take antifungal drugs continuously to prevent the recurrence of fungal disease.[4,5] Moreover, drug resistance has developed because of the growing application of antifungals.[6] Furthermore, an increase in the incidence of invasive candidiasis has been reported due to the antifungal resistance of *Candida* species.[7]

Considering the treatment failures associated with antifungal resistance and the need to produce newer antifungals or improve existing antifungals for better efficacy and fewer side effects, the study of using plants with antifungal properties for treating candidiasis has been trending.[6] Herbal compounds have fewer adverse effects and are less expensive.[8] Herbal compounds exhibit different mechanisms of action against Candida species, including inhibition of fungal cell wall synthesis, disruption of cell membrane integrity, interference with fungal cell proliferation and metabolism, modulation of host immune responses, and attenuation of virulence factors.[4,9,10] These multifaceted mechanisms contribute to the antifungal efficacy of herbal remedies and highlight their potential as alternative therapeutic agents for candidiasis.

Therefore, this systematic review aimed to investigate the improvement of oral candidiasis by herbal compounds compared to conventional antifungal drugs.

MATERIALS AND METHODS

The present study is a systematic review of English or Persian articles comparing the effectiveness of herbal compounds with conventional antifungals in treating oral candidiasis in adults (Project ID: 3400898, Code of Ethics: IR.MUI.RESEARCH.REC.1400.439). The protocol has been also registered in Center for Reviews and Dissemination, University of York, UK with the registration number of CRD42024604440.

PICO was determined as follows:

- Population: Oral candidiasis infections of adult patients
- Intervention: herbal drugs in different forms such as mouthwash, gel, ointment, etc.
- Comparison: Antifungal available drugs in different forms such as mouthwash, gel, and ointment (nystatin, miconazole, clotrimazole, fluconazole, ketoconazole, amphotericin B, posaconazole, and itraconazole)
- Outcomes:
  i. Primary outcome: clinical improvement including the reduction in severity of the disease based on the Newton's classification[11] (Newton's type I (localized erythematous), Newton's type II (diffuse erythematous), or Newton's type III (hyperplastic granular)), clinical cure rate, reduction of white plaque or erythema by measuring the length of the lesion or surface, pain reduction using VAS or qualitative questions, and itching
  ii. Secondary outcome: improvement of mycological analysis (reduction of Colony-Forming Unit [CFU] in culture experiments), minimum inhibitory concentration, minimal fungicidal concentration, and zone of inhibition
  iii. Safety outcome: side effects and drug tolerance by patients. English databases including Medline (via PubMed), Scopus, Web of

Science, Cochrane Library, and the Persian Magiran database were searched. In the manual search, the references of the related extracted articles were checked and new related articles were added. The search protocol was developed by one of the principal investigators (BT). The search strategy is available in Appendix 1.

Inclusion and exclusion criteria

The title and abstract of the articles that were in English or Persian were reviewed. Randomized controlled trials (RCTs) that were conducted on adult (above 18 years old) patients with stomatitis with good general health or having systematic disease and tested herbal compounds compared to one of the antifungals (nystatin, miconazole, clotrimazole, etc.) were included. Studies that were conducted on animal samples or compared their herbal compounds with other substances such as chlorhexidine, triclosan, and placebo were excluded. Then, the full text of the remaining articles was extracted.

Critical appraise

Two of the researchers (BT and NG) reviewed the extracted articles. A third-party adjudicator was involved if the scores differed dramatically (more than 3 points). The modified CONSORT checklist [Appendix 2] was used for the critical appraisal of RCT articles. Articles that scored at least 70% (21 out of 30) were accepted.[12] Therefore, they were categorized as low quality or reject (scoring 20 or below), moderate quality (scoring 21–25), and high quality (Scoring 26 or more). To assess the risk of bias the Cochrane tool adapted from Higgins and Altman[13] was used [Appendix 3]. Based on this tool, five main sources of bias needed to be assessed; to address the selection bias, a description about the method used to generate the allocation sequence and to conceal the allocation sequence should be provided in the article. Performance bias might be resolved if the measures to blind trial participants and researchers have been used. Detection bias could be addressed by assessing the explanations about the measures used to blind outcome assessment from knowledge of which intervention a participant received. Attrition bias describes the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Reporting bias states how selective outcome reporting was examined and what was found. The total bias level was judged based on the fact that how much they were to alter the results seriously.

RESULTS

Search results

After removing duplicates and checking the title and abstract of the articles, 98 articles from 1995 to November 2021 remained, and their full text was reviewed. 83 RCTs were excluded due to non-relevancy and 15 remained for critical appraisal [Figure 1].

Results of risk of bias assessment

of the 15 remaining articles, 5 had low quality and were rejected. The major areas of losing scores were randomization, concealment of interventions, and reporting the results. In total, 10 articles were eligible, with 7 articles rated as medium and 3 as high quality. Scoring details are available in Appendix 2. The risk of bias was assessed for accepted RCTs. 1 article had low risk, 6 articles had unclear risk and 3 articles had a high risk of bias. The details are available in Table 1. Considering that most of the articles had an unclear risk, the overall risk of bias was unclear.

The data from accepted articles were extracted for qualitative review. It included the author, year of publication, characteristics of samples and participants, study design, description of the intervention, measured outcomes (primary, secondary, and safety), and their results are available in Table 2.

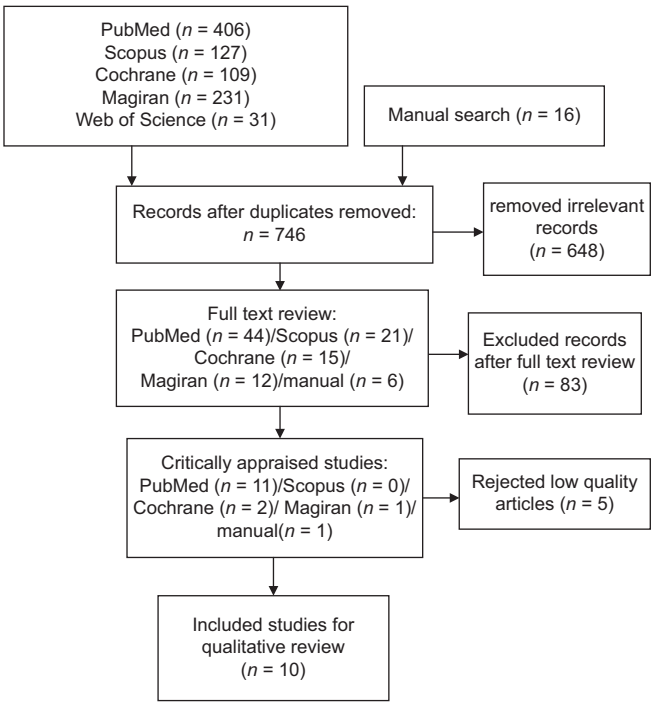

Figure 1: PRISMA chart of included articles.

Table 1: Risk of bias scores of the included articles

Authors	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	The overall risk of bias
Tatapudi *et al*.[21]	High	High	Unclear	Unclear	Low	Low	High
de Araújo *et al*.[4]	Low	Low	Low	Unclear	Low	Low	Unclear
Gonoudi *et al*.[14]	Low	Low	Unclear	Unclear	Low	Low	Unclear
Eslami *et al*.[15]	Low	Unclear	Low	Unclear	Low	Low	Unclear
Najafi *et al*.[16]	Low	Low	Low	Low	Low	Low	Low
Tay *et al*.[18]	Low	Unclear	Unclear	Low	Low	Low	Unclear
Pinelli *et al*.[17]	High	High	High	High	Low	Low	High
Bakhshi *et al*.[10]	Unclear	Low	Low	Low	Low	Low	Unclear
Amanlou *et al*.[19]	Unclear	Unclear	Low	Low	Low	Low	Unclear
Vasconcelos *et al*.[20]	High	Unclear	Unclear	Unclear	Low	Low	High

Out of 10 reviewed articles, the type of herbal product in 6 articles was mouthwash (in one article, in addition to mouthwash, the spray was also used for dental hygiene). In 3 articles, the products were tested in the form of gel, and in one article, ointment was used. The drugs compared in these studies were nystatin mouthwash, miconazole gel, and clotrimazole ointment, respectively. (In one article, nystatin mouthwash and miconazole gel were compared with herbal product mouthwash.)

Articles related to the mouthwash of herbal products

According to the study by de Araújo *et al*. in 2021, mouthwash and spray containing the essential oil of *Cinnamomum zeylanicum* leaves ($P = 0.0339$) and nystatin ($P = 0.0139$) both showed significant clinical effects and reduced the degree of Newton's classification in denture stomatitis. Furthermore, the number of *Candida* spp. was reduced after 15 days of using the spray and mouthwash in both groups.[4]

Investigations by Gonoudi *et al*. in 2021 showed that after 14 days, *Zataria multiflora* essential oil was as effective as nystatin in reducing the size of palatal erythema ($P < 0.001$ for both groups) and the number of *Candida* colonies ($P < 0.001$ for both groups).[14]

The study by Eslami *et al*. in 2015 stated that *Zingiber officinale* (ginger) and nystatin mouthwashes had a similar and acceptable effect on reducing the size of erythema and treating candidiasis ($P < 0.001$ for both groups), but patients' satisfaction with *Z. officinale* mouthwash (86.7%) was more than nystatin (13.3%). Therefore, it suggested *Z. officinale* mouthwash as an alternative to nystatin.[15]

The study by Najafi *et al*. in 2015 showed that there was no significant difference between *Camellia sinensis* (green tea) extract mouthwash and nystatin in reducing the size of erythema and the number of fungal colonies.[16]

Pinelli *et al*.'s study in 2013 showed that the effectiveness of *Ricinus communis* mouthwash in reducing clinical signs was the same as miconazole gel and it can be a suitable alternative to conventional treatments in institutionalized elderly. In this study, nystatin drop was the other comparison group, which after 30 days, unlike *R. communis* ($P = 0.011$) and miconazole ($P = 0.018$), did not show significant clinical improvement in terms of reduction in Newton's classification degree. The number of fungal colonies did not change significantly in any of the three groups after 15 and 30 days.[17]

The study by Bakhshi *et al*. in 2012 introduced garlic mouthwash as a suitable replacement for nystatin due to the lack of side effects and enhanced patient satisfaction. According to this study, both groups of mouthwash had a significant effect on reducing the length ($P < 0.001$) and width ($P < 0.0001$) of erythema in different time courses. There was a significant difference between the patients' satisfaction of the two groups ($P < 0.0001$), which was higher in the garlic group (85%).[10]

Articles related to the gel of herbal products

In the study by Tay *et al*. in 2014, the effect of *Uncaria tomentosa* gel was measured in comparison with miconazole gel and placebo. The severity of the disease based on Newton's classification ($P < 0.05$ for all groups) and the number of fungal colonies ($P < 0.05$ for all groups) reduced with no significant difference among the groups. Therefore,

Table 2: Data extracted from included articles

Author, year	Participants (number, age, sex, region, systemic conditions)	Study design	Interventions (study groups, treatment protocol, follow-up)	Outcomes (primary, secondary, immunologic)	Results and *P*-value
Tatapudi *et al*., 2021	Patients with history of denture stomatitis *n*=50 (female=23, male=17) Healthy=28 Medically compromised=22 (8 Diabetes, 7 Hypertension, 2 Asthma, 2 Monoplegia, 2 Hypothyroidism, 1 Vitiligo)	Double-blind RCT	a. 25 curcumin ointment (Male=12, healthy=15) b. 25 clotrimazole (Male=5, healthy=13) (3×/day, 14 days) Follow=day 7, 14, 21, 28	Primary 1. Complete resolution of the lesion Secondary 2. Colony counts mean number 3. Mycological eradication (%) Immunologic 4. Tolerability 5. Side effects	1. Complete resolution of the lesion No significant difference between the two groups (*P*=0.765) a. Curcumin 14 after 14 days 10 after 21 days 1 after 28 days b. Clotrimazole 12 after 14 days 11 after 21 days 2 after 28 days 2. Colony counts a. Curcumin 37.08 before 3.72 after b. Clotrimazole 63.96 before 14.08 after 3. Mycological eradication100% for both after 28 days, no significant difference between the two groups (*P*=0.404) 4, 5. Both treatments were well tolerated with no side effects
Araújo *et al*., 2021	Patients aged 40–70 visiting the oral diagnosis clinic of Federal University of Paraiba with oral candidiasis wearing maxillary dentures *n*=36 (female=27)	Double-blind RCT	a. 18 *C. zeylanicum* EO (0.5 mg/mL) Mouth wash + spray b. 18 nystatin (100,000 IU/mL) Mouth wash + spray (3×/day, 15 days) Follow=day 16	Primary 1. Newtonian DS degree reduction (%) Secondary 2. CFU count reduction (%) Immunologic 3. Unpleasant taste (%) 4. Undesirable effects (%)	1 a. *C. zeylanicum* EO had efficacy (*P*=0.0339) Type I (9% reduction) Type II (60% reduction) Type III (0% reduction) b. Nystatin had efficacy (*P*=0.0139) Type I (27% reduction) Type II (71% reduction) Type III (0% reduction) 2. CFU count reduction a. *C. zeylanicum* EO Oral mucosa 61% (*n*=11) Denture 33% (*n*=6) b. Nystatin Oral mucosa 89% (*n*=16) Denture 83% (*n*=15) 3. Unpleasant taste a. *C. zeylanicum* EO 16.7% (*n*=3) b. Nystatin 38.9% (*n*=7) 4. Undesirable effects a. *C. zeylanicum* EO 16.7% (*n*=3) (numbness=2, burning=1) b. Nystatin 5.6% (*n*=1) (Tongue sensitivity)
Gonoudi *et al*., 2021	Patients (>18 years old) of dental clinic of the Islamic Azad University of Tehran suffering from type II or III denture stomatitis *n*=28 (female=7, male=21)	Single-blind RCT	a. 14 *Z. multiflora* EO 0.05% (rinse one teaspoon [5 mL]) b.14 nystatin (rinse 40 drops of 100,000-unit suspension) (4×/day, 14 days) Follow=Day 14	Primary 1. Mean erythema (mm^2) Secondary 2. Mean number of CFUs	1. Mean erythema a. *Z. multiflora* EO 0.05 % 75 mm^2 before 42.86 mm^2 after b. Nystatin 68.93 mm^2 before 21.07 mm^2 after both nystatin and *Z. multiflora* significantly decreased the erythema (*P*<0.001) they had no significant difference from each other in this regard (*P*=0.256) 2. Mean number of CFUs a. *Z. multiflora* EO 0.05 % 67,857.14 before 19,071.43 after b. nystatin 78,714.29 before 22,000 after both nystatin and *Z. multiflora* caused a significant reduction of *C. albicans* colony count (*P*<0.001) they had no significant difference from each other in this regard (*P*=0.593)

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Table 2: Contd...

Author, year	Participants (number, age, sex, region, systemic conditions)	Study design	Interventions (study groups, treatment protocol, follow-up)	Outcomes (primary, secondary, immunologic)	Results and *P*-value
Eslami *et al*., 2015	Patients with type II denture stomatitis visiting Tabriz University Dentistry clinics in 2014 *n*=30	Double-blind RCT	a. 15 ginger mouthwash 20 mL b. 15 nystatin mouthwash 500,000 IU (3×/day, 20 day) Follow=day 5, 10, 15, 20	Primary 1. Length and width of erythema (mm) Immunologic 2. Patients satisfaction (%)	1. Erythema (length, width) a. Ginger D0: (26.22±5.70, 32.20±4.37) mm D5: (22.91±5.54, 28.81±4.35) mm D10: (17.73±4.71, 20.32±5.10) mm D15: (8.55±3.75, 10.49±3.79) mm D20: (1.16±1.77, 1.28±2.02) mm b. Nystatin D0: (26.28±6.24, 31.06±9.01) mm D5: (22.63±6.88, 27.22±6.82) mm D10: (17.53±7.50, 21.92±7.21) mm D15: (6.34±10.18, 7.60±11.32) mm D20: (4.02±10.60, 4.49±11.56) mm both treatments significantly reduced the width and length of the erythema (P<0.001) the changes between groups were not significant (P=0.9) 2. Patients satisfaction a. Ginger 10 very good=66.7% 3 good=20% 2 fair=13.3% 0 poor=0% b. Nystatin 0 very good=0% 2 good=13.3% 7 fair=46.7% 6 poor=40% Ginger group (86.7%) were significantly more satisfied than nystatin group (13.3%) (P<0.001)
Najafi *et al*., 2015	Patients aged 45–60 with denture stomatitis who were referred to the Department of Oral Medicine, Tehran University of Medical Sciences *n*=27 (female=20, male=7)	Double-blind RCT	a. 15 green tea extract mouthwash 0.58% b. 12 nystatin mouthwash rinse 15–20 drops (4×/day, 14 days) Follow= day 7, 14	Primary 1. Erythema surface 1=0–5 cm^2 2=5–10 cm^2 3=10–15 cm^2 4=15–20 cm^2 5=20–25 cm^2 6=25 and more 2. Degree of inflammation Secondary 3. Density of colony count 1=No growth 2=1–9 colonies 3=10–100 colonies 4=More than 100 5=Uncountable	1. Erythema surface was significantly reduced in both groups at follow-up visits There was no significant difference between the two groups at the same visits (D0: P=0.858 D7: P=0.535 D14: P=0.498) 2. In both nystatin and green tea groups the degree of inflammation was different (P=000.0) Green tea D0–7: P=0.001 D0–14: P=0.001 D7–14: P=0.040 Nystatin No P-values 3. No significant difference in the colony numbers between the two groups at all visits (D0: P=0.786 D7: P=0.980 D14: P=0.612) colony counts significantly reduced at all visits in both groups compared with starting day (P=0.000) Comparing colony count at each time in both groups: D0–7: P=0.000 D7–14: P=0.074 D0–14: P=0.006
Tay *et al*., 2014	Individuals of 45–85 years with good general health, with denture stomatitis type I, II, and III from the Department of Dentistry of the State University	Double-blind RCT	a. 16 *Uncaria tomentosa* 2% gel b. 15 Miconazole 2% gel c. 17 hydroxyethyl cellulose (placebo) 2.5 mL (one teaspoonful)	Primary 1. Newtonian DS degree Secondary 2. CFU/mL (Log)	1. Severity diminished with no significant differences between the treatments (P>0.05) 2. CFU diminished with no significant differences between the groups (P>0.05). On day 7, there was a lower number of CFU in miconazole group

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Table 2: Contd...

Author, year	Participants (number, age, sex, region, systemic conditions)	Study design	Interventions (study groups, treatment protocol, follow-up)	Outcomes (primary, secondary, immunologic)	Results and *P*-value
	of Ponta Grossa *n*=48 (female=43, male=5)		of gel (3×/day, 7 days) Follow=day 7, 14		
Pinelli *et al*., 2013	Patients over 60 years who were residents at long-term care institution Lar Sao Francisco de Assis *n*=30 (female=24, male=6)	RCT	a. 10 *R. communis* mouthwash b. 10 Miconazole oral gel c. 10 Nystatin an eyedropper on the tongue (4×/day, 30 days) Follow=day 15, 30	Primary 1. Newtonian DS degree Secondary 2. Mean CFU/mL (Log)	1. Clinical improvement a. *R. communis* D1–30 (*P*=0.011) D15–30 (*P*=0.011) b. Miconazole D1–30 (*P*=0.018) D15–30 (*P*=0.018) c. Nystatin D1–30 (*P*=0.06) D15–30 (*P*=0.22) 2. Mean CFU/mL a. *R. communis* D1: 4.45±0.74 D15: 4.29±0.88 D30: 4.37±0.94 b. Miconazole D1: 4.36±0.70 D15: 3.87±0.71 D30: 3.96±1.15 c. Nystatin D1: 5.10±0.98 D15: 4.39±1.37 D30: 4.63±1.52 Intragroup CFU/mL comparisons showed no significance a. *R. communis* D1–15 (*P*=0.44) D1–30 (*P*=0.83) D15–30 (*P*=0.74) b. Miconazole D1–15 (*P*=0.09) D1–30 (*P*=0.46) D15–30 (*P*=0.79) c. Nystatin D1–15 (*P*=0.08) D1–30 (*P*=0.23) D15–30 (*P*=0.44)
Bakhshi *et al*., 2012	Aged people with DS living in Kahrizak elderly home in Tehran *n*=40 (female=24, male=16)	Double-blind RCT	a. 20 Garlic aqueous solution 40 mg/mL b. 20 Nystatin mouthwash 100,000 U/mL rinse 20 drops (3×/day, 28 days) Follow=day 7, 14, 21, 28	Primary 1. Erythema length and width (cm) Immunologic 2. Side effects (%) 3. Patient satisfaction (%)	1. Both had significant effect on length (*P*<0.001) and width (*P*<0.0001) of erythema in different time courses a. Garlic (width, length) D1 (3.63, 3.53) D7 (2.3, 2.33) D14 (1.48, 1.48) D21 (1.09, 0.99) b. Nystatin (W, L) D1 (3.03, 3.61) D7 (1.65, 2.08) D14 (0.7, 0.79) D21 (0.08, 0.11) 2. Side effects a. Garlic 1 itching (2.5%) 4 bad taste (10%) b. Nystatin 17 bad taste (42.5%) 6 nausea (15%) 1 vomiting (2.5%) 5 diarrhea (12.5%)

Contd...

Table 2: Contd...

Author, year	Participants (number, age, sex, region, systemic conditions)	Study design	Interventions (study groups, treatment protocol, follow-up)	Outcomes (primary, secondary, immunologic)	Results and *P*-value
					1 anorexia (2.5%) 1 burning (2.5%) 3. Significant difference between the degree of satisfaction among the two groups was found ($P<0.0001$) a. Garlic 5 very good (25%) 14 good (70%) 1 moderate (5%) b. Nystatin 8 good (40%) 12 moderate (60%)
Amanlou *et al*., 2006	Patients from 45 to 83 with moderate or severe (type II or III) Erythematous denture stomatitis confirmed by microbiologic cultures from the Department of Oral Medicine, Tehran University of Medical Sciences *n*=24 (female=14, male=10) 10 patients had history of systemic disease	Open RCT	a. 12 *Z. multiflora* essential oil 0.1% gel (systemic disease=6) b. 12 Miconazole 2% gel (systemic disease=4) Apply 2.5 mL (one teaspoonful) on denture (4×/day, 14 day) Follow=day 7, 14, 21, 28	Primary 1. Erythema surface 1=0–5 cm^2 2=5–10 cm^2 3=10–15 cm^2 4=15–20 cm^2 5=20–25 cm^2 6=25 and more Secondary 2. Density of mycological cultures 1=No growth 2=1–9 colonies 3=10–100 colonies 4=More than 100 5=Uncountable Immunologic 3. Adverse reactions (%)	1. The erythema surface of the palatal surface was significantly reduced in both groups. No significant difference between the two groups (D7: $P=0.44$ D14: $P=0.14$ D21: $P=0.59$ D28: $P=0.75$) 2. Colony numbers Palatal mucosa: *Z. multiflora* had significant reduction compared with D0 apart from days 21 and 28 (D21 $P=0.07$, D28 $P=0.08$) No statistical differences between two groups (no *P*-value) Maxillary denture: Colonies were reduced more efficiently in Miconazole than in *Z. multiflora* except for D21 when both groups were similar ($P=0.17$) significant reduction of denture colonies in both groups compared with D0 except D7 in *Z. multiflora* ($P=0.65$) 3. Adverse reaction a. *Z. multiflora*=59.3% (itching, burning, vertigo, nausea, vomiting and bad taste) b. Miconazole= 50%(burning, vomiting and bad taste)
Vasconcelos *et al*., 2003	Denture wearers of 19–62 years with candidosis from the dental clinic at the Federal University of paraıba. They had no systemic disorder *n*=60	Double-blind RCT	a. 30 *P. granatum* gel b. 30 miconazole gel (3×/day, 15 days) Follow=day 17	Primary 1.Clinical response (number of patients with satisfactory regular unsatisfactory responses) Secondary 2. Laboratorial results (number of patients with positive or negative results) Immunologic 3. Side effect	1. Clinical response a. *P. granatum* Satisfactory + Regular 7+14=21 Unsatisfactory=9 b. Miconazole Satisfactory+ Regular=19+8=27 Unsatisfactory=3 This difference between the groups was significant ($P<0.01$) 2. Laboratorial results a. *P. granatum* Positive=7 Negative=23 b. Miconazole Positive=5 Negative=25 This outcomewas similar for both groups ($P>0.01$) 3. Side effect a. *P. granatum* No complaints b. Miconazole Reported by all subjects. Nausea and gastric disorders were the most frequent

P. granatum: Punica granatum, Z. multiflora: Zataria multiflora, R. communis: Ricinus communis, C. albicans: Candida albicans, C. zeylanicum: Cinnamomum zeylanicum, RCT: Randomized controlled trials

it suggested *U. tomentosa* gel as an effective topical adjuvant treatment.[18]

The study by Amanlou *et al*. in 2006 stated that *Z. multiflora* essential oil gel can be used to treat denture stomatitis and has the same effect as miconazole gel. Both had improved palatal erythema and decreased the number of fungal colonies of the mucosa with no significant difference. Miconazole was more effective than *Z. multiflora* in decreasing the colony counts of the denture surface. Side effects were also reported in both groups.[19]

Vasconcelos *et al*.'s study in 2003 concluded that *Punica granatum* extract gel may be used as a topical antifungal in treating oral candidiasis. This product was not significantly different from miconazole gel in terms of laboratory results, but the difference between the two groups was significant in clinical response ($P < 0.01$) and miconazole gel performed better. Side effects were reported by all patients in the miconazole group, while there were no complaints in the *P. granatum* group.[20]

Articles related to the ointment of herbal products

The study by Tatapudi *et al*. in 2021 found that curcumin ointment (produced by the rhizome of *Curcuma longa*) could be an effective treatment as an alternative to clotrimazole ointment. There was no significant difference in the number of recovered patients between the two groups. The number of fungal colonies decreased after treatment in both groups, and there was no significant difference between them. Both treatments were tolerable for patients and had no side effects.[21]

DISCUSSION

The present study is a systematic review to investigate the effectiveness of herbal compounds compared to common antifungals in the treatment of oral candidiasis in terms of clinical improvement of the lesion, laboratory findings from fungal culture tests, and reported side effects by patients. Regarding the clinical improvement, herbal compounds have generally had the same effect as conventional antifungals. This was measured in different ways in the studies, such as the size of the erythema area, Newton's classification, and the percentage of treated people. Patients with history of denture stomatitis with good general health were recruited in 8 out of ten studies. In two studies patients with systemic disease such as diabetes were also included. Most of the participants were in the age group of 18–60 years. 4 studies included also people above 60 years old.

Z. multiflora, *Z. officinale*, *C. sinensis,* and garlic mouthwashes reduced the size of oral erythema similarly to nystatin mouthwash.[10,14,16] Having a wide range of antimicrobial properties, *Z. officinale* is used in traditional medicine to treat many infectious diseases, and its antifungal effect on *C. albicans* along with anti-inflammatory and antibacterial activities can help to improve oral candidiasis.[15] In addition to its antimicrobial properties, *C. sinensis* has other properties such as anti-inflammatory, antioxidant, antimutagenic, and antidiabetic, which can play an important role in reducing erythema and mucosal inflammation.[16] Allicin is the most potent antimicrobial substance in garlic, which also plays a role in strengthening the immune system. This substance increases the production of cytokines and, at the same time, enhances the activity of macrophages, lymphocytes, and other cells of the immune system.[10] It has been also reported that herbal allicin from garlic might interfere with essential fungal processes, including DNA replication, protein synthesis, and energy metabolism, and could target specific molecular pathways within fungal cells, inhibiting cell proliferation and growth. In addition, herbal compounds may modulate fungal virulence factors, such as hyphal morphogenesis and adhesion to host tissues, thereby attenuating Candida pathogenicity and virulence.[9] Amanlou *et al*. reported that the use of *Z. multiflora* gel caused a more significant reduction in the level of erythema compared to miconazole gel, which could be due to the anti-inflammatory properties of this herbal compound.[19]

R. communis mouthwash and *U. tomentosa* gel reduced the severity of the disease based on Newton's classification like miconazole gel.[17,18] *C. zeylanicum* mouthwash also had the same effect compared to nystatin mouthwash.[4] According to Pinelli *et al*.[17], *R. communis* mouthwash and miconazole gel caused clinical improvement in elderly people, whereas using nystatin drop was ineffective. This could be attributed to the resistance of *C. albicans* to nystatin as the first line of treatment and the low adherence of elderly patients to the treatment. The latter can be due to the bitter and unpleasant taste of nystatin, and the motor difficulties in the elderly; applying nystatin with a dropper seems to be more difficult than using *R. communis* mouthwash or miconazole gel.[15]

Placebo, reported by Tay *et al*., reduced the severity of the disease with no significant difference from the *U. tomentosa* gel and miconazole; as a result, it cannot be confirmed that *U. tomentosa* gel was solely responsible for the reduction.[18]

In terms of the "percentage of people with complete clinical recovery" variable, the results were similar when comparing curcumin ointment with clotrimazole. This can be related to curcumin inhibiting the binding of Candida species to mucosal epithelial cells.[21] On the contrary, in the study by Vasconcelos *et al*., the miconazole group had a higher percentage of people with acceptable clinical results than the *P. granatum* gel group; this finding could be associated with better oral hygiene by the first group and greater adhesion of miconazole to the mucosa.[20] Laboratory findings also have reported that herbal compounds and antifungals had almost the same results. Some of these compounds exert their antifungal activity by affecting the fungal cell wall or membrane.[22] Some others prevent the adhesion of fungal cells to each other and biofilm formation.[23] Some have antibacterial properties that, along with antifungal activity, can prevent the formation of multispecies biofilms and co-infection.[4]

C. sinensis mouthwash and *P. granatum* gel had similar laboratory results compared to antifungals in reducing fungal colonies. Polyphenols are the main metabolites in these two plants, which have high molecular weight and can combine with other large molecules such as proteins, starch, cellulose, and alkaloids.[24] Precipitation of cell membrane proteins is the possible mechanism of the antifungal activity of these metabolites.[20] *Z. multiflora* essential oil mouthwash and gel acted the same as antifungals in reducing fungal colonies on the palate.[14,19] The essential oil of this plant contains thymol and carvacrol, which disrupt the integrity of the fungal cell membrane by inhibiting ergosterol biosynthesis.[22] Furthermore, they prevent cell adhesion and biofilm formation.[23] Regarding the reduction of denture surface colonies, *Z. multiflora* gel was less effective than miconazole gel; it seems that miconazole could penetrate denture plaque better. On the other hand, *C. zeylanicum* essential oil contains eugenol, which similar to the thymol and carvacrol, has antiadhesion and antibiofilm effects and also affects the fungal cell wall synthesis.[4,25] de Araújo *et al*. reported that the use of mouthwash and spray of this product are effective in reducing the number of mucosa and denture colonies.[4]

Pinelli *et al*.[17] in a study conducted on *R. communis* mouthwash, miconazole gel, and nystatin drop reported that despite the clinical improvement in the first two groups, the average number of fungal colonies did not decrease significantly after treatment in any of the groups. It could be partly justified by the fact that *C. albicans* is found in the normal oral microflora. According to studies, the colony count in 50% of carriers is about 1000 CFU/mL, while it ranges from 4000 to 20,000 CFU/mL in infected patients, and if a treatment decreases the counts from 10,000 to 20,000 CFU/mL to a few hundred could be considered successful. Moreover, non-invasive forms of Candida may grow in the culture medium. Therefore, a positive result of the cell culture does not necessarily indicate a pathogenic condition and the presence of invasive species. Another possible explanation might be related to bacterial coinfection and its role in pathogenesis. As a result of the antibacterial activity of *R. communis* and miconazole, clinical manifestations improved without a reduction in fungal colonies.[15,26] In the study on *U. tomentosa*, miconazole, and placebo, the number of fungal colonies decreased in all three groups without a significant difference. This might be associated with reducing predisposing factors – including patients' compliance with oral hygiene and removing dentures while sleeping – as the first step in treating candidiasis.[18]

Side effects and patient satisfaction with treatment were reviewed in 6 articles. The findings of 4 articles show that herbal compounds have fewer adverse effects than usual antifungals[4,10,15,20] and one article stated that no side effects were observed in any of the groups.[21] Complaints of unpleasant taste were less frequent with using cinnamon and garlic mouthwashes than with nystatin.[4,10] According to de Araújo *et al*., burning and numbness were the side effects of cinnamon mouthwash and nystatin caused tongue sensitivity.[4] Bakhshi *et al*. reported nausea, diarrhea, anorexia, and burning as side effects of nystatin and itching for garlic mouthwash. In this study, overall patient satisfaction with garlic mouthwash was significantly higher than with nystatin.[10] The satisfaction of patients was also assessed by Eslami *et al*., and was reported that patients were significantly more satisfied with *Z. officinale* mouthwash than with nystatin as *Z. officinale* has gastroprotective and antiemetic effects. In contrast, nystatin caused gastrointestinal problems such as nausea and diarrhea that might result in poor patient adherence to treatment.[15] In the study by Amanlou *et al*., *Z. multiflora* gel application was associated with

burning, itching, dizziness, nausea, or a bad taste in some patients (59.3%), and some patients (50%) in the miconazole group complained of burning, nausea, or a bad taste. In total, the side effects of both groups were relatively high, and this rate was higher in the *Z. multiflora* group.[19] Furthermore, Vasconcelos *et al*. reported miconazole had adverse effects on all the patients in the group, commonly nausea and gastric disorders, while there were no complications in the *P. granatum* gel group.[20]

It seems that mouthwashes of herbal compounds have the same performance as conventional antifungal drugs, but in the case of the gel of herbal compounds, it is not possible to declare a single conclusion and results have been variable (better, similar, and weaker). Perhaps, in addition to the antifungal activity, the effectiveness of the product in gel form depends on its ability to adhere to the oral mucosa and not be washed away by saliva. The different stickiness of the herbal compound gels that-were prepared manually in the studies- and the usual antifungal gels -that had standard formulations might have affected the retention and concentration of the product at the site and altered its effectiveness.[19,20] On the other hand, the washing effect of mouthwashes helps them reduce the overall count of fungal colonies in the mouth, thereby reducing the severity of the disease.

While there are some other systematic reviews performed on the subject of comparing herbal medicine and antifungal drugs on Candidiasis, they did not fully covered the aims of the current study; In a systematic review conducted by Li *et al*.[27] in 2023, they evaluated the clinical efficacy of traditional Chinese medicine compounds in the treatment of oral candidiasis and found that total effective rate of the experimental groups was better than that of the control group (chemical drugs). However, most of the articles included in their systematic review were written in Chinese and there was no clinical or objective definition of effectiveness rate provided. In another study conducted by Megawati *et al*. in 2021[28], articles in a 5-year interval (2016–2021) and just limited to Asian products were included. In their study also, just one clinical trial was included and the remaining articles were all *in vitro* studies.

Limitations

most of the articles had an unclear or high risk of bias; it is suggested to conduct more RCTs with higher accuracy in random sequence generation, allocation concealment, and blinding the personnel or outcome assessment domains to achieve more reliable results.

CONCLUSION

In general, herbal compounds with different chemical substances have a wide range of therapeutic effects that work in synergy to treat diseases.[29] In the reviewed articles, potential anti-inflammatory, antibacterial, antioxidant, analgesic, and other properties found in the investigated herbal compounds along with their antifungal activity, could improve oral candidiasis.[4,10,16] The combination of active ingredients in herbal compounds with other substances brings a biological balance and reduces toxicity and side effects. This can increase patients' satisfaction and encourage them to complete their treatment process.[30] Factors such as safety, availability, and compatibility with the philosophy of holistic treatment that integrates emotional, mental, and spiritual levels and emphasizes the use of natural products lead to a higher acceptance of herbal compounds and a positive attitude toward them.[29,30] It is important to know that herbal medications are currently used by about 80% of the world's population for health-related purposes, mostly by a majority of citizens at rural communities of developing countries.[31]

In addition to a suitable drug prescription and treatment method, items like the severity of the disease, patient cooperation, and elimination of local or systemic predisposing factors play a significant role in the successful treatment and prevention of recurrence. In the reviewed studies, there was no significant difference between the tested groups in terms of the initial severity of the disease; however, factors such as neglecting the treatment protocol, poor oral hygiene habits, or unreported systemic conditions by patients may have affected the effectiveness of the therapeutic intervention.[4,30]

Declaration of generative AI and AI-assisted technologies in the writing proce

No AI or AI technologies were used.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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APPENDIXES

Appendix 1: Search strategy

Database	Strategy
Pubmed	(“Colony Count, Microbial”[Mesh] OR cure OR taste OR soreness OR plaque OR “fungal culture” OR “minimum inhibitor concentration” OR “Zone of inhibition” OR lesion OR erythema OR improvement OR clinical) AND ((“Herbal Medicine”[Mesh] OR plant OR natural OR nature OR leaf OR green OR biological OR root OR fruit OR flower OR seed OR “essential oil”) OR (liquorice OR “green tea” OR “punica granatum” OR garlic OR ginger OR “cinnamomum zeylanicum” OR glycyrrhiza OR ricinus OR “uncaria tomentosa” OR “syzygium aromaticum”)) AND (“Candidiasis, Oral”[Mesh] OR ((candidosis OR thrush OR candidia*) AND oral)) AND (nystatin OR antifungal OR miconazole OR clotrimazole OR fluconazole OR ketoconazole OR amphotericin B OR posaconazole OR itraconazole)
Scopus	(“Colony Count, Microbial” OR cure OR taste OR soreness OR plaque OR “fungal culture” OR “minimum inhibitor concentration” OR “Zone of inhibition” OR lesion OR erythema OR improvement OR clinical) AND ((“Herbal Medicine” OR plant OR natural OR nature OR leaf OR green OR biological OR root OR fruit OR flower OR seed OR “essential oil”) OR (liquorice OR “green tea” OR “punica granatum” OR garlic OR ginger OR “cinnamomum zeylanicum” OR glycyrrhiza OR ricinus OR “uncaria tomentosa” OR “syzygium aromaticum”)) AND (“Candidiasis, Oral” OR ((candidosis OR thrush OR candidia*) AND oral)) AND (nystatin OR antifungal OR miconazole OR clotrimazole OR fluconazole OR ketoconazole OR amphotericin AND b OR posaconazole OR itraconazole)
Cochrane library	(“Candidiasis, Oral” OR ((candidosis OR thrush OR candidia*) AND oral))AND((“Herbal Medicine” OR plant OR natural OR nature OR leaf OR green OR biological OR root OR fruit OR flower OR seed OR “essential oil”) OR (liquorice OR “green tea” OR “punica granatum” OR garlic OR ginger OR “cinnamomum zeylanicum” OR glycyrrhiza OR ricinus OR “uncaria tomentosa” OR “syzygium aromaticum”))
Magiran	English: Candidiasis AND oral persian: کاندیدا + دهان
WoS	((TS=(herbal OR Plant)) AND TS=(Candidiasis OR candidia*)) AND TS=(antifungal OR nystatin OR antifungal OR miconazole OR clotrimazole OR fluconazole OR ketoconazole OR amphotericin OR posaconazole OR itraconazole), Final Publication Year: 2021

Appendix 2: Critical appraise checklist and scores

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
		Title and abstract	
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
		Introduction	
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
		Methods	
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
		Results	
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
		Discussion	
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	

Contd...

Section/Topic	Item No	Checklist item	Reported on page No
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

	Tatapudi	Araújo	Gonoudi	Najafi21	Ghorbani	Maghu	Eslami	Najafi15	Tay	Pinelli	Bakhshi	Catalán	Amanlou	Sabitha	Vasconcelos
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1
5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
8	0	1	0	0	0	0	0	1	1	0	0	0	0	0	0
9	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
10	0	1	0	0	0	0	1	1	0	0	0	0	1	0	0
11	0	1	1	0	0	0	1	1	1	0	0	0	0	0	0
12	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0
13	0	1	1	0	0	0	0	1	0	0	1	0	1	0	0
14	0	1	0	1	0	0	1	1	1	0	1	0	1	0	0
15	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1
16	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
17	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
18	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
19	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
20	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
21	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
22	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0
23	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
24	0	1	1	0	0	0	1	1	1	1	1	1	1	1	1
25	0	1	1	0	0	0	1	1	1	1	1	1	1	1	1
26	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1
27	1	1	0	0	0	0	1	0	1	0	1	1	1	1	1
28	1	1	0	1	1	1	0	0	1	1	0	0	0	1	1
29	1	1	1	1	1	0	0	1	1	1	1	0	0	0	0
30	1	1	1	1	1	0	0	1	1	1	1	0	0	0	0
total	21	30	25	20	19	18	24	27	27	21	24	20	23	20	21
result	moderate	high	moderate	low/reject	low/reject	low/reject	moderate	high	high	moderate	moderate	low/reject	moderate	low/reject	moderate

Appendix 3: Cochrane Collaboration's tool for assessing risk of bias

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias	Blinding of outcome assessment*	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what was found	Reporting bias due to selective outcome reporting

Approach to formulating summary assessments of risk of bias for each important outcome (across domains) within and across trials

Risk of bias	Interpretation	Within a trial	Across trials
Low risk of bias	Bias, if present, is unlikely to alter the results seriously	Low risk of bias for all key domains	Most information is from trials at low risk of bias
Unclear risk of bias	A risk of bias that raises some doubt about the results	Low or unclear risk of bias for all key domains	Most information is from trials at low or unclear risk of bias
High risk of bias	Bias may alter the results seriously	High risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results