INTRODUCTION

Tinea pedis is a dermatophyte infection of the feet or toes affecting 10% of the population at any given time.\(^1\) It is most commonly caused by *Trichophyton rubrum*, *T. mentagrophytes* and *Epidermophyton floccosum*, and appears to be related to occlusive footwear.\(^2\) Tinea pedis occurs as one of four clinical variants: intertriginous, papulosquamous, vesicular and acute ulcerative.\(^3\) Chronic, intertriginous tinea pedis is characterized by a scaling and fissuring of the lateral toe webs caused by dermatophyte invasion of the stratum corneum; macerated, erosive infections may follow as a result of secondary overgrowth of commensal bacteria, including Micrococcaceae (usually staphylococci), aerobic coryneforms and Gram-negative organisms.\(^4\) Microscopy and culture of skin scrapings are used to identify the relevant organism.

The treatment of interdigital tinea pedis includes measures aimed at reducing hyperhidrosis, such as talcum powder and wearing open-toed shoes. Topical antibacterial measures such as 25% acetic acid soaks and colourless Castellani’s paint (phenolated resorcinol) are helpful in treating macerated infections.\(^5\) Topical antifungal treatments for interiginous tinea pedis include tolnaftate, the imidazoles and terbinafine; short-term oral treatments include itraconazole 400 mg daily for 1 week and terbinafine 250 mg daily for 2 weeks.\(^6\)

Tea tree oil (melaleuca oil) is an essential oil extracted primarily from the leaves of *Melaleuca alternifolia*, a shrub-like tree native to northern New South Wales and southern Queensland. Tea tree oil has antimicrobial properties and has been used as a natural remedy for a variety of skin complaints for many years. During World War I, tea tree oil was included in the first-aid kits of Australian troops to treat burns, bites, and infections. Tea tree oil is widely available in Australian pharmacies and natural therapy stores in various preparations, including antifungal gel 50 mg/g, acne gel 200 mg/g, antiseptic cream 50 mg/mL, antiseptic solution 15% and 100%, head lice solution 10%, insect repellant 18.9 mg/mL and shampoo and conditioner. Clinical studies have suggested tea tree oil is effective in treating tinea pedis,\(^7\) onychomycosis\(^8\) trichomonal vaginitis,\(^9\) acne\(^10\) and dandruff.\(^11\)

Tea tree oil is a complex mixture of hydrocarbons and terpenes, consisting of almost 100 substances, and the antimicrobial activity appears to be related to the major component, terpinen-4-0 L.\(^12\) which accounts for one-third of the final volume of tea tree oil. The minimum

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**SUMMARY**

Tea tree oil has been shown to have activity against dermatophytes *in vitro*. We have conducted a randomized, controlled, double-blinded study to determine the efficacy and safety of 25% and 50% tea tree oil in the treatment of interdigital tinea pedis. One hundred and fifty-eight patients with tinea pedis clinically and microscopy suggestive of a dermatophyte infection were randomized to receive either placebo, 25% or 50% tea tree oil solution. Patients applied the solution twice daily to affected areas for 4 weeks and were reviewed after 2 and 4 weeks of treatment. There was a marked clinical response seen in 68% of the 50% tea tree oil group and 72% of the 25% tea tree oil group, compared to 59% in the placebo group. Mycological cure was assessed by culture of skin scrapings taken at baseline and after 4 weeks of treatment. The mycological cure rate was 64% in the 50% tea tree oil group, compared to 51% in the placebo group. Four (3.8%) patients applying tea tree oil developed moderate to severe dermatitis that improved quickly on stopping the study medication.

Key words: athlete’s foot, melaleuca oil, natural therapy.
inhibitory concentration of tea tree oil for *T. rubrum* is 1.0% volume/volume and *T. mentagrophytes* 0.3–0.4% volume/volume. The activity of tea tree oil against dermatophytes prompted our department to trial its use in tinea pedis. In an earlier study of 104 patients randomly assigned to receive either 10% tea tree oil cream, tolnafate 1% cream or placebo, we found that 10% tea tree oil cream significantly improved the condition clinically, but the mycological cure rate, while improved, was not significantly greater than placebo. Therefore, it was considered that an increased concentration of tea tree oil might be more effective in achieving mycological cure. At high concentrations tea tree oil is not stable in a cream. In this study we have compared 25% and 50% tea tree oil with placebo in a randomized, double-blind study of patients with intertriginous tinea pedis.

METHODS

The study was approved by the Ethics Review Committee of the Royal Prince Alfred Hospital in Sydney, Australia, and informed consent was obtained. One hundred and fifty-eight patients, aged 14 or older, with typical clinical features of intertriginous tinea pedis were recruited by advertising in local newspapers. A skin scraping was taken for microscopy and culture and only those with microscopy suggestive of a dermatophyte infection were enrolled into the study. Patients excluded from the study were those treated with systemic antifungals within the preceding 6 months or topical antifungals within the preceding 7 days, and those with dermatitis, immunosuppression or a history of hypersensitivity to tea tree oil.

Patients were randomized to receive either placebo (20% ethanol, 80% polyethylene glycol), or 25% or 50% tea tree oil mixed in ethanol and polyethylene glycol solution. They were instructed to wash their feet with soap and water, dry between the toes and apply the solution to the affected areas twice daily for 4 weeks. They were given advice about the wearing of open footwear and requested not to use other antifungal treatments.

The patients were reviewed at weeks 2 and 4 of the treatment. At each visit an assessment was made of scaling and inflammation by the investigator, and burning and itching by the patient. Each of these was graded as absent, mild, moderate, severe or very severe and given a corresponding score of 0–4; the four scores added together to give the ‘clinical score’. Assessments were made without referring back to previous scores. A marked clinical response was considered to be a reduction of three or more in the clinical score to a final value less than three, or a final value of zero. The mycological cure rate was determined from culture of skin scrapings taken at baseline and at the end of the 4-week treatment period. ‘Effective cure’ was considered to be both a marked clinical response and mycological cure.

It was anticipated that at least one of the tea tree oil groups would have a response rate of at least 60%, and it was assumed there would be a 20% response rate in the placebo group. In order to be able to declare this difference as statistically different at the 0.025 level, it was determined that there should be 32 patients in each treatment group. It was also assumed, based on previous work by this department, that approximately 40% of patients who present with positive microscopy will have a negative culture for dermatophyte infection. As the culture takes approximately 2–4 weeks to grow, all patients with a positive microscopy were enrolled in the study, but only

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Enrolled</th>
<th>No. males (%)</th>
<th>Mean age (years)</th>
<th>Initial clinical score</th>
<th>Dermatophyte infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>55</td>
<td>55 (61)</td>
<td>39</td>
<td>5.78</td>
<td>49</td>
</tr>
<tr>
<td>25%</td>
<td>54</td>
<td>54 (65)</td>
<td>38</td>
<td>5.79</td>
<td>43</td>
</tr>
<tr>
<td>50%</td>
<td>51</td>
<td>51 (77)</td>
<td>45</td>
<td>5.40</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>158</td>
<td>104 (65)</td>
<td>41</td>
<td>5.66</td>
<td>137</td>
</tr>
</tbody>
</table>

### Table 2 Mycologic response at the end of 4 weeks treatment

<table>
<thead>
<tr>
<th></th>
<th>Dermatophyte infection</th>
<th>Completed treatment</th>
<th>Week 4 culture obtained</th>
<th>Mycological cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>49</td>
<td>46</td>
<td>45</td>
<td>14 (51)</td>
</tr>
<tr>
<td>25%</td>
<td>45</td>
<td>36</td>
<td>35</td>
<td>18 (55)</td>
</tr>
<tr>
<td>50%</td>
<td>45</td>
<td>38</td>
<td>36</td>
<td>23 (64)</td>
</tr>
<tr>
<td>Total</td>
<td>137</td>
<td>120</td>
<td>114</td>
<td>55 (48)</td>
</tr>
</tbody>
</table>

### Table 3 Clinical response at the end of 4 weeks treatment

<table>
<thead>
<tr>
<th></th>
<th>Clinical score</th>
<th>Reduction in score (%)</th>
<th>Clinical response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>46</td>
<td>5.78</td>
<td>1.43</td>
</tr>
<tr>
<td>25%</td>
<td>56</td>
<td>5.79</td>
<td>1.92</td>
</tr>
<tr>
<td>50%</td>
<td>58</td>
<td>5.40</td>
<td>1.86</td>
</tr>
</tbody>
</table>
those patients who later showed a positive culture for dermatophytes were included in the evaluation. Thus, a sample of 54 patients per treatment group was chosen to ensure at least 32 patients with confirmed dermatophyte infections in each group. The significance of the differences between the 25% tea tree oil group, the 50% tea tree oil group and the placebo group was assessed using the \( \chi^2 \)-squared test. \( P \) values of \(<0.05\) were considered significant.

RESULTS

There were 158 patients enrolled into the study, of whom 104 (66%) were male and 54 (34%) were female. Their ages ranged from 17 to 83, with a mean age of 41 years. There were 55 patients randomized to the placebo group, 54 to the 25% tea tree oil group and 51 to the 50% tea tree oil group. The three groups were similar in sex distribution, mean age, baseline clinical scores and skin scraping culture results (Table 1).

All 158 enrolled into the study had typical clinical features of tinea pedis, as well as microscopy suggestive of a dermatophyte infection. However, only 157 (86.7%) patients subsequently cultured a dermatophyte: 49 (92.5%) in the placebo group, 45 (79.6%) in the 25% tea tree oil group and 45 (88.2%) of the 50% tea tree oil group. Of the 137 patients with a confirmed dermatophyte infection, 120 (87.6%) completed the study. One patient in the 50% tea tree oil group was withdrawn because of an adverse reaction and 16 patients were lost to follow up: three (2.19%) in the placebo group, seven (5.11%) in the 25% tea tree oil group and six (4.38%) in the 50% tea tree oil group. The higher loss to follow up in the tea tree oil groups was not statistically significant (Table 1).

Mycological cure could be determined for 114 of the 120 patients who completed the study: six patients (one placebo, three 25% and two 50% tea tree oil) did not have follow-up skin scrapings taken. Mycological cure was achieved in 18 (55%) of the 25% tea tree oil group and 23 (64%) of the 50% tea tree oil group. Of the 137 patients with a confirmed dermatophyte infection, 120 (87.6%) completed the study. One patient in the 50% tea tree oil group was withdrawn because of an adverse reaction and 16 patients were lost to follow up: three (2.19%) in the placebo group, seven (5.11%) in the 25% tea tree oil group and six (4.38%) in the 50% tea tree oil group. The higher loss to follow up in the tea tree oil groups was not statistically significant (Table 1).

The number of patients with a marked improvement in the clinical score (a final clinical score of zero or a reduction of three or more to a final value less than three) was also significantly higher in the tea tree oil groups compared with placebo (Table 3). Marked improvement in the clinical score was seen in 26 (72%) of the 25% tea tree oil group and 26 (68%) of the 50% tea tree oil group, compared with 18 (39%) in the placebo group. This too was statistically significant (\( P < 0.005\)). The clinical severity score fell 68% and 60% in the 25% and 50% tea tree oil groups, respectively, compared with 41% in the placebo group.

Effective cure, defined as both mycological cure and marked clinical response, was again higher in the tea tree oil groups: 16 (48%) in the 25% tea tree oil group, 18 (50%) in the 50% tea tree oil group and 6 (13%) in the placebo group (\( P < 0.0005\)).

All patients enrolled in the study, including those without dermatophyte infections, were included in the safety population. Dermatitis occurred in one patient applying 25% tea tree oil and three patients applying 50% tea tree oil, one of whom was withdrawn from the study. These dermatitis reactions responded quickly to stopping the study medication and topical corticosteroids were used in two patients. Stinging on application was reported in two patients applying 25% tea tree oil and two patients applying placebo, and was described as mild, lasting for a few seconds. There were no serious adverse events reported.

DISCUSSION

There has been increasing interest in the use of natural therapies. Tea tree oil is one such product and is already widely available in Australia for the treatment of superficial infections such as tinea pedis.

One clinical study performed by our group has already shown that 10% tea tree oil cream was effective in improving the tinea clinically, although the mycological cure rate was not significantly better than placebo. In order to improve the mycological cure rate, we have used higher concentrations (25% and 50%) of tea tree oil, prepared in solution rather than as a cream because of the immiscibility of tea tree oil in aqueous media.

The study was conducted as a double-blind study, although it could be argued that the study was single-blinded because the distinctive odour of tea tree oil identifies it to the patient. However, this information was not volunteered to the patients, and it is not possible to distinguish between 25% and 50% tea tree oil. Of the 158 patients with clinically apparent tinea pedis and skin scrapings demonstrating fungal elements on microscopy, a dermatophyte was cultured in 137 (87%). This was higher than expected based on previous work in this department. Only those patients who remained in the study and had a repeat skin scraping (114 patients) could be used to determine the cure rate. The rate of loss was higher in the tea tree oil groups, although this was not statistically significant. It would be reasonable, then, to draw conclusions based on the results of only those patients completing the study.

Mycological cure rates of 55% and 64% in the 25% and 50% tea tree oil groups, respectively, are somewhat lower than those obtained for clotrimazole (90%) and terbinafine (90%) in similarly designed studies. The mycological response observed in the placebo group (51%) was not unexpected, because all patients were asked to wash their feet with soap and water and dry between the toes before applying the solution, and were given advice about wearing open footwear.

The effective cure rate, which required both a marked clinical improvement and mycological cure, was seen in 48% of the 25% tea tree oil group and 50% of the 50% tea tree oil group; both significantly better than the placebo group (15%). Again, these rates are lower than for standard topical treatments. Three studies, each with a similar design to this one, have been reviewed. These studies compared clotrimazole with terbinafine and estimated that the average effective cure rate for subjects applying clotrimazole was 65% (95% confidence interval (CI) = 56–69%) and terbinafine 74% (95% CI = 68–81%).

Dermatitis occurred in four (3.8%) patients treated with tea tree oil and three patients applying 50% tea tree oil, one of whom was withdrawn from the study. These dermatitis reactions responded quickly to stopping the study medication and topical corticosteroids were used in two patients. Stinging on application was reported in two patients applying 25% tea tree oil and two patients applying placebo, and was described as mild, lasting for a few seconds. There were no serious adverse events reported.
tree oil. It is unclear whether these were irritant or allergic reactions. All reactions developed after 2 weeks and patch testing was not done. While it has been reported that 25% tea tree oil is not an irritant, there is no published information regarding the irritancy of 50% tea tree oil.

Tea tree oil has been reported to cause allergic contact dermatitis, although there are only a few reports despite its popularity and the fact that it is often applied to already irritated or broken skin. Interestingly, in patch testing of 28 normal volunteers, it was found that three volunteers reacted strongly to 25% tea tree oil, and all three patients subsequently reacted strongly to preparations containing sesquiterpenoid fractions of the oil. This suggests allergic contact dermatitis is not uncommon. Reported allergens within tea tree oil include monoterpenes such as terpinen-4-ol, D-limonene and α-terpinene, the sesquiterpenoid fraction and 1,8 cineol.

In summary, we have found in a large, randomized, placebo-controlled study that both 25% and 50% tea tree oil solutions are effective in treating tinea pedis, and that 25% tea tree oil is associated with fewer complications than 50% tea tree oil solution. We recommend that 25% tea tree oil be considered in those patients keen to use natural agents in the treatment of tinea pedis, although 25% tea tree oil is less effective than standard topical treatments.

ACKNOWLEDGEMENT

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REFERENCES