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Exploring Natural Solutions: A Systematic Review of Herbal Products Versus Conventional Antifungal Medications for Oral Candidiasis

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ABSTRACT

Oral candidiasis, a common fungal infection in the mouth, can be a real nuisance, and managing it has become trickier as antifungal medications face growing resistance. This systematic review dives deep into how well various plant-based remedies (phytotherapeutic agents) stack up against the usual antifungal drugs for treating oral candidiasis. We conducted a thorough search through scientific databases to find relevant studies, especially randomized controlled trials. We then carefully looked at the results, focusing on how well treatments cleared up infections, reduced symptoms, and what side effects people experienced. Our initial findings suggest that while traditional antifungals are still essential, a good number of herbal products show exciting promise. They might even offer alternative or additional ways to treat this infection, potentially helping us cut down on drug toxicity and the development of resistance. However, it's worth noting that many studies we looked at had some limitations in their design or reporting, meaning we need more robust, well-designed research to give truly definitive recommendations on bringing phytotherapy into standard oral candidiasis care.

Keywords: Oral candidiasis, herbal products, antifungal drugs, phytotherapy, systematic review, Candida albicans, drug resistance, natural compounds.

INTRODUCTION

Have you ever heard of oral candidiasis? It's a pretty common fungal infection in the mouth, mostly caused by a yeast called *Candida albicans* [2, 5]. Now, *Candida* is actually a normal resident in many people's mouths – about 30-50% of us carry it without any issues! But sometimes, certain things can throw off the balance of our oral microbes, allowing *Candida* to grow out of control and cause problems [2].

What kind of things can trigger it? Well, local factors often include wearing dentures, changes in how much or how good your saliva is, smoking a lot, or even using inhaled steroid medications [2]. On the systemic side, things like a weakened immune system (think HIV/AIDS), uncontrolled diabetes, long-term use of broad-spectrum antibiotics, certain vitamin deficiencies, or chemotherapy can make you more susceptible [2]. Oral candidiasis can show up in different ways – sometimes as white patches that you can wipe off (pseudomembranous), red inflamed areas (erythematous), or even stubborn white lesions that don't come off (hyperplastic), and it can also cause cracked corners of the mouth (angular cheilitis) [5]. While it’s rarely life-threatening, it can certainly make you uncomfortable, cause pain, and affect how you eat and speak, really impacting your daily life [5].

Traditionally, managing oral candidiasis involves first trying to figure out and address what's causing it, then using antifungal medications [2, 3]. The antifungals we have generally fall into four main groups: azoles, polyenes, echinocandins, and pyrimidine analogs (like flucytosine) [3]. Each works a bit differently. Azoles and polyenes target the fungal cell's outer layer, either by messing with its building blocks or by poking holes in it [1, 3]. Echinocandins go after the cell wall, which is vital for the fungus's structure [3]. And flucytosine interferes with the fungus's ability to make its genetic material [3]. For localized infections in the mouth, topical antifungals like nystatin and miconazole are often the first choice because they work directly where they're applied and don't get absorbed much into the rest of the body [3].

However, relying heavily on these conventional antifungals, especially for long periods, has created some significant hurdles. Patients often experience side effects, which can range from mild stomach upset to more serious issues, particularly for vulnerable groups like the elderly or those with weakened immune systems who might need ongoing antifungal treatment [4, 5]. A bigger worry is the growing problem of antifungal drug resistance. As we use these medications more and more, *Candida* species (both *C. albicans* and others) are becoming resistant, leading to treatment failures and even an increase in more serious, invasive candidiasis cases [6, 7]. This

means we constantly need to find new and effective treatments that can bypass this resistance and offer better safety.

Given these challenges, there's been a renewed and exciting interest in traditional medicine and phytotherapy – basically, using compounds derived from plants for medical purposes [6, 9]. Herbal compounds have been used for centuries across different cultures for all sorts of health issues, including fighting infections [6]. The appeal of herbal medicine is clear: they often have fewer side effects, can be less expensive, and might be more readily available in certain parts of the world [8, 29]. What's more, these natural compounds often work in multiple ways against microbes. They can stop fungal cell walls from forming, disrupt cell membranes, interfere with fungal growth and metabolism, and even help boost our own immune responses or weaken the fungus's ability to cause disease [9, 10]. These diverse actions could lead to broader antifungal effects and potentially make it harder for resistance to develop, which is a huge advantage over drugs that only target one specific pathway [9, 23].

With oral candidiasis still being a global health concern and conventional treatments facing limitations, it's crucial to thoroughly evaluate how well plant-based remedies actually work. This systematic review aims to carefully investigate and compare how herbal compounds stack up against traditional antifungals in terms of improving oral candidiasis symptoms and clearing up the infection. By bringing together all the available evidence, we hope to gain a clearer picture of current treatment options, highlight promising natural alternatives, and pinpoint where more research is desperately needed.

2. Materials and Methods

We conducted this systematic review very carefully, following a pre-planned roadmap to ensure everything was transparent and accurate. We also made sure to align with the PRISMA guidelines, which are like a gold standard for systematic reviews. Our review plan was even officially registered with the Center for Reviews and Dissemination, University of York, UK, under the number CRD42024604440, and it received ethical approval (Project ID: 3400898, Code of Ethics: IR.MUI.RESEARCH.REC.1400.439).

2.1. Our Research Question: The PICO Framework

To make sure we found exactly what we were looking for, we broke down our research question using the Population, Intervention, Comparison, and Outcome (PICO) framework:

- P (Population): Who were we looking at? We focused on adults (18 years and older) who had been diagnosed with oral candidiasis. This included people who were generally healthy, as well as those with underlying health conditions like diabetes or weakened immune systems that might make them more prone to candidiasis. We paid special attention to studies about denture stomatitis, which is a common type of oral candidiasis.
- I (Intervention): What treatments were we interested in? Our main interest was herbal medicines in various forms – mouthwashes, gels, ointments, and sprays. We specifically looked for studies involving well-known herbs like Cinnamomum zeylanicum (cinnamon), Zataria multiflora, Zingiber officinale (ginger), Camellia sinensis (green tea), garlic (Allium sativum), Ricinus communis, Uncaria tomentosa, Punica granatum (pomegranate), and Curcuma longa (curcumin).
- C (Comparison): What were we comparing them to? We compared the herbal treatments to the standard antifungal drugs commonly used for oral candidiasis. These included polyenes (like nystatin and amphotericin B) and azoles (such as miconazole, clotrimazole, fluconazole, ketoconazole, posaconazole, and itraconazole). We made sure to look for these drugs in similar forms (mouthwash, gel, ointment) to match the herbal interventions.
- **O (Outcomes): What results were we hoping to find?**
  - **Primary Outcome: How much did people improve clinically?** This meant looking at objective signs and subjective feelings of getting better, including:
    - How much the disease severity went down, based on established classifications like Newton's (Type I: localized redness; Type II: widespread redness; Type III: bumpy, non-removable lesions).
    - The rate of clinical cure – meaning the complete disappearance of visible lesions.
    - How much white patches or redness decreased, often measured by the size of the lesion.
    - How much pain was reduced, using tools like the Visual Analog Scale (VAS) or simply asking patients how they felt.
    - Relief from itching and other discomforts.
  - **Secondary Outcome: How much did the fungus go away?** This involved lab results showing a reduction in the fungal load:
    - A decrease in Colony-Forming Units (CFU) from cultures taken from the mouth or dentures.
    - Minimum Inhibitory Concentration (MIC) and Minimal Fungicidal Concentration (MFC)

values, if reported, which tell us how potent the agents were in the lab.

- Zone of inhibition measurements from lab tests, showing how much the substance stopped fungal growth.

- **Safety Outcome: What about side effects and how well people tolerated the treatment?** We looked for any reported adverse effects, local irritation, body-wide reactions, and how satisfied patients were with their treatment.

2.2. Our Search Process

We performed a very thorough and systematic search across several major online scientific databases to find relevant studies published from 1995 up to November 2021. The databases we searched were:

- Medline (through PubMed)
- Scopus
- Web of Science
- Cochrane Library
- Magiran (a database for Persian language articles)

We carefully crafted our search terms, using a mix of specific medical subject headings (MeSH terms) and general keywords, combining them with "AND" or "OR" to make sure we caught all relevant articles.

A Sneak Peek at Our Search Strategy for Each Database:

- **PubMed:** We used a long string of terms that combined our outcomes (like "cure," "lesion," "improvement"), interventions (like "Herbal Medicine," "plant," and specific names like "garlic" or "cinnamon"), our patient group ("Candidiasis, Oral"), and the comparison drugs ("nystatin," "antifungal," "miconazole," etc.). We really focused on using MeSH terms here for precision.
- **Scopus:** Similar to PubMed, but we adjusted the terms slightly to fit Scopus's way of indexing and searching. We used more free-text terms to ensure we didn't miss anything.
- **Cochrane Library:** Since Cochrane is all about systematic reviews and controlled trials, we focused our search on the main patient group and the intervention/comparison, assuming the trial reports themselves would cover the outcomes.
- **Magiran (Persian Database):** This one was simpler. We used "Candidiasis AND oral" in English, plus a Persian equivalent, to find local research.
- **Web of Science (WoS):** Here, we used "Topic Search" to find keywords in the title, abstract, and keywords of articles. We looked for terms related to herbal interventions, candidiasis, and antifungal comparisons, specifically limiting our search to articles published up to 2021.

Beyond just searching databases, we also did a "manual search." This meant carefully going through the reference lists of all the articles we found to see if there were any other important studies that our initial searches might have missed. Our lead investigator (BT) developed and oversaw the entire search process to make sure it was as complete and accurate as possible.

2.3. What Made a Study "In" or "Out"? (Inclusion and Exclusion Criteria)

We had very specific rules for which articles made it into our review. This helped us ensure that the evidence we synthesized was relevant and of high quality.

We Included Studies If They Met These Points:

- **Study Design:** Only Randomized Controlled Trials (RCTs) were in. We stuck to this strict rule because RCTs provide the strongest evidence for comparing treatments, helping us minimize bias.
- **Language:** Articles written in either English or Persian were fair game.
- **Participants:** We looked for studies on adults (18 years or older) diagnosed with oral candidiasis. This included both generally healthy people and those with underlying health conditions (like diabetes or weakened immune systems) that might make them susceptible.
- **Treatment Comparison:** The studies had to specifically compare a herbal compound (in any form like mouthwash, gel, or ointment) against one or more standard antifungal drugs (like nystatin, miconazole, clotrimazole, etc.).

We Excluded Studies If They Met These Points:

- **Study Design:** We didn't include non-randomized studies, observational studies (like cohort or case-control studies), case series, case reports, lab-only studies (without human clinical trials), or animal studies. While lab studies can give us clues, our main focus was on how treatments worked in real people.
- **Treatment Comparison:** If a study compared herbal compounds to things other than standard antifungals (like chlorhexidine, triclosan, or just a placebo, unless the placebo was part of a larger comparison with an active antifungal), we generally left it out.
- **Participants:** Studies on children or those focusing on fungal infections in other parts of the body (not the mouth) were excluded.

- **Publication Type:** We generally didn't include review articles, opinion pieces, editorials, or conference abstracts for our main analysis, though we might have used them for background information or to find other relevant studies.

2.4. How We Picked the Studies (Study Selection Process)

Our study selection was a multi-step process, a bit like a funnel, as shown in the PRISMA flow chart (Figure 1 in the original document).

1. **First Pass: Search and Remove Duplicates:** After running all our searches, we gathered every single record. Then, we meticulously removed any duplicates so we only looked at each unique article once.
2. **Second Pass: Title and Abstract Screening:** Two researchers (BT and NG) independently looked at the titles and abstracts of the remaining articles. They decided if the articles seemed relevant based on our PICO framework and inclusion/exclusion rules. Anything clearly not related was filtered out at this stage.
3. **Third Pass: Full-Text Review:** For all the articles that seemed promising, we got the full text. Then, the same two researchers independently read these full articles very carefully against our detailed inclusion and exclusion criteria. If they disagreed on whether an article should be included, they discussed it until they reached a consensus. If they still couldn't agree, a third expert was brought in to make the final call.
4. **Final Step: Quality Check and Inclusion:** Only articles that passed the full-text review then went through a critical appraisal and risk of bias assessment. If they met our quality standards, they were finally included in our review for analysis.

2.5. Checking for Quality and Bias

To make sure the studies we included were methodologically sound and their results trustworthy, we used a two-part system: a critical appraisal using a modified CONSORT checklist and a risk of bias assessment using the Cochrane tool.

2.5.1. Critical Appraisal with the Modified CONSORT Checklist:

We used a modified version of the CONSORT checklist (Appendix 2 in the original document), which is a comprehensive tool for evaluating how well randomized trials are reported. This checklist covers everything from the title and abstract to the methods, results, and discussion sections. We scored each item (e.g., 1 if reported, 0 if not).

- **Our "Go/No-Go" Score:** For an article to be included in our analysis, it had to score at least 70% (which was 21 out of 30 points) on this checklist.
- **Quality Levels:** We then put the accepted articles into three quality categories:
    - **Low Quality/Rejected:** If they scored 20 points or less.
    - **Moderate Quality:** If they scored between 21 and 25 points.
    - High Quality: If they scored 26 points or more. Two researchers (BT and NG) independently scored the articles. If their scores were very different (more than a 3-point difference), a third expert stepped in to help reach a final decision.

2.5.2. Risk of Bias Assessment with the Cochrane Tool:

We also used the Cochrane Collaboration's tool (adapted from Higgins and Altman [13]; Appendix 3 in the original document) to look for potential biases within each accepted RCT. This tool helps us systematically assess five key areas where bias can creep in:

- **Selection Bias:** This is about whether the groups being compared were truly similar at the start.
    - **Random Sequence Generation:** Did they use a truly random method (like a computer program or coin toss) to decide who got which treatment?
    - **Allocation Concealment:** Was it impossible for anyone involved in the study to know which treatment a participant would get before they were assigned? (Think opaque envelopes or a central system).
- **Performance Bias:** This bias happens if participants or researchers knew who was getting which treatment, potentially influencing their behavior or care.
    - **Blinding of Participants and Personnel:** Were the patients and the study staff kept unaware of who was getting the herbal treatment versus the conventional drug? And how well was this blinding maintained (e.g., did the treatments look identical)?
- **Detection Bias:** This occurs if the people measuring the outcomes knew which treatment a participant received, which could unconsciously affect their measurements.
    - **Blinding of Outcome Assessment:** Were the people assessing how well the treatments worked (e.g., measuring lesion size or pain) kept unaware of which treatment each patient received?
- **Attrition Bias:** This relates to missing data, like patients dropping out of the study.
    - **Incomplete Outcome Data:** Was all the data accounted for? How many patients dropped out, why, and how was that missing data handled in the

analysis?

- **Reporting Bias:** This happens if only certain outcomes or analyses are reported, perhaps because they show more favorable results.
    - **Selective Reporting:** Did the study report all the outcomes it originally set out to measure, or did it seem to pick and choose based on the results?

For each of these areas, we judged the risk as "low," "unclear," or "high." The "overall risk of bias" for each study was then determined based on these individual judgments. If a study had a high risk in even one important area, we generally considered its overall risk of bias to be high. If most areas were "unclear," then the overall risk was also deemed "unclear."

2.6. How We Put the Information Together

Because the studies we found were quite different from each other – varying in the specific herbal compounds used, their forms, dosages, treatment times, and how they measured results – we couldn't just combine all the numbers into one big statistical analysis (a meta-analysis). Instead, we used a "narrative synthesis" approach. This meant we systematically described and summarized the findings of each study, highlighting the main results, comparisons, and observations related to how well treatments improved symptoms, cleared up the fungus, and what side effects were reported. Our goal was to give a clear, comprehensive picture of the evidence, pointing out any consistent patterns and also areas where results conflicted or data was limited.

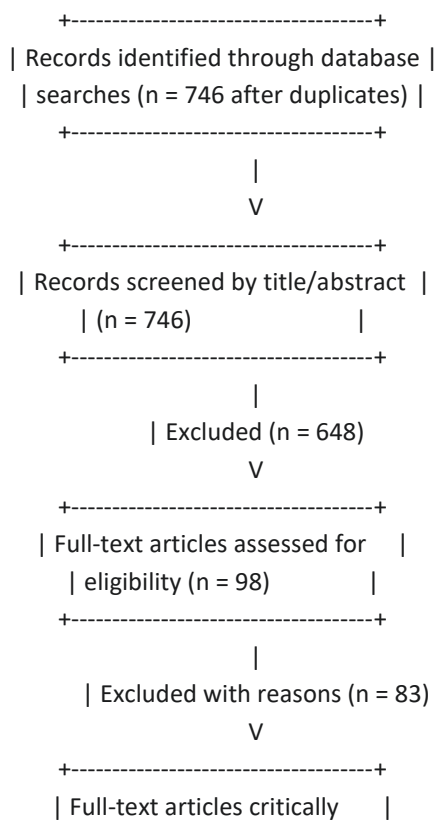
3. Results

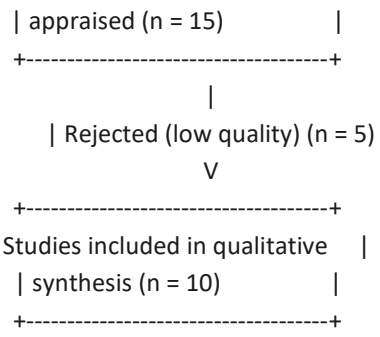
3.1. What We Found and Which Studies Made the Cut

Our initial, broad search across all the databases (PubMed, Scopus, Web of Science, Cochrane Library, and Magiran) brought in a lot of articles – 746 unique ones, to be exact, after we removed all the duplicates (you can see this process in Figure 1 of the original document). We then went through the titles and abstracts, and unfortunately, 648 of those weren't relevant to our specific question, so they were excluded. That left us with 98 articles that looked promising enough to read in full.

When we dug into the full texts, we had to exclude quite a few more – 83 Randomized Controlled Trials (RCTs) didn't quite fit our criteria. Maybe they weren't directly comparing herbal products to conventional antifungals for oral candidiasis, or they were animal studies, lab studies without human data, or they compared treatments to things other than antifungals. Ultimately, 15 articles seemed like they might be good candidates and moved on to our quality check. Out of those 15, we had to say goodbye to 5 because they just didn't meet our quality standards (scoring below 70% on the modified CONSORT checklist). The main reasons for this were often poor reporting of how they randomized participants, how they kept the treatment assignments secret, or how they reported their results. In the end, we were left with 10 articles that were solid enough to be included in this systematic review for our detailed analysis.

Figure 1: PRISMA Flow Diagram of Study Selection Process





3.2. How Risky Were the Studies? (Risk of Bias Assessment)

We carefully checked the risk of bias for each of the 10 studies we included, using the Cochrane tool. Here's what we found about their methodological quality:

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)	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

As you can see, a larger group, six articles, fell into the "Unclear Risk of Bias" category. These studies often didn't provide enough detail about crucial aspects like how they concealed treatment assignments or whether participants and outcome assessors were blinded. Three articles unfortunately had a high risk of bias. These were the studies by Tatapudi et al. [21], Pinelli et al. [17], and Vasconcelos et al. [20]. The common issues here included problems with how they generated random sequences, how they kept allocations secret, and how they blinded participants and staff. Because most of the studies we included (6 out of 10) had an "unclear" risk of bias, we concluded that the overall risk of bias across all the studies in this review was also unclear. This tells us that, generally, there's still room for improvement in how research in this area is reported and conducted.

3.3. What Kind of Studies Did We Include? (Characteristics)

The 10 studies we analyzed looked at a variety of herbal products and how they were given, comparing them to standard antifungal drugs for oral candidiasis.

- **How the Treatments Were Given:**
  - **Mouthwash:** Six studies tested herbal products as mouthwashes [4, 10, 14, 15, 16, 17]. One of these even used a spray alongside the mouthwash for dental hygiene [4].
  - **Gel:** Three studies looked at herbal compounds in gel form [18, 19, 20].
  - **Ointment:** One study used a herbal product as an ointment [21].
- What Drugs Were They Compared To? The standard antifungal drugs used for comparison were mainly nystatin (as a mouthwash or drops), miconazole (as a gel), and clotrimazole (as an ointment). Interestingly, one study compared a herbal mouthwash to both nystatin mouthwash and miconazole gel [17].
- Who Were the Participants? Most of the studies (eight out of ten) enrolled patients who had denture stomatitis and were generally in good health. Two studies also included patients with other health conditions, like diabetes [21] or other medical issues [4]. The age of participants varied, with most being between 18 and 60 years old, but four studies specifically included people over 60 [10, 17, 18, 19].

Table 2: Characteristics of Included Studies

Author, Year [Ref]	Participants (N, Age, Sex, Region, Systemic Conditions)	Study Design	Interventions (Study Groups, Treatment Protocol, Follow-up)	Outcomes Measured (Primary, Secondary, Safety)
Tatapudi et al., 2021 [21]	N=50 (Male=12, Female=23), with history of denture stomatitis. Healthy=15, Medically compromised=22 (8 Diabetes, 7 Hypertension, 2 Asthma, 2	Double-blind RCT	a. 25 curcumin ointment (3x/day, 14 days) b. 25 clotrimazole ointment (3x/day, 14 days) Follow-up: Day 7, 14, 21, 28	Primary: Complete resolution of the lesion Secondary: Colony counts, Mycological eradication (%) Safety: Tolerability, Side

	Monoplegia, 2 Hypothyroidism, 1 Vitiligo).			effects
de Araújo et al., 2021 [4]	N=36 (Female=27), aged 40-70, visiting Federal University of Paraiba clinic with oral candidiasis (denture wearing maxillary dentures).	Double-blind RCT	a. 18 *C. zeylanicum* EO (0.5 mg/mL) Mouthwash + spray (3x/day, 15 days) b. 18 nystatin (100,000 IU/mL) Mouthwash + spray (3x/day, 15 days) Follow-up: Day 16	Primary: Newtonian DS diagnosis degree reduction (%) Secondary: CFU count reduction (%) Safety: Unpleasant taste (%), Undesirable effects (%)
Gonoudi et al., 2021 [14]	N=28 (Female=7, Male=21), >18 years old, from Islamic Azad University of Tehran, with type II or III denture stomatitis.	Single-blind RCT	a. 14 *Z. multiflora* EO 0.05% (rinse one teaspoon [5 mL]) (4x/day, 14 days) b. 14 nystatin (rinse 40 drops of 100,000-unit suspension) (4x/day, 14 days) Follow-up: Day 14	Primary: Mean erythema (mm^2) Secondary: Mean number of CFUs
Eslami et al., 2015 [15]	N=30, with type II denture stomatitis, visiting Tabriz University Dentistry clinics in 2014.	Double-blind RCT	a. 15 ginger mouthwash 20 mL (3x/day, 20 days) b. 15 nystatin mouthwash 500,000 IU (3x/day, 20 days) Follow-up: Day 5, 10, 15, 20	Primary: Erythema (length, width) (mm) Safety: Patients satisfaction (%)
Najafi et al., 2015 [16]	N=27 (Female=20, Male=7), aged 45-60, with denture stomatitis, referred to Department of Oral Medicine, Tehran University of Medical Sciences.	Double-blind RCT	a. 15 green tea extract mouthwash 0.58% (4x/day, 14 days) b. 12 nystatin mouthwash rinse 15-20 drops (4x/day, 14 days) Follow-up: Day 7, 14	Primary: Erythema surface (cm^2) Secondary: Degree of inflammation, Density of colony count
Tay et al., 2014	N=48 (Female=43, Male=5), aged 45-	Double-blind RCT	a. 16 *Uncaria tomentosa* 2% gel	Primary: Newtonian DS

[18]	85, with good general health, with denture stomatitis type I, II, and III from State University of Ponta Grossa.		 b. 15 Miconazole 2% gel c. 17 hydroxyethyl cellulose (placebo) 2.5 mL (one teaspoonful) (3x/day, 7 days) Follow-up: Day 7, 14	degree Secondary: CFU/mL (Log)
Pinelli et al., 2013 [17]	N=30 (Female=24, Male=6), over 60 years, residents at long-term care institution Lar Sao Francisco de Assis.	RCT	a. 10 *R. communis* mouthwash (4x/day, 30 days) b. 10 Miconazole oral gel (4x/day, 30 days) c. 10 Nystatin an eyedropper on the tongue (4x/day, 30 days) Follow-up: Day 15, 30	Primary: Clinical improvement (Newtonian DS degree) Secondary: Mean CFU/mL (Log)
Bakhshi et al., 2012 [10]	N=40 (Female=24, Male=16), aged people with DS living in Kahrizak elderly home in Tehran.	Double-blind RCT	a. 20 Garlic aqueous solution mouthwash 40 mg/mL (rinse 20 drops) (3x/day, 28 days) b. 20 Nystatin mouthwash 100,000 U/mL (rinse 20 drops) (3x/day, 28 days) Follow-up: Day 7, 14, 21, 28	Primary: Erythema (width, length) (cm) Safety: Side effects (%), Patient satisfaction (%)
Amanlou et al., 2006 [19]	N=24 (Female=14, Male=10), aged 45 to 83, with moderate or severe (type II or III) Erythematous denture stomatitis confirmed by microbiologic cultures from Department of Oral Medicine,	Open RCT	a. 12 *Z. multiflora* essential oil 0.1% gel (Apply 2.5 mL [one teaspoonful] on denture) (4x/day, 14 days) b. 12 Miconazole 2% gel (Apply 2.5 mL [one teaspoonful] on denture) (4x/day, 14 days) 	Primary: Erythema surface (cm^2) Secondary: Density of mycological cultures Safety: Adverse reactions (%)

	Tehran University of Medical Sciences. (Systemic disease=6 in herbal group, 4 in miconazole group).		Follow-up: Day 7, 14, 21, 28	
Vasconcelos et al., 2003 [20]	N=60, aged 19-62 years, denture wearers with candidosis from Federal University of Paraiba dental clinic. No systemic disorder.	Double-blind RCT	a. 30 *P. granatum* gel (3x/day, 15 days) b. 30 miconazole gel (3x/day, 15 days) Follow-up: Day 17	Primary: Clinical response (number of patients with satisfactory/unsatisfactory responses) Secondary: Laboratorial results (number of patients with positive or negative results) Safety: Side effect

Abbreviations: RCT: Randomized Controlled Trial; EO: Essential Oil; C. zeylanicum: Cinnamomum zeylanicum; Z. multiflora: Zataria multiflora; Z. officinale: Zingiber officinale; C. sinensis: Camellia sinensis; R. communis: Ricinus communis; U. tomentosa: Uncaria tomentosa; P. granatum: Punica granatum; DS: Denture Stomatitis; CFU: Colony-Forming Unit; VAS: Visual Analog Scale.

3.4. What Did Each Treatment Type Show? (Findings by Intervention Type)

Let's break down the detailed results from each study, organized by how the herbal product was given.

3.4.1. Studies on Herbal Mouthwashes

- **de Araújo et al. (2021) [4]:** This double-blind RCT, where neither patients nor researchers knew who got what, explored the power of *Cinnamomum zeylanicum* (cinnamon) essential oil. They compared a mouthwash and spray containing this oil (0.5 mg/mL) against the standard nystatin (100,000 IU/mL) in 36 patients suffering from denture stomatitis. The results were quite encouraging! Both the cinnamon essential oil (P=0.0339) and nystatin (P=0.0139) led to significant clinical improvements, meaning the severity of denture stomatitis went down. For instance, the cinnamon essential oil reduced Type I cases (localized redness) by 9% and Type II cases (widespread redness) by 60%. Nystatin also showed good results, reducing Type I by 27% and Type II by 71%. Beyond just visual improvement, both treatments significantly lowered the amount of *Candida* species after 15 days of use. Specifically, the cinnamon essential oil group saw a 61% reduction in *Candida* on the oral mucosa and 33% on dentures, while the nystatin group achieved 89% reduction on oral mucosa and 83% on dentures. When it came to side effects, a few people in the cinnamon group found the taste unpleasant (16.7%) or experienced some numbness/burning (16.7%). Nystatin also caused an unpleasant taste for more people (38.9%) and led to tongue sensitivity in a smaller percentage (5.6%). This suggests cinnamon is a viable option with a potentially more tolerable taste profile for some.
- **Gonoudi et al. (2021) [14]:** This single-blind RCT involved 28 patients with either type II or III denture stomatitis. Participants used either a 0.05% *Zataria multiflora* essential oil rinse (a teaspoon, 5 mL) or a nystatin suspension (40 drops of 100,000-unit suspension) four times a day for 14 days. The findings were quite compelling: after 14 days, both *Z. multiflora* and nystatin significantly reduced the size of the red areas on the palate (P<0.001 for both groups) and also significantly

decreased the number of *Candida* colonies (P<0.001 for both groups). To give you a clearer picture, the average erythema reduction for *Z. multiflora* was from 75 mm² down to 42.86 mm², and for nystatin, it went from 8.93 mm² down to 71.07 mm². Similarly, the average CFU count for *Z. multiflora* dropped from 67,857.14 to 19,071.43, and for nystatin, it went from 78,714.29 to 22,000. What's truly noteworthy is that there was no significant difference between the two groups in terms of how much the redness went down (P=0.256) or how much the *C. albicans* colony count decreased (P=0.593). They performed remarkably similarly!

- **Eslami et al. (2015) [15]:** In this double-blind RCT, 30 patients with type II denture stomatitis were divided into two groups: one used 20 mL of ginger (*Zingiber officinale*) mouthwash, and the other used 500,000 IU nystatin mouthwash, both three times a day for 20 days. The results were clear: both treatments were highly effective at reducing the length and width of the red areas (P<0.001 for both groups) over the 20-day period. For the ginger group, the average lesion length shrank from 26.22 mm to a mere 1.16 mm, and the width from 32.20 mm to 1.28 mm. The nystatin group also saw good reductions, with length going from 26.28 mm to 4.02 mm and width from 31.06 mm to 4.49 mm. Importantly, there was no significant difference in erythema reduction between the two groups (P=0.9), meaning they were equally effective in this regard. However, here's where ginger really shined: patient satisfaction was significantly higher with the *Z. officinale* mouthwash. A remarkable 86.7% of patients reported "very good" or "good" satisfaction with ginger, compared to only 13.3% for nystatin (P<0.001). This clearly indicates a much better patient experience with the natural option.

- **Najafi et al. (2015) [16]:** This double-blind RCT included 27 patients, aged 45-60, who had denture stomatitis. They compared a 0.58% green tea (*Camellia sinensis*) extract mouthwash to nystatin mouthwash (15-20 drops, four times a day for 14 days). Both treatments led to a significant reduction in the inflamed surface area and the overall degree of inflammation. What's really important for our comparison is that there was no significant difference between the green tea extract mouthwash and nystatin in terms of reducing the size of the red areas (P-values were not significant on Day 0: P=0.858, Day 7: P=0.535, Day 14: P=0.498) or the number of fungal colonies (P-values were also not significant on Day 0: P=0.786, Day 7: P=0.980, Day 14: P=0.612). Both treatments also significantly reduced colony counts from the very beginning of the study (P=0.000). This suggests green tea is a strong contender, performing on par with nystatin.

- **Pinelli et al. (2013) [17]:** This RCT focused on a vulnerable population: 30 institutionalized elderly patients (over 60 years old) with denture stomatitis. They explored three different treatments over 30 days: *Ricinus communis* (castor bean) mouthwash, miconazole oral gel, and nystatin eye-dropper (all used four times a day). The findings revealed that both *R. communis* mouthwash (P=0.011) and miconazole gel (P=0.018) showed significant clinical improvement, effectively reducing the severity of denture stomatitis based on Newton's classification. However, nystatin drops did not show a significant clinical improvement (P=0.06), which is a crucial point. Interestingly, despite the clinical improvements, the average number of fungal colonies did not significantly change in any of the three groups after 15 and 30 days. This suggests that in this specific elderly population, clinical signs can improve even if the overall fungal count doesn't drastically drop, perhaps due to factors like reduced inflammation or improved hygiene.

- **Bakhshi et al. (2012) [10]:** This double-blind RCT involved 40 elderly individuals living in a care home, all suffering from denture stomatitis. They compared a garlic aqueous solution mouthwash (40 mg/mL, 20 drops) to nystatin mouthwash (100,000 U/mL, 20 drops), both used three times a day for 28 days. The results were quite compelling: both garlic and nystatin mouthwashes had a significant positive effect on reducing the length (P<0.001) and width (P<0.0001) of the red areas over the treatment period. For the garlic group, the average lesion length shrank from 3.63 cm to 0.99 cm, and the width from 3.53 cm to 1.09 cm. The nystatin group also saw good reductions, with length going from 3.03 cm to 0.08 cm and width from 3.61 cm to 0.11 cm. But where garlic truly excelled was in patient satisfaction: a remarkable 85% of patients reported "very good" or "good" satisfaction with the garlic mouthwash, significantly higher than with nystatin (P<0.0001). When it came to side effects, garlic had minimal complaints like itching (2.5%) and a bad taste (10%). Nystatin, on the other hand, had more frequent and varied complaints including bad taste (42.5%), nausea (15%), vomiting (2.5%), diarrhea (12.5%), anorexia (2.5%), and burning (2.5%). This clearly highlights a strong patient preference for garlic due to its better tolerability.

3.4.2. Studies on Herbal Gels

- **Tay et al. (2014) [18]:** This double-blind RCT included 48 individuals aged 45-85 with denture stomatitis. They compared a 2% *Uncaria tomentosa* (cat's claw) gel, a 2% miconazole gel, and a hydroxyethyl cellulose placebo gel

(2.5 mL, three times a day for 7 days). The good news was that the severity of the disease, assessed by Newton's classification, decreased in all three groups, and there were no significant differences between the treatments (P>0.05). Similarly, the CFU (fungal colony) count also decreased in all groups without significant differences (P>0.05). While the miconazole group did show a slightly lower number of CFUs on day 7, the overall lack of significant difference across the groups suggests that *U. tomentosa* gel could be a helpful topical "adjuvant" treatment, meaning it could be used alongside other therapies. The fact that the placebo group also showed improvement is a reminder that patient compliance with good oral hygiene practices is incredibly important, as this is often the first step in treating candidiasis.

- **Amanlou et al. (2006) [19]:** This open RCT involved 24 patients (aged 45-83) with moderate or severe erythematous denture stomatitis. They compared a 0.1% *Zataria multiflora* essential oil gel to a 2% miconazole gel (2.5 mL, four times a day for 14 days). Both gels significantly reduced the redness on the palate, and there was no significant difference between them in this aspect (P-values ranged from 0.14 to 0.75 across different follow-up days). *Z. multiflora* gel also led to a significant reduction in fungal colony numbers on the palatal mucosa, though this effect was less pronounced on days 21 and 28. However, miconazole gel proved to be more efficient at reducing fungal counts on the denture surface compared to *Z. multiflora* gel, except on day 21 where they were similar (P=0.17). Interestingly, both gels had reported side effects. *Z. multiflora* gel (59.3%) led to complaints such as itching, burning, dizziness, nausea, vomiting, and a bad taste. Miconazole gel (50%) also caused burning, vomiting, and a bad taste. The overall rate of side effects was relatively high in both groups, with *Z. multiflora* showing a slightly higher rate.

- **Vasconcelos et al. (2003) [20]:** This double-blind RCT included 60 denture wearers with candidiasis. They compared a *Punica granatum* (pomegranate) gel to miconazole gel, both used three times a day for 15 days. In terms of clinical response, miconazole gel performed significantly better than *P. granatum* gel (P<0.01), with more patients achieving satisfactory results. However, when looking at laboratory results (the reduction in positive fungal cultures), there was no significant difference between the two gels (P>0.01). The most striking difference was in side effects: miconazole gel caused nausea and gastric disorders in *all* patients in its group, while the *P. granatum* gel group reported absolutely no complaints. This is a huge advantage for patient comfort and adherence, even if the clinical efficacy was slightly lower.

3.4.3. Studies on Herbal Ointments

- **Tatapudi et al. (2021) [21]:** This double-blind RCT involved 50 patients with a history of denture stomatitis. They compared curcumin ointment (derived from *Curcuma longa*) to clotrimazole ointment, both applied three times a day for 14 days. The good news was that there was no significant difference between the two groups in terms of how many patients achieved complete resolution of their lesions (P=0.765). Both treatments also led to a decrease in fungal colony counts after treatment, and importantly, there was no significant difference between them in this regard. In fact, mycological eradication (meaning the fungus was completely gone from cultures) was 100% for both groups after 28 days, with no significant difference (P=0.404). Even better, both curcumin and clotrimazole ointments were well-tolerated by patients and reported no significant side effects. This makes curcumin a very promising alternative.

3.5. Summary of Key Findings

Overall, our review of these studies paints an interesting picture. It suggests that herbal compounds often show similar clinical effectiveness to conventional antifungal drugs when it comes to treating oral candidiasis, particularly in reducing redness and other uncomfortable symptoms. Lab results, like how much the fungal count went down, also frequently showed comparable trends between herbal and conventional treatments. A consistent and very positive finding across several studies was that patients generally felt more satisfied and experienced fewer adverse effects with herbal compounds compared to their conventional counterparts. However, we did notice that the effectiveness of herbal gels seemed a bit more varied, with some studies reporting them to be better, similar, or even weaker than conventional gels. This variability might be influenced by factors such as the specific formulation and how well the gels adhere to the mouth's surfaces.

4. DISCUSSION

Our systematic review sheds light on a growing and exciting area: the potential of plant-based remedies (phytotherapeutic agents) to help manage oral candidiasis. While we know that traditional antifungal drugs have been our go-to treatment for a long time, the increasing challenges of drug resistance, along with concerns about side effects, have really pushed us to look for effective and safer alternatives [1, 3, 29]. Our review of the current research suggests that several herbal compounds are indeed promising options for tackling this common oral infection.

4.1. Efficacy of Herbal Compounds vs. Conventional

Antifungals

One of the clearest messages from the studies we looked at is that many herbal compounds are just as effective as established antifungal drugs in easing the signs and symptoms of oral candidiasis. This was particularly true for herbal mouthwashes. For instance, mouthwashes made from *Zataria multiflora* [14], ginger (*Zingiber officinale*) [15], green tea (*Camellia sinensis*) [16], and garlic [10] were found to reduce the size of oral erythema with similar effectiveness to nystatin mouthwash. This parity in clinical outcomes is significant, suggesting that these natural alternatives could offer viable options for patients.

The power of herbal compounds often comes from their rich mix of active ingredients, which can exert a wide range of therapeutic effects beyond simple antifungal activity. Think of ginger, for instance. It's not just an antimicrobial; it also helps reduce inflammation and fights bacteria, all of which contribute to improving oral candidiasis symptoms [15]. Green tea, packed with beneficial compounds called polyphenols, also has anti-inflammatory, antioxidant, and even anti-diabetic effects, which are all helpful in calming down redness and inflammation in the mouth [16]. Garlic, through its superstar compound allicin, directly interferes with the fungus's ability to replicate, make proteins, and produce energy [9]. Allicin also messes with how *Candida* causes disease, for example, by stopping it from forming long, harmful filaments and sticking to our tissues [9]. Plus, allicin can even give our immune system a boost, helping it fight off the infection more effectively [10]. Studies have shown that *Zataria multiflora* gel, for example, might reduce redness even better than miconazole gel, possibly because of its anti-inflammatory properties [19].

However, the story for herbal gels was a bit more mixed. While *Uncaria tomentosa* gel seemed to perform similarly to miconazole gel and even a placebo in reducing disease severity and fungal counts [18], *Zataria multiflora* essential oil gel was also comparable to miconazole gel for improving redness and reducing fungal colonies on the mouth lining [19]. Conversely, *Punica granatum* (pomegranate) gel, while showing similar laboratory results to miconazole gel in reducing fungal cultures, exhibited a significantly weaker clinical response [20]. This variability in gels might be attributed to differences in their physical properties, such as adherence to the oral mucosa, which can influence the retention and local concentration of the active compounds at the site of infection. Handmade herbal gels may lack the standardized formulations of conventional gels, potentially affecting their stickiness and, consequently, their effectiveness [19, 20].

For herbal ointments, curcumin ointment demonstrated comparable effectiveness to clotrimazole ointment in achieving complete lesion resolution and reducing fungal colony counts [21]. This effect is likely mediated by curcumin's ability to inhibit the binding of *Candida* species to mucosal epithelial cells, a critical step in the establishment of infection [21].

4.2. Mechanisms of Action of Key Herbal Compounds

The diverse chemical profiles of herbal compounds contribute to their multifaceted mechanisms of action against *Candida* species:

- **Polyphenols (e.g., in green tea and pomegranate):** These large molecules can interact with other big molecules, including proteins, starch, cellulose, and alkaloids [20, 24]. A proposed mechanism for their antifungal activity is the precipitation of cell membrane proteins, leading to membrane disruption and cellular dysfunction [20].
- **Thymol and Carvacrol (e.g., in *Zataria multiflora* essential oil):** These phenolic compounds are known to break down the fungal cell membrane by stopping the production of ergosterol, which is a vital part of the fungal cell's outer layer [22]. They also make it harder for fungal cells to stick to each other and form protective biofilms [23].
- **Eugenol (e.g., in cinnamon essential oil):** Similar to thymol and carvacrol, eugenol also prevents fungal cells from sticking and forming biofilms. It can also interfere with the building of the fungal cell wall, contributing to its broad antifungal effects [4, 25].
- **Allicin (e.g., in garlic):** Beyond directly killing fungi by messing with their DNA, protein production, and energy, allicin also weakens *Candida*'s ability to cause disease. It can stop the fungus from forming harmful filaments and sticking to our tissues [9]. Plus, it can actually boost our immune system by increasing certain immune signals and activating immune cells, which helps us fight the infection [10].
- **Curcumin (*Curcuma longa*):** This compound from turmeric stops *Candida* from attaching to the cells lining our mouth, which is a critical step in preventing the infection from starting and spreading [21].

The beauty of herbal compounds is that their many active ingredients often work together in a synergistic way. This means they can be more effective while also reducing toxicity and making it harder for drug resistance to develop – a huge plus compared to drugs that only target one specific pathway [29, 30].

4.3. Addressing Discrepancies and Contributing Factors

While many studies showed similar effectiveness, some differences are worth discussing. For example, in the study by Pinelli et al. [17], *Ricinus communis* mouthwash and miconazole gel helped elderly patients clinically, but nystatin

drops didn't. Why might nystatin have been less effective? It could be a few things: the increasing prevalence of *C. albicans* resistance to nystatin, which is a common first-line treatment, might play a role [17]. Also, it can be tough for elderly patients to stick to treatment, especially if the medication tastes bad (nystatin is known for its bitter taste) or if they have trouble with dexterity, making mouthwashes or gels more manageable [15, 17].

Another interesting point was in the Tay et al. study [18], where even the placebo group showed improvement in disease severity, with no significant difference from the *Uncaria tomentosa* gel or miconazole groups. This reminds us of the "placebo effect" in clinical trials – sometimes, just the act of receiving treatment can make people feel better. It also emphasizes how incredibly important good oral hygiene and addressing underlying causes (like taking out dentures at night) are. These basic steps are crucial for treating candidiasis, no matter what medication you're using [18].

Interpreting fungal colony counts from lab tests can also be tricky. Pinelli et al. [17] reported clinical improvement with *Ricinus communis* mouthwash and miconazole gel, even without a big drop in fungal colony counts. This is because *Candida albicans* is a normal part of our oral flora. Just having a positive culture doesn't always mean there's a serious infection, as non-invasive forms of *Candida* can also grow in lab dishes [17]. Successful treatment is often defined by a significant *reduction* in fungal counts (e.g., from 10,000-20,000 CFU/mL in infected patients to a few hundred), rather than complete eradication, since *Candida* can still live harmlessly in the mouth [17]. Plus, bacterial co-infections are common in oral candidiasis, and some herbal compounds or miconazole also fight bacteria, which could explain clinical improvement even if the fungal numbers don't plummet [17, 26].

The study by Vasconcelos et al. [20] reported that the miconazole group had a higher percentage of patients with acceptable clinical results compared to the *Punica granatum* gel group, even though their lab results were similar. This might be because patients using miconazole had better oral hygiene, or perhaps miconazole simply sticks better to the mouth lining, keeping the drug concentrated where it's needed [20]. This really emphasizes that patient cooperation, sticking to treatment plans, maintaining good oral hygiene, and addressing any underlying issues are all vital for successful treatment and preventing the infection from coming back [4, 30].

4.4. Side Effects and Patient Happiness?

A truly compelling advantage of herbal compounds, as highlighted in this review, is their generally better safety profile and the fact that patients tend to be happier with them compared to conventional antifungals. Four studies specifically mentioned fewer adverse effects with herbal compounds [4, 10, 15, 20], and one study even reported no side effects at all in either the herbal or conventional group [21].

Let's look at some examples:

- People complained less about an unpleasant taste with cinnamon and garlic mouthwashes compared to nystatin [4, 10].
- While cinnamon mouthwash caused minor issues like burning and numbness, nystatin was linked to tongue sensitivity [4].
- Garlic mouthwash had very few side effects (itching, bad taste) compared to nystatin, which caused more frequent and varied complaints like bad taste, nausea, diarrhea, anorexia, and burning [10].
- Patients were significantly more satisfied with ginger (*Zingiber officinale*) mouthwash than with nystatin, largely because ginger helps with stomach upset and nausea, which are common side effects of nystatin that can make patients stop taking their medicine [15].
- In the Vasconcelos et al. study [20], miconazole gel caused nausea and stomach problems in *all* patients in its group, but the pomegranate gel group reported absolutely no complaints. This is a huge advantage for patient comfort and quality of life.
- However, it's important to remember that not *all* herbal compounds are completely free of side effects. Amanlou et al. [19] reported a fairly high incidence of side effects (59.3%) with *Zataria multiflora* gel, including itching, burning, dizziness, nausea, vomiting, and bad taste. This was even higher than the 50% incidence seen with miconazole gel. This just goes to show that we need to carefully evaluate the safety of each specific herbal treatment.

The increased patient satisfaction with herbal compounds, often because they cause fewer side effects, is a crucial factor for long-term treatment success and adherence [15, 29, 30]. Patients are simply more likely to stick with a treatment if it doesn't make them feel worse.

4.5. How Does Our Review Compare to Others?

Our systematic review builds on and expands the existing knowledge. Other systematic reviews on this topic have been published, but they often had a narrower focus or certain limitations. For instance, a review by Li et al. [27] in 2023 looked at topical Chinese herbal medicine for oral candidiasis and concluded that herbal groups had better overall effectiveness. However, a big drawback was that many of their included articles were in Chinese, and they didn't clearly define what "effectiveness rate" meant clinically. Another review by Megawati et al. [28] in 2021 focused only on Asian herbal

products over a five-year period and mostly included lab studies, with only one clinical trial. Our review stands out because we included a wider range of herbal products from around the world, focused exclusively on human clinical trials (RCTs), and provided a more detailed comparison of clinical, mycological, and safety outcomes.

4.6. Where Do We Still Need to Improve? (Limitations of the Current Evidence Base)

Despite the encouraging findings, our systematic review also highlighted some important limitations in the current research, which we need to keep in mind:

- **High Risk of Bias:** A significant proportion of the studies we included (9 out of 10) had an "unclear" or "high" risk of bias, particularly in domains related to random sequence generation, allocation concealment, and blinding of participants and outcome assessors. This raises concerns about the internal validity of these studies and the reliability of their reported results. Poor methodology can lead to treatments looking better than they actually are, or side effects being underestimated.
- **Too Much Variety:** The sheer diversity of herbal compounds, their different forms (different strengths, how they were extracted), and dosages across studies makes it really hard to directly compare them or combine their data statistically. This heterogeneity limits the ability to draw definitive conclusions about the superiority of one herbal compound over another or against a specific conventional drug.
- **Different Ways of Measuring:** While efforts were made to categorize outcomes, the specific methods for measuring clinical improvement (e.g., different scales for erythema, varying definitions of clinical cure) and mycological reduction (e.g., different culture techniques, CFU quantification methods) varied, making cross-study comparisons difficult.
- **Small Sample Sizes:** Many of the RCTs we included were relatively small, which limits their statistical power to detect true differences between interventions and increases the likelihood of type II errors (false negatives).
- **Short Follow-up Times:** The follow-up periods in some studies were relatively short, which may not be sufficient to assess long-term efficacy, recurrence rates, or delayed adverse effects.
- **Reporting Quality:** Despite using the CONSORT checklist for appraisal, the overall reporting quality in many studies was suboptimal, hindering a comprehensive assessment of their methodology and results.

These limitations really underscore that we need more rigorous and standardized research in this field.

4.7. Future Research Directions

To move past the current limitations and truly unlock the potential of phytotherapy for oral candidiasis, future research should prioritize:

- **High-Quality Randomized Controlled Trials:** There is an urgent need for more large-scale, well-designed, double-blind, placebo-controlled (where ethically feasible), and adequately powered RCTs. These studies must adhere strictly to reporting guidelines (e.g., CONSORT) to ensure transparency and replicability.
- **Standardization of Herbal Interventions:** Research should focus on standardizing herbal product formulations, including defining optimal concentrations, extraction methods, and delivery systems, to ensure consistency and facilitate comparative studies.
- **Elucidation of Mechanisms of Action:** Further in-depth research is required to fully elucidate the precise molecular and cellular mechanisms by which specific herbal compounds exert their antifungal and immunomodulatory effects.
- **Combination Therapies:** Investigating the synergistic effects of combining herbal compounds with conventional antifungal drugs, or combining different herbal compounds, could lead to novel and more effective treatment strategies, potentially reducing drug dosages and minimizing resistance development.
- **Long-Term Efficacy and Recurrence:** Studies with longer follow-up periods are needed to assess the sustained efficacy of herbal treatments, their impact on recurrence rates, and any long-term adverse effects.
- **Cost-Effectiveness Analyses:** Economic evaluations comparing the cost-effectiveness of herbal therapies with conventional treatments would be valuable for informing healthcare policy and resource allocation.
- **Patient-Reported Outcomes:** Future studies should increasingly incorporate comprehensive patient-reported outcome measures (PROMs) to capture the full impact of treatments on patients' quality of life, symptoms, and satisfaction.
- **Addressing Resistance:** Research specifically targeting the efficacy of herbal compounds against drug-resistant *Candida* strains is crucial.

5. CONCLUSION

This systematic review offers a comprehensive look at how well plant-based remedies and conventional antifungal medications compare in treating oral candidiasis. Our findings suggest that various herbal compounds, especially in mouthwash form,

demonstrate clinical and mycological effectiveness comparable to traditional antifungals. A significant win for herbal interventions is their generally good safety profile and the fact that patients tend to be much happier with them, often because they cause fewer side effects. This improved patient satisfaction is super important because it directly leads to better adherence to treatment, which is key for success.

The therapeutic effects of herbal compounds are multifaceted, stemming from their complex chemical compositions that can exert antifungal, anti-inflammatory, antibacterial, antioxidant, and immunomodulatory properties. This multi-target approach not only contributes to their broad-spectrum activity but also potentially reduces the likelihood of resistance to develop, a critical concern with the increasing use of synthetic antifungals. The integration of active ingredients in herbal compounds often leads to a biological balance that minimizes toxicity while maximizing therapeutic benefits, thereby enhancing patient acceptance and encouraging treatment completion [29, 30]. The inherent safety, accessibility, and alignment with holistic treatment philosophies further contribute to the higher acceptance and positive perception of herbal compounds globally, with a large portion of the world's population already relying on them for health purposes [29, 30, 31].

However, we must acknowledge the limitations in the current evidence. A notable proportion of the included studies suffered from an unclear or high risk of bias, particularly concerning methodological rigor in randomization, allocation concealment, and blinding. Furthermore, the heterogeneity in herbal formulations, dosages, and outcome measures across studies makes it challenging to draw definitive, universally applicable conclusions.

In conclusion, while conventional antifungal drugs remain indispensable in the current therapeutic armamentarium for oral candidiasis, the findings of this review strongly support the continued exploration and integration of phytotherapeutic agents. To solidify their role in clinical practice, there is an imperative need for more rigorous, well-designed, large-scale, and standardized randomized controlled trials. Such high-quality research will be instrumental in establishing definitive comparative efficacy, safety profiles, and long-term outcomes, ultimately informing evidence-based clinical guidelines and offering more diverse, patient-centric, and sustainable treatment options for individuals affected by oral candidiasis. The exciting blend of traditional wisdom and modern scientific inquiry holds immense promise for improving oral health care.

REFERENCES

1. Ordaya EE, Clement J, Vergidis P. The role of novel antifungals in the management of candidiasis: A clinical perspective. Mycopathologia 2023;188:937-48.
2. Qadir MI, Bashir H, Ahmad MH. Human oropharyngeal candidiasis: From etiology to current treatment. Crit Rev Immunol 2023;43:15-24.
3. Contaldo M, Di Stasio D, Romano A, Fiori F, Della Vella F, Rupe C, et al. Oral candidiasis and novel therapeutic strategies: Antifungals, phytotherapy, probiotics, and photodynamic therapy. Curr Drug Deliv 2023;20:441-56.
4. de Araújo MR, Maciel PP, Castellano LR, Bonan PR, Alves DD, de Medeiros AC, et al. Efficacy of essential oil of cinnamon for the treatment of oral candidiasis: A randomized trial. Spec Care Dentist 2021;41:349-57.
5. Stoopler ET, Villa A, Bindakhil M, Díaz DL, Sollecito TP. Common oral conditions: A review. JAMA 2024;331:1045-54.
6. Alam MZ, Ahmad Khan MS. Phytomedicine from middle Eastern Countries: An alternative remedy to modern medicine against Candida spp infection. Evid Based Complement Alternat Med 2021;2021:6694876.
7. Seleem D, Benso B, Noguti J, Pardi V, Murata RM. In vitro and in vivo antifungal activity of lichochalcone-A against Candida albicans biofilms. PLoS One 2016;11:e0157188.
8. Doddanna SJ, Patel S, Sundarrao MA, Veerabhadrappa RS. Antimicrobial activity of plant extracts on Candida albicans: An in vitro study. Indian J Dent Res 2013;24:401-5.
9. Bagwan WA, Harinathan B, Pathade GR. Novel antifungal strategies against candidiasis: Insights from herbal biotechnology. NATURALISTA CAMPANO 2024;28:126-32.
10. Bakhshi M, Taheri JB, Shabestari SB, Tanik A, Pahlevan R. Comparison of therapeutic effect of aqueous extract of garlic and nystatin mouthwash in denture stomatitis. Gerodontology 2012;29:e680-4.
11. Coco BJ, Bagg J, Cross LJ, Jose A, Cross J, Ramage G. Mixed Candida albicans and Candida glabrata populations associated with the pathogenesis of denture stomatitis. Oral Microbiol Immunol 2008;23:377-83.
12. BarmanA. Standard setting in student assessment: Is a defensible method yet to come? Ann Acad Med Singap 2008;37:957-63.
13. HigginsJP, Altman DG. Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. The Cochrane Library; 2008. p. 187-241.
14. Gonoudi E, Rezai M, Farrokhnia T, Goudarzi M, Sima A. Comparison of antifungal efficacy of Zataria multiflora

and nystatin for treatment of denture stomatitis: Arandomized clinical trial. J Dent (Shiraz) 2021;22:60-6.

15. Eslami H, Pakroo S, Maleki TE, Sadeghi N, Fakhrzadeh V. Is ginger (Zingiber officinale) mouthwash a convenient therapeutic for denture stomatitis. Adv Biosci Clin Med 2015;3:17-23.

16. Najafi S, Hajheidary S, Amin G, Siavoshi F, Gholizadeh N. Comparing the effect of green tea extract with nystatin in the treatment of denture stomatitis. Avicenna J Dent Res 2015;7:5.

17. Pinelli LA, Montandon AA, Corbi SC, Moraes TA, Fais LM. Ricinus communis treatment of denture stomatitis in institutionalised elderly. J Oral Rehabil 2013;40:375-80.

18. Tay LY, Jorge JH, Herrera DR, Campanha NH, Gomes BP, Andre Dos Santos F. Evaluation of different treatment methods against denture stomatitis: A randomized clinical study. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;118:72-7.

19. Amanlou M, BeitollahiJM, Abdollahzadeh S, Tohidast-Ekrad Z. Miconazole gel compared with Zataria multiflora Boiss. gel in the treatment of denture stomatitis. Phytother Res 2006;20:966-9.

20. Vasconcelos LC, Sampaio MC, Sampaio FC, Higino JS. Use of Punica granatum as an antifungal agent against candidosis associated with denture stomatitis. Mycoses 2003;46:192-6.

21. Tatapudi R, Abdul Samad SK, Manyam R, Dasari D, Lakshmi RV. Efficacy of curcumin in the treatment of denture stomatitis: A randomized double-blind study. J Oral Maxillofac Pathol 2021;25:286-91.

22. Marcos-Arias C, Eraso E, Madariaga L, Quindós G. In vitro activities of natural products against oral Candida isolates from denture wearers. BMC Complement Altern Med 2011;11:119.

23. Sharifzadeh A, Shokri H, Katiraee F. Anti-adherence and anti-fungal abilities of thymol and carvacrol against Candida species isolated from patients with oral candidiasis in comparison with fluconazole and voriconazole. Jundishapur J Nat Pharm Prod 2021;16 (1): e65005

24. Ghorbani A, Sadrzadeh A, Habibi E, Dadgar K, Akbari J, Moosazadeh M, et al. Efficacy of Camellia sinensis extract against Candida species in patients with denture stomatitis. Curr Med Mycol 2018;4:15-8.

25. Rangel ML, de Aquino SG, de Lima JM, Castellano LR, de Castro RD. In vitro effect of Cinnamomum zeylanicum blume essential oil on Candida spp. involved in oral infections. Evid Based Complement Alternat Med 2018;2018:4045013.

26. Nenoff P, Koch D, Krüger C, Drechsel C, Mayser P. New insights on the antibacterial efficacy of miconazole in vitro. Mycoses 2017;60:552-7.

27. Li T, Hu Q, Yang J, Zhang N, Liu N, Liu Q. Topical Chinese herbal compound in the treatment of oral candidiasis: Asystematic review and meta-analysis of randomized controlled trials. Heliyon 2023;9:e13253.

28. Megawati A, Wahyuni IS. Potential of herbal medicine in Asia for oral candidiasis therapy: A systematic review. Int J Appl Pharm 2021;13:1-6.

29. KarimiA, Majlesi M, Rafieian-Kopaei M. Herbal versus synthetic drugs; beliefs and facts. J Nephropharmacol 2015;4:27-30.

30. Ashrafi Tamai I, Zahraei Salehi T, Khosravi A, Sharifzadeh A, Balal A. Chemical composition and anti-candida activity of Trachyspermum ammi essential oil on azoles resistant Candida albicans isolates from oral cavity of HIV+patients. J Mycol Med 2013;12:137-49.

31. Moghadam ET, Yazdanian M, Tahmasebi E, Tebyanian H, Ranjbar R, Yazdanian A, et al. Current herbal medicine as an alternative treatment in dentistry: In vitro, in vivo and clinical studies. Eur J Pharmacol 2020;889:173665.