

Acaricidal Activity of *Melaleuca alternifolia* (Tea Tree) Oil

In Vitro Sensitivity of *Sarcoptes scabiei* var *hominis* to Terpinen-4-ol

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Objective: To compare the acaricidal activity of *Melaleuca alternifolia* (tea tree) oil (TTO) and some of its individual active components on the itch mite *Sarcoptes scabiei* var *hominis*.

Design: In vitro acaricide sensitivity assessment.

Setting: The Menzies School of Health Research laboratory, located near the Infectious Diseases Ward of the Royal Darwin Hospital, Australia, where patients are admitted and treated for crusted scabies.

Participants: Scabies mites (*S scabiei* var *hominis*) were collected from a 20-year-old Aboriginal woman admitted to the Royal Darwin Hospital with crusted scabies.

Interventions: Within 3 hours of collection, scabies mites were placed in continuous direct contact with the TTO products and control acaricides and were observed at regular intervals.

Main Outcome Measures: Percentage of mites dead at regular observation intervals between 5 minutes and

24 hours during continuous exposure to the TTO products and acaricides.

Results: The 5% TTO and active component terpinen-4-ol were highly effective in reducing mite survival times. Statistically significant differences in mite survival curves were observed for 5% TTO, 2.1% terpinen-4-ol, 5% permethrin, and ivermectin (100 µg/g of Emulsifying Ointment British Pharmacopoeia 88). In vivo effectiveness was also observed.

Conclusions: Documentation of resistance against antiectoparasitic compounds is increasing. Reported *S scabiei* treatment failures with lindane, crotamiton, and benzyl benzoate, as well as likely emerging resistance to 5% permethrin and oral ivermectin, are of concern and advocate for the identification and development of novel acaricidal drugs. Tea tree oil is a membrane-active biocide extracted from the tree *M alternifolia*. It is a principal antimicrobial in a wide range of pharmaceuticals sold in Australia, with the main active component being oxygenated terpenoids. The results suggest that TTO has a potential role as a new topical acaricide and confirm terpinen-4-ol as the primary active component.

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SCABIES IS A WORLDWIDE ECTOPARASITIC disease of skin caused by the itch mite *Sarcoptes scabiei*.¹ It is a major problem in many developing countries, related primarily to poverty and overcrowding.² Despite the availability of topical acaricides, individuals often transmit the disease to others before receiving therapy. Current treatment for ordinary scabies consists primarily of various topical therapies, although oral ivermectin has been used and recently approved for treatment of ordinary scabies in France.³ Prevalences of up to 50% in children have been described in some remote Aboriginal communities in Australia, with most children having repeated scabies infestations.⁴ Preventing sca-

abies has become a priority in many of these communities, as the intensely itching lesions engender significant morbidity, often becoming secondarily infected with group A streptococcus.⁵ Prevention of the spread of scabies in these at-risk populations is based on mass community treatment. Mass treatment of people with acaricides in these endemic communities creates an environment for emerging drug tolerance or resistance. Recently published findings of in vitro acaricide efficacy in northern Australia indicate that *S scabiei* mites are becoming increasingly tolerant to 5% permethrin.⁶ Other evidence documents treatment failures with lindane, crotamiton, and benzyl benzoate, as well as likely emerging resistance to 5% permethrin.⁶⁻¹⁰ Manage-

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Table 1. Products Used in the In Vitro Assay of *Sarcoptes scabiei*

Retail Name	Active Constituent	Concentration	Source in Australia
Lyclear	Permethrin	5%	Warner Lambert, Caringbah, NSW
Equimec Paste, 18.7 g/kg	Ivermectin	100 µg/g	Merial Australia Pty Ltd, Parramatta, NSW
Thursday Plantation 100% Pure Tea Tree Oil	Melaleuca oil	5%	Thursday Plantation Laboratories, Ballina, NSW
NA	Terpinen-4-ol	2.1%	P. Hart*
NA	α-Terpineol	0.15%	P. Hart
NA	1,8-Cineole	0.1%	P. Hart
Emulsifying Ointment	British Pharmacopoeia 88	NA	Sigma Pharmaceuticals Pty Ltd, Clayton, Victoria

Abbreviations: NA, not applicable; NSW, New South Wales.

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ment of drug resistance is difficult, and development of novel therapies to protect against the emergence of acaricide resistance would be advantageous to the individual, to the Aboriginal community, and to society at large.

A rare, more serious infestation can also occur, known as crusted scabies, in which large populations of mites are found beneath scabs and exfoliative crusts on many parts of the body. Because of the enormous burden of mites, crusted scabies is considerably more contagious than ordinary scabies. Crusted scabies has been linked with immune deficiency but has been observed in otherwise immunocompetent individuals. For crusted scabies, treatment is usually based on a combination of multiple doses of ivermectin and topical acaricides.^{11,12} Investigations on the efficacy of ivermectin treatment of crusted scabies indicate early recrudescence of disease following a single dose, whereas 3 doses usually result in cure.¹³ In 1998, a 5-dose regimen (each at 200 µg/kg of body weight) was, however, introduced at the Royal Darwin Hospital for treatment of crusted scabies because of relapses in up to half of patients.¹⁴ Subsequently, treatment failure with combination therapy of oral ivermectin and topical 5% permethrin has occurred in some patients with severe crusted scabies (S.F.W. and B.J.C. unpublished data, 2000).

The essential oil of the tea tree is an Australian Aboriginal traditional medicine for bruises, insect bites, and skin infections.¹⁵ Studies^{16,17} have demonstrated its antimicrobial activity against gram-positive (eg, *Staphylococcus aureus*), gram-negative (eg, *Escherichia coli*), yeast (eg, *Candida albicans*), and viral (eg, herpes simplex viruses) organisms, but there is little information on its antiectoparasitic activity. The chemical composition of tea tree oil (TTO) is well defined, and the primary active components are the oxygenated terpenoids.¹⁸ A large variation in oil composition occurs naturally, but 2 identified significant components include terpinen-4-ol and 1,8-cineole. Terpinen-4-ol can constitute up to approximately 40% of some TTOs.¹⁸ This study was undertaken to investigate the in vitro activity of TTO and some of its components against *S scabiei* var *hominis*.

METHODS

Detection of in vitro acaricide sensitivity was based on a simple laboratory assay previously described.⁵ In vivo effectiveness of scabies treatment was also recorded.

A 20-year-old Aboriginal woman, repeatedly admitted to the Royal Darwin Hospital with crusted scabies for 3 to 4 years,

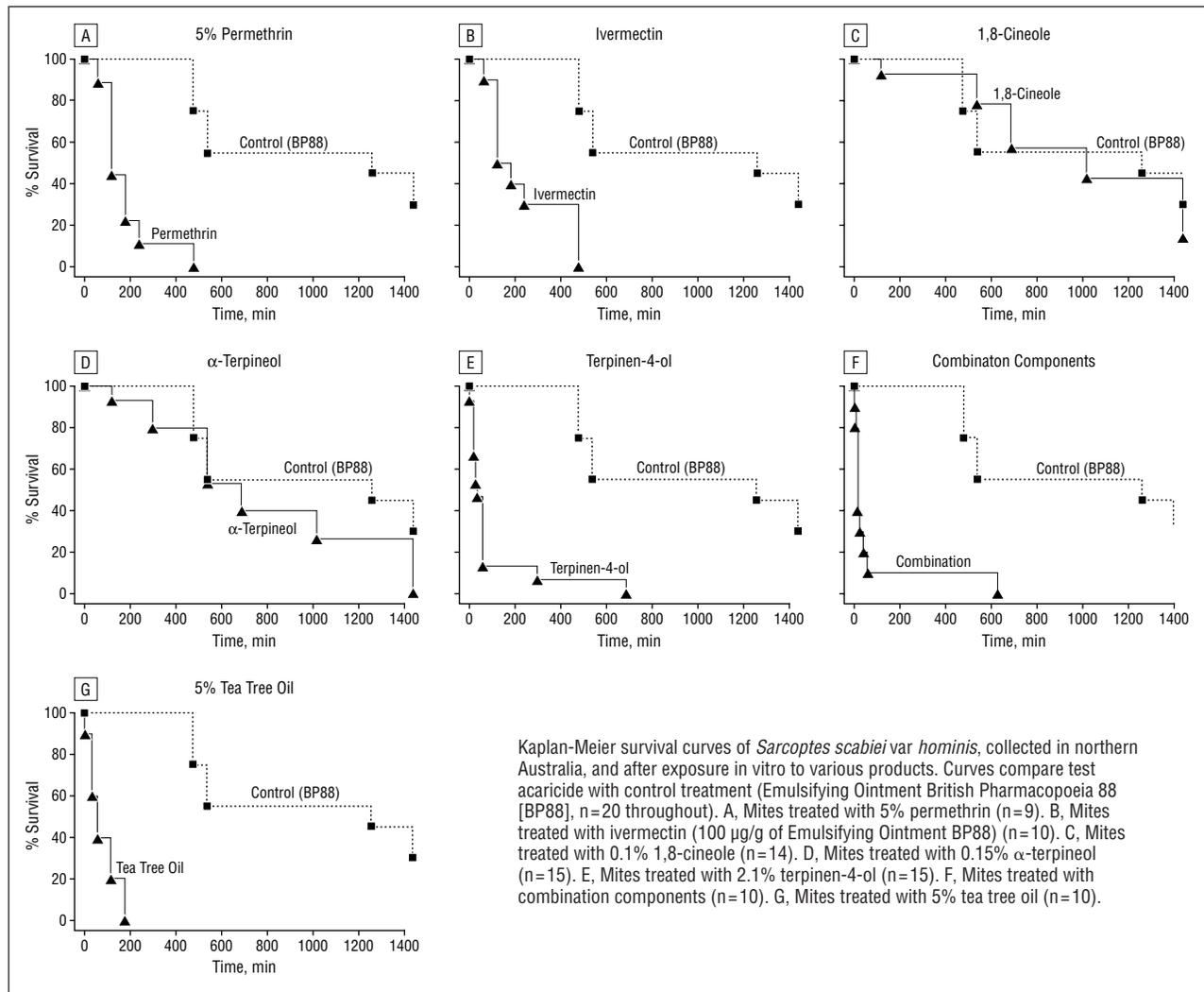
re-presented in August 2001 with crusted scabies. Informed and written consent to collect skin scrapings was obtained from the patient, and 103 larvae, nymphal instars, and adult mites were collected and tested within 3 hours against selected acaricides. Ethics approval was obtained from the Human Research Ethics Committee of the Menzies School of Health Research and Royal Darwin Hospital.

The various acaricides and the concentrations of the active constituents used in the in vitro assay are given in **Table 1**. All products were within their expiration dates and were stored at 4°C or room temperature in the dark when not in use. The TTO components terpinen-4-ol, α-terpineol, and 1,8-cineole were tested in vitro at concentrations equivalent to those found in 5% TTO: terpinen-4-ol comprises 42% of TTO and was therefore tested at a concentration of 2.1%, α-terpineol comprises 3% of TTO and was tested at a concentration of 0.15%, and 1,8-cineole comprises 2% of TTO and was tested at a concentration of 0.1%. In addition, mites were exposed to all 3 components in a combination mix and to 5% TTO. An ivermectin solution of 100 µg/g of Emulsifying Ointment British Pharmacopoeia 88 (BP88) was chosen, adapted from previous in vitro acaricidal experiments.^{6,19} Concentrations of ivermectin (Equimec Paste; Merial Australia Pty Ltd, Parramatta, New South Wales) and individual and combination TTO components were prepared by dilution in Emulsifying Ointment BP88 (Sigma Pharmaceuticals Pty Ltd, Clayton, Victoria, Australia) (comprising emulsifying wax [3 parts], white soft paraffin [5 parts], and liquid paraffin [2 parts]). The Emulsifying Ointment BP88 was also used as the control compound.

Results were analyzed as interval survival data using GraphPad Prism version 3.02 (GraphPad Software, San Diego, Calif), using the log-rank test to examine the null hypothesis that the survival curves are identical.

RESULTS

The 5% TTO and active component terpinen-4-ol were effective in reducing mite survival times (**Figure**). Statistically significant differences in mite survival curves were observed for 5% TTO, terpinen-4-ol, permethrin, and ivermectin compared with the control Emulsifying Ointment BP88 (**Table 2**). However, there was variability in survival times among individual components of TTO. Eighty-five percent of mites were dead at 1 hour when exposed to 2.1% terpinen-4-ol. In contrast, approximately 40% and 60% of mites were still viable after 16 hours of exposure to 0.15% α-terpineol and 0.1% 1,8-cineole, respectively. Interestingly, 90% and 60% of mites were dead after 1 hour of exposure to the combination mix and 5% TTO, respectively. In contrast, after 1 hour of exposure, only 10% of mites tested against 5% permethrin and iver-



mectin were dead and 100% of mites tested against the Emulsifying Ointment BP88 were still viable.

The patient was successfully treated with topical 25% benzyl benzoate containing 5% TTO in combination with oral ivermectin, both in multiple doses.

COMMENT

Ectoparasitic infestations are primarily controlled by topical drugs. In scabies-endemic overcrowded populations in northern Australia, community-based intervention programs are often required that are labor-intensive and costly, and they frequently fail to sustain long-term reduction in disease prevalence. In addition, the increasing regular use of acaricides in endemic communities could create an environment conducive for drug resistance. This is of particular concern for the widespread use of 5% permethrin for scabies. Resistance in head lice to 1% permethrin is well recognized and is extensive.²⁰⁻²² In contrast, 5% permethrin has been a standard treatment for scabies for more than 20 years, with no apparent evidence of clinical resistance (D. Taplin, AIMLT, oral communication, 2000). Permethrin was introduced for scabies therapy in Australia in 1994, and the slow in vitro killing time and clinical failure now ob-

Table 2. *Sarcoptes scabiei* var *hominis* Log-Rank Test Pairwise Survival Time Comparisons Between Different Products and the Control Product Emulsifying Ointment British Pharmacopoeia 88 (BP88)

No. of Mites Tested	Product Tested (Concentration)	Median Survival Time, min	P Value
10	Ivermectin (100 µg/g)	150	<.001
9	Permethrin (5%)	120	<.001
10	Tea tree oil (5%)	60	<.001
15	Terpinen-4-ol (2.1%)	35	<.001
15	α -Terpineol (0.15%)	690	.09
14	1,8-Cineole (0.1%)	1020	.72
10	Combination components	20	<.001
20	BP88*	1260	

*Control product.

served in crusted scabies may herald emerging permethrin resistance in *S scabiei*. Once resistance is established in a population of parasites, it becomes difficult to manage. Vaccines may ideally provide a more effective and preventative control in such situations, but they require considerable effort and prohibitive costs to develop and often cannot be

afforded by those needing them the most. With an effective vaccine for scabies not yet in sight and the development of new drugs limited, the emergence of drug resistance in scabies is a serious public health problem. Monitoring scabies mite drug sensitivities can assist in (1) developing tools to recognize resistance early in infection and prevent useless or toxic levels of chemotherapy, (2) allowing a more rational use of available drugs and drug combinations to minimize the development of resistance, and (3) providing a tool for the assessment of novel compounds.

The data presented herein reveal that TTO may be an effective novel agent for the treatment of scabies, as demonstrated by the fast in vitro killing time observed in this study and in previous studies⁶ and its in vivo effectiveness when combined with benzyl benzoate. These results are encouraging when considered with those of other studies on microorganisms demonstrating that TTO at similar concentrations is efficacious against acne and fungal infections in vitro and in vivo,²³⁻²⁵ as well as against methicillin-resistant *S aureus* and recurrent herpes labialis in vivo.^{26,27} Limited data are available from controlled clinical trials, but the use of TTO is generally well tolerated, although development of occasional skin allergy and dermatitis may result in some individuals with use.²⁸ Evidence of probable anti-inflammatory properties of TTO (specifically terpinen-4-ol) has also been demonstrated, with the ability of TTO to suppress the production of tumor necrosis factor α , interleukin (IL) 1 β , IL-8, IL-10, and prostaglandin E₂ by lipopolysaccharide-activated human peripheral blood monocytes.²⁹ Further investigations also suggest selective down-regulation of superoxide production by monocytes in the presence of terpinen-4-ol and α -terpineol.³⁰ Anecdotally, our patients tolerate the burning sensation of 25% benzyl benzoate better when it is combined with 5% TTO.

Terpinen-4-ol alone had an effect on the viability of the scabies mites similar to that when combined with α -terpineol and 1,8-cineole. On their own, α -terpineol and 1,8-cineole were relatively inactive against the scabies mite. This suggests that terpinen-4-ol is the active component, as demonstrated in studies¹⁸ with other microorganisms. Notably, the presence of the other terpenes neither inhibited nor enhanced this activity. Interestingly, 5% TTO gave the best result, with all scabies mites dead by 3 hours, compared with terpinen-4-ol alone, which required 11.5 hours for 100% mortality. Other investigations have indicated that the mixing of different terpenoid components of TTO can reduce or increase antimicrobial efficacy, depending on their relative concentrations and the overall susceptibility of the target organism.¹⁸ Given that γ -terpinene constitutes approximately 17.8% of the total content of TTO, this or another component may contribute to the overall activity of TTO against the scabies mite.

In summary, TTO has excellent in vitro activity against *S scabiei* var *hominis* and is likely to become a useful topical therapy for scabies alone (eg, 5% TTO) or in combination therapy (eg, 25% benzyl benzoate with 5% TTO).

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