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Herbal medicines for treatment of bacterial infections: a review of controlled clinical trials

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Objectives: Many hundreds of plant extracts have been tested for *in vitro* antibacterial activity. This review is a critical evaluation of controlled clinical trials of herbal medicines with antibacterial activity.

Methods: Four electronic databases were searched for controlled clinical trials of antibacterial herbal medicines. Data were extracted and validated in a standardized fashion, according to predefined criteria, by two independent reviewers.

Results: Seven clinical trials met our inclusion criteria. Four of these studies were randomized. Three trials of garlic and cinnamon treatments for *Helicobacter pylori* infections reported no significant effect. Bacterial infections of skin were treated in four trials. Positive results were reported for an ointment containing tea leaf extract in impetigo contagiosa infections. Two trials of tea tree oil preparations used for acne and methicillin-resistant *Staphylococcus aureus*, and one trial of *Ocimum gratissimum* oil for acne, reported results equivalent to conventional treatments.

Conclusions: Few controlled clinical trials have been published and most are methodologically weak. The clinical efficacy of none of the herbal medicines has so far been demonstrated beyond doubt. This area seems to merit further study through rigorous clinical trials.

Keywords: herbal medicines, antibacterial, clinical trials

Introduction

Many hundreds of plants worldwide are used in traditional medicine as treatments for bacterial infections. Some of these have also been subjected to *in vitro* screening but the efficacy of such herbal medicines has seldom been rigorously tested in controlled clinical trials. Conventional drugs usually provide effective antibiotic therapy for bacterial infections but there is an increasing problem of antibiotic resistance and a continuing need for new solutions. Although natural products are not necessarily safer than synthetic antibiotics, some patients prefer to use herbal medicines. Thus healthcare professionals should be aware of the available evidence for herbal antibiotics. This review was undertaken to assess critically those antibacterial herbal medicines that been have subjected to controlled clinical trials.

Materials and methods

Computerized literature searches were performed on MEDLINE (via PubMed), EMBASE, CISCOM and Cochrane Library from their inception until October 2002. Primary search terms used were 'herb' or 'plant' and 'antibacterial' and 'clinical trials'. Further searches were undertaken using the names of individual plants with antimicrobial effects as documented *in vitro* and also individual bacteria reported in clinical trials. Departmental files were searched and the bibliographies of articles located from all sources were searched for relevant clinical trials. No restriction on the language of publication was applied. Controlled clinical trials were included in the analysis if they reported experimental use of a single, whole plant extract for reduction or elimination of disease-producing bacterial populations colonizing humans. Trials of herbal rinses used for oral hygiene were considered to form a subject in their own right and were not included. Herbal mixtures were excluded as well as treatments solely for the prevention of bacterial infections or for stimulation of immunity. Single constituents derived from plant extracts are by definition not herbal medicines and were therefore excluded. All data were extracted by the first author according to predefined criteria (Table 1) and validated by the second

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Table 1. Clinical trials of herbal antibacterial preparations

Reference	Study design (Jadad score)	Study sample	Condition/bacterium treated	Experimental intervention	Control interventions	Main outcome measure	Main results
Aydin et al.[2]	blinding not stated, non-randomized, comparative trial with two parallel groups	20 dyspeptic patients	*H. pylori*	275 mg garlic oil, 3 times a day for 14 days	275 mg garlic oil, 3 times a day with 20 mg omeprazole twice a day for 14 days	negative histology and urease test 1 month after end of treatment	neither therapy had significant effect on outcome measures
Graham et al.[3]	open, non-randomized, crossover trial	12 healthy adults with *H. pylori*	*H. pylori*	(1) 10 cloves fresh garlic with 3 meals per test day (2) 6 jalapeno peppers with 3 meals per test day	(3) bismuth subsalicylate with 3 meals per test day (4) no intervention with 3 meals per test day	reduction of urea breath test value	no significant changes with experimental interventions, significant reduction after bismuth
Nir et al.[4]	blinding not stated, placebo-controlled RCT with two parallel groups (2)	32 patients undergoing gastroscopy (23 completed treatment)	*H. pylori*	40 mg cinnamon extract twice a day for 4 weeks	placebo	reduction of urea breath test value	no significant changes in breath test values
Caelli et al.[5]	blinding not stated, RCT with two parallel groups (2)	30 inpatients (18 completed treatment)	methicillin-resistant *S. aureus*	tea tree oil 4% nasal ointment and 5% body wash for 1–34 days	2% mupirocin nasal ointment and triclosan body wash 2–14 days	eradication of MRSA colonization	no significant difference between groups
Sharquie et al.[6]	blinding not stated, non-randomized, controlled trial with four parallel arms	104 patients with impetigo contagiosa (88 completed treatment)	impetigo contagiosa	(1) 1% aqueous tea extract, several times a day for 7–10 days (2) 5% tea extract in vaseline, 3–4 times a day for 7–10 days	(3) 15 mg/g framycetin and 0.05 mg/g gramicidin ointment for 7–10 days (4) 40–50 mg/kg/day oral cefalexin for 7–10 days	cure rate	(1) 37.5% cure (2) 81.3% cure (3) 72.2% cure (4) 78.6% cure
Bassett et al.[7]	investigator blind, comparative RCT with two parallel groups (2)	124 patients with mild to moderate acne (119 completed treatment)	acne	tea tree oil 5% water-based gel for 3 months	benzoyl peroxide 5% water-based lotion for 3 months	changes in total numbers of inflamed and non-inflamed lesions	both treatments effective in reducing lesions, TTO has slower onset of action
Orafidiya et al.[8]	blinding not stated, placebo-controlled RCT with 18 parallel groups (2)	126 subjects	acne	*O. gratissimum* oil preparations, 0.5–5% in four different bases, twice a day for 4 weeks	(1) benzoyl peroxide 10% lotion (2) placebo	product activity = reciprocal value of number of days to 50% reduction in lesion count	(1) 2–5% oil in alcohol and 5% oil in cetomacrogol base significantly more effective than benzoyl peroxide (2) no 50% lesion reduction in placebo group in test period

RCT, randomized controlled trial.

author. The methodological quality of randomized trials was evaluated according to a score designed by Jadad *et al.*[1] (maximum score 5).

Results

Helicobacter pylori infections

Three trials were found that tested the efficacy of herbal products for the eradication of *H. pylori*; two tested different preparations of garlic (*Allium sativum*). A group of 20 *H. pylori*-infected patients suffering from dyspeptic complaints for >2 months were recruited by Aydin *et al.*[2] A 2 week treatment with capsules containing an oil macerate of garlic (275 mg, three times a day) was compared with the combination of garlic with omeprazole (20 mg, twice a day) for the eradication of *H. pylori*. All subjects underwent endoscopy before and 1 month after the end of treatment, and the presence of *H. pylori* in biopsy specimens was confirmed by the urease test and by microscopy. Symptom scores and degree of gastritis, as judged by histological examination, were recorded pre- and post-treatment. Neither intervention resulted in the elimination of the organism, change in the severity of gastritis or a significant change in symptom scores (9.2 ± 1.55 versus 8.7 ± 1.70 in the garlic oil group, 9.0 ± 1.49 versus 8.5 ± 1.51 in the garlic oil plus omeprazole group). The authors considered that low levels of the antibacterial component allicin in the garlic capsules might account for the lack of effect. This trial has obvious weaknesses: it was not randomized, probably not patient-blind and its sample size was small.

Extracts of fresh garlic and capsaicin-containing peppers can inhibit *H. pylori in vitro* and were tested for their ability to inhibit the bacterium *in vivo* in a crossover trial involving 12 individuals infected with *H. pylori*.[3] Test substances were included in morning, noon and evening, Mexican-style meals. Subjects participated in a minimum of 3 trial days (negative and positive controls and one experimental ingredient). At least 2 days elapsed between test substances, with bismuth always being the last intervention tested to preclude lasting anti-*H. pylori* effects. During each test meal participants received one intervention: garlic (10 freshly sliced cloves), capsaicin (six freshly sliced jalapeno peppers), two tablets of bismuth subsalicylate (Pepto-Bismol, positive control) or no additions (negative control). The urea breath test was performed before the first meal of the day, before the evening meal and the morning after each test day. The results were used to evaluate the effectiveness of the therapies. Ten subjects received garlic, six received jalapenos and 11 received bismuth. Neither garlic nor jalapenos had any effect on urease levels (median urease activity pre- and post-garlic 28.5 versus 39.8 and jalapenos 43.7 versus 46.6; $P > 0.8$) but there was a marked reduction after ingestion of bismuth (55.8 versus 14.3; $P < 0.001$). Two patients experienced nausea and

diarrhoea graded as severe after eating the jalapenos and 70% of those eating garlic complained of taste disturbance and body odour. This study suffered from lack of randomization and small sample size.

Nir *et al.*[4] investigated the effects of treatment with an extract of cinnamon (*Cinnamonum cassia*) in 23 patients who were undergoing gastroscopy and had a positive urea breath test. Thirty-two patients were randomly allocated in a 2:1 ratio to the study and control groups but only 23 could be included in the final analysis. Fifteen received 80 mg/day cinnamon and eight received placebo for 4 weeks. Breath tests were repeated at the end of the trial period. There were some increased and some decreased urea breath test values in both groups, but overall mean values (pre- and post-cinnamon treatment 22.1 versus 24.4, placebo 23.9 versus 25.9) showed no significant changes. This trial was well designed but its sample size was small and therefore the possibility of a type II error cannot be excluded.

Staphylococcus aureus and Streptococcus pyogenes infections

One clinical trial compared the use of a combination of 4% tea tree oil (TTO) nasal ointment and 5% TTO body wash (intervention) with a standard 2% mupirocin nasal ointment and triclosan body wash (routine) for eradication of methicillin-resistant *Staphylococcus aureus* (MRSA).[5] A total of 30 in-patients, either infected or colonized with MRSA, were recruited and randomly assigned to be treated with TTO or standard routine care for a minimum of 3 days. Infected patients also received intravenous vancomycin and all participants were screened for MRSA carriage 48 and 96 h after the cessation of topical treatment. Only 18 patients completed the trial. More patients in the intervention than in the control group cleared infection (5/8 versus 2/10). Two patients in the intervention group received 34 days treatment and one cleared the infection while the other remained chronically colonized. The inter-group differences were not statistically significant. This trial was too small to generate a conclusive result.

Strains of *S. aureus* and *Streptococcus pyogenes* are the causative agents of the painful and unsightly skin condition impetigo contagiosa. Sharquie *et al.*[6] tested *in vitro* antibacterial properties of crude preparations of black tea (*Thea assamica*) and proceeded to a clinical trial in 104 patients with impetigo contagiosa. Tea extracts were incorporated in an aqueous lotion at a concentration of 1% (Group 1) and a vaseline base at a concentration of 5% (Group 2), and these preparations were applied at least three or four times a day. Cure rates in these groups were compared with cure rates in groups given framycetin and gramicidin ointment (Group 3) or oral cefalixin (Group 4). The 5% tea extract was as effective as antibiotic treatments (Groups 2–4 cure rates 81.3%, 72.2%

and 78.6%, respectively). The cure rate in Group1 was 37.5%. Even though the total sample size of this trial seems large, the patient numbers in each treatment arm were low. Moreover, this study suffered from the fact that it was not randomized.

Acne

A single-blind randomized clinical trial (RCT) compared the use of 5% TTO gel with 5% benzoyl peroxide lotion for the treatment of mild to moderate acne in a group of 124 patients.[7] Numbers of inflamed and non-inflamed lesions were counted at baseline and at monthly intervals for 3 months and both treatments were effective, although improvements were slower in the TTO group. There was a significantly greater reduction in inflamed lesions in the benzoyl peroxide group at all three follow-up visits. Skin discomfort during treatment was reported less frequently in the TTO group than in those using benzoyl peroxide (44% versus 79%). Without a placebo group it is difficult to decide whether this study demonstrates the presence or absence of a treatment effect and it may also have lacked statistical power to test equivalence between the two therapies.

A recent study tested a range of concentrations of *Ocimum gratissimum* oil in comparison with 10% benzoyl peroxide and a placebo, over a period of 4 weeks, for the reduction of acne lesions in a population consisting mainly of students.[8] *O. gratissimum* oil was incorporated at concentrations of 0.5%, 1%, 2% and 5% v/v in four different bases (polysorbate 80, cetomacrogol, petrolatum and alcohol) resulting in 16 parallel experimental groups. The number of lesions were counted daily by investigators throughout the test period and the time taken to achieve a 50% reduction relative to pre-treatment was noted for each subject. Preparations containing 2% and 5% *Ocimum* oil in alcohol and 5% in cetomacrogol were significantly more active than benzoyl peroxide ($P < 0.05$), while 2% oil in cetomacrogol had similar activity to the reference product. The most active 5% preparations produced skin irritation but the authors considered a 2% preparation in cetomacrogol to be suitable for the management of acne. The sample size of the individual treatment groups was too small to exclude a type II error.

Discussion

Perhaps the most striking result of this review is the extreme paucity of controlled clinical trials testing herbal antibiotics. In light of the long history and present popularity of their use, it is surprising that so few trials have tested the efficacy of herbal antibiotics. One obvious reason is the lack of patent rights on herbal medicines. Another reason could be that traditionally, herbal medicine has been hesitant to embrace modern methods for efficacy testing.

Although our search strategy was comprehensive, we cannot be sure that all clinical trials were located. Herbal medicine research is sometimes published in journals not readily accessible through electronic databases and negative trials may not be published at all. It might have been anticipated that trials of cranberry extracts would have been located since it has been used for decades in the management of urinary tract infection. Although a number of studies have examined the use of cranberry for prevention of recurrences of urinary tract infections,[9] there are no published clinical trials of its use for treatment of infections[10] and it therefore did not meet the inclusion criteria of this review.

Most of the clinical trials located had few participants. Herbal therapies were reported as being as effective as conventional treatments in two trials[5,7] and one of the two herbal preparations used in a third trial was as efficacious as two conventional antibiotic regimens.[6] The results imply that an *O. gratissimum* oil preparation is a promising treatment for acne.[8] It was as effective as benzoyl peroxide but described as having an unpleasant odour that may, of course, render it less acceptable to patients.

H. pylori infection is common even in asymptomatic individuals and has been shown to be a risk factor for gastric cancer.[11] Eradication of the organism can be difficult to achieve with conventional antibiotic therapies, requiring combinations of antibiotics, proton pump inhibitors and bismuth preparations.[12] Moreover, adverse effects are regularly associated with these conventional treatments.[11]

Garlic is one of the most extensively researched medicinal plants.[13] Its antibacterial action depends on allicin and is thought to be due to multiple inhibitory effects on various thiol-dependent enzymatic systems.[14] Allicin is formed catalytically by crushing raw garlic or adding water to dried garlic, when the enzyme allicinase comes into contact with allicin. Steam distillation of mashed garlic produces garlic oil containing methyl and allyl sulphides of allicin, having the practical advantage of being more stable than allicin itself.

Two controlled trials of garlic preparations used to eradicate *H. pylori* infection recorded failure.[2,3] A further two small trials[15,16] without control groups (thus not meeting inclusion criteria of this review) similarly reported no significant results although the garlic preparations used were different in all four trials. Individual constituents of garlic oil and garlic powder have shown a range of potencies when tested *in vitro* against human enteric bacteria including *H. pylori*.[17,18] Analysis of the herbal preparations used in clinical trials was reported and discussed by McNulty *et al.*,[16] who suggested that active ingredients were at low levels or absent in the preparations used in trials published by Ernst[15] and Aydin *et al.*[2] Although the steam-distilled garlic oil preparation used in her own pilot trial had high levels of allicin sulphides, it also proved ineffective. It is possible that an effective treatment might be produced by optimizing the active antibacterial con-

tent of preparations and/or judicious use of a combination of conventional and herbal therapies. Garlic and omeprazole have demonstrated synergic properties when tested *in vitro* against some strains of *H. pylori*[19,20] and the fact that their concurrent use was not effective in the trial reported by Aydin *et al.*[2] may be due to low levels of active garlic components.

Cinnamon extracts *in vitro* exerted an inhibitory effect on the growth and urease activity of a number of strains of *H. pylori*[21] and encouraged Nir *et al.*[4] to conduct a clinical trial. At the concentration chosen the extract was ineffective *in vivo* and the authors suggested the possibility that eradication of the organism might be achieved using higher cinnamon concentrations or a regimen combining antibiotic and herbal therapy.

TTO products are widely used as topical treatments by the general public and have proved as effective as conventional treatments for the control of skin bacteria involved in acne[7] and of MRSA in a hospital setting.[5] Recent research suggests that TTO and its components compromise cytoplasmic membranes of *S. aureus*,[22] weakening the cells' ability to withstand the effects of other cytocidal agents. The public perception and potentially devastating results of uncontrolled MRSA spread in hospitals make it a prime target for a new strategy for eradication, and TTO could have a contribution to make in that context. RCTs of TTO have recently been reviewed and the authors concluded that, while it may prove useful as a topical antimicrobial, evidence from well-designed RCTs was lacking.[23]

A black tea leaf extract, presumed to derive its antibacterial effect from tannins and catechins, demonstrated results equivalent to antibiotic treatments for curing impetigo contagiosa.[6] This simple and inexpensive alternative to conventional treatment may be worthy of further rigorous investigation.

In conclusion, the evidence summarized above tentatively suggests possible benefits from some herbal preparations with antibacterial activity. Further large-scale, well-designed clinical trials are required to provide more conclusive proof of their efficacy.

Acknowledgements

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