Herbal medicines for treatment of fungal infections: a systematic review of controlled clinical trials
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CRD summary
This review concluded that herbal antifungal medicines have rarely been tested in trials. The authors stated that tea tree oil holds some promise, but all herbal remedies require further investigation in rigorous clinical trials. These conclusions seem appropriate given the limited amount of high-quality evidence found in this review.

Authors' objectives
To critically assess the evidence of efficacy of herbal antifungal medicines.

Searching
MEDLINE (via PubMed), EMBASE, CISCOM and the Cochrane Library were searched from inception to August 2002 for studies published in any language; the search terms were reported. In addition, departmental files and bibliographies were screened.

Study selection
Study designs of evaluations included in the review
Controlled clinical trials were eligible for inclusion in the review.

Specific interventions included in the review
Studies evaluating single herbal medicines for the reduction or elimination of disease-producing fungal populations colonising humans were eligible for inclusion. Herbal mixtures, isolated plant chemicals, synthetic preparations, and treatments solely for the prevention of infection or stimulation of immunity were excluded. The specific interventions included Solanum nigrescens, Solanum chrysotrichum, oil of bitter orange (OBO) and tea tree oil (TTO). The control interventions included placebo treatments and active conventional antifungal agents.

Participants included in the review
Studies including humans with fungal infections were eligible for inclusion. The specific infections included were vaginal candidosis, tinea infections (tinea pedis, corporis and cruris) and onchomycosis.

Outcomes assessed in the review
The authors did not state any inclusion criteria relating to the outcomes. The outcomes reported in the selected studies included conversion to negative culture and clinical assessment or resolution of symptoms.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The methodological quality of all trials was assessed according to the Jadad scale, which scores studies on randomisation, blinding and the handling of withdrawals. The studies were awarded a score up to a maximum of 5 points. It was unclear how many reviewers performed the validity assessment.

Data extraction
The authors stated that the data were extracted according to predefined criteria by one reviewer and checked by a second. Data were extracted on key study characteristics and results. The data appears to have been extracted as
reported by the original study authors.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a narrative.

How were differences between studies investigated?
The main differences between the included studies were apparent from the table of study characteristics. These studies were presented in the narrative synthesis according to the type of fungal infection being treated (vaginal candidosis, tinea infections or onchomycosis).

**Results of the review**

Seven studies (n=654) were included in the review: five randomised and two non-randomised.

The included studies varied in terms of their methodological quality, with Jadad scores ranging from 1 to 5.

**Vaginal candidosis.**

One study found no significant differences between women supplied with either Solanum nigrescens or commercial nystatin suppositories, with 90% of the experimental and 94% of the comparative group being culture negative at the end of treatment.

**Tinea infections.**

One non-randomised study evaluated OBO in 70 patients with tinea corporis, cruris or pedis. The patients were assigned to treatment with 25% emulsion of OBO, 20% OBO in alcohol, 100% OBO or an imidazole derivative, for up to 4 weeks. One-quarter of patients using 100% OBO dropped out of the trial. Those patients completing the therapy in this group were reported to have been cured the most rapidly (33% in 1 week). The other two OBO preparations also produced more rapid cure rates than imidazole.

One randomised clinical trial (RCT) compared the efficacy of 10% w/w TTO, 1% tolnaftate and placebo creams applied twice daily for 4 weeks in 121 patients with tinea pedis. Significantly more tolnaftate-treated patients (85%) than TTO patients (30%) and placebo-treated patients (21%) showed conversion to negative culture by the end of treatment. Toluante and TTO groups showed significantly greater improvement in symptomatology than the placebo group. Tolerability was reported to be excellent and only one adverse reaction was noted; the adverse effect occurred in the tolnaftate group.

A second RCT evaluated higher concentrations (25% and 50%) of TTO applied twice daily for 4 weeks, compared with placebo, in 158 patients with tinea pedis. Mycological cure was achieved in significantly more patients in both TTO groups than in those using placebo (55% and 64% versus 31%). Statistically significant improvements in clinical scores were also observed in the TTO groups (72% and 68% versus 39%). Tolerability was generally good. Three patients reported dermatitis: one with 25% TTO and two with 50% TTO.

**Onchomycosis.**

One double-blind RCT compared TTO with clotrimazole in 117 patients with subungual onychomycosis. There were no statistically significant differences between TTO and clotrimazole in negative culture at the end of treatment (18% versus 11%) or full or partial resolution of symptoms (60% versus 61% post-treatment and 56% versus 55% at 3 months' follow-up).

One double-blind RCT evaluated 8 weeks’ treatment with a combination of 2% butenafine hydrochloride and 5% TTO cream against a cream containing TTO only in 60 patients with toenail onychomycosis. The overall cure rates after 36 weeks were 80% (combination) and 0% (TTO), respectively.
Authors' conclusions
There were few controlled clinical trials of herbal antifungal medicines, the most frequently evaluated being TTO, which holds some promise. All herbal remedies require further investigation in clinical trials.

CRD commentary
In this review, the question was defined in terms of inclusion criteria relating to the participants, interventions and study design. An attempt was made to identify all the relevant published evidence (in any language), but it was unclear how extensive the attempts were to locate unpublished material, thus publication bias may affect the findings. The validity of the included studies was assessed using an established scale and study details were presented in the text and tables. However, it was unclear how many reviewers were involved in the study selection and validity assessment processes, which may have led to the incorporation of errors or bias. The use of a narrative synthesis seems appropriate given the heterogeneity of the included studies. Overall, given the small number of often poor-quality studies included in the review, the authors' conclusions about the limited evidence base from controlled trials in this area appear justified.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further well-designed clinical trials are required to establish the most effective concentrations for use, and/or possible dual therapies with conventional antifungal preparations.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.