

Extended Abstracts for Tea Tree Oil

Natural Standard Database – Secondary Resource

Source:

Natural Standard. Natural Standard Professional Monograph <Tea tree oil>. 2012. www.naturalstandard.com. Last updated 07/07/12. Accessed 07/07/12.

Summary:

Tea tree oil may play a role in topical treatment of tinea pedis (athlete's foot) based on *in vitro* studies as well as studies done in humans. At this time, there is insufficient evidence in humans to determine whether or not it should be recommended by pharmacists for athlete's foot, however, it is generally safe in concentrations up to 100% when used as a topical agent. It has been traditionally used to treat fungal infections (tinea pedis, onychomycosis) in addition to acne vulgaris and vaginal infections. Tea tree oil should not be recommended as oral therapy due to case reports of CNS toxicity when ingested. It should also not be recommended in patients with known allergies to tea tree oil or eucalyptol.

Comments:

Although the exact mechanism of action of tea tree oil is unclear due to its multiple constituents, there is evidence to suggest its benefit in the treatment of a number of different conditions. Although the evidence is not extensive in humans, there are well designed studies showing that its benefit in humans is similar to that of patients using other pharmacological remedies such as tolnaftate 1% cream¹. Trials in humans have been relatively small but have shown benefit nonetheless^{1,2}. A systematic review concluded that it is one of the most thoroughly tested herbal antifungal medicines although it requires further investigation in clinical trials³.

Tea tree oil has been known to cause skin reactions⁴⁻⁷ (especially in patients with prior exposure) and should be used cautiously for this reason. However, skin reactions generally appear to be the only adverse effect of topical tea tree oil administration. Anecdotal evidence of tea tree oil use in various populations throughout history independently suggests a benefit.

Overall, its proven efficacy in small trials, desirable safety profile and historical significance make it a reasonable option for topical treatment of tinea pedis. In the future, tea tree oil clinical testing in special populations (ie. pregnancy, pediatric, renal, hepatic) would further support its use as an antifungal agent for tinea pedis.

References:

- 1) Tong MM, Altman PM, Barnetson RS. Tea tree oil in the treatment of tinea pedis. *Australas J Dermatol*. 1992; 33(3):145-9.

<http://onlinelibrary.wiley.com.proxy.lib.uwaterloo.ca/doi/10.1111/j.1440-0960.1992.tb00103.x/pdf>. Accessed 07/07/2012.

2) Satchell AC, Saurajen A, Bell C, Barnetson RS. Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: a randomized, placebo-controlled, blinded study. *Australas J Dermatol*. 2002; 43(3):175-8. <http://onlinelibrary.wiley.com/doi/10.1046/j.1440-0960.2002.00590.x/pdf>. Accessed 07/07/2012.

3) Martin KW, Ernst E. Herbal medicines for treatment of fungal infections: a systematic review of controlled clinical trials. *Mycoses*. 2004; 47(3-4):87-92. <http://onlinelibrary.wiley.com/doi/10.1046/j.1439-0507.2003.00951.x/pdf>. Accessed 07/07/2012.

4) Rubel DM, Freeman S, Southwell IA. Tea tree oil allergy: What is the offending agent? Report of three cases of tea tree oil allergy and review of the literature. *Australas J. Dermatol*. 1998; 39:244-247. <http://onlinelibrary.wiley.com.proxy.lib.uwaterloo.ca/doi/10.1111/j.1440-0960.1998.tb01482.x/pdf>. Accessed 07/07/2012.

5) Apted JH. Contact dermatitis associated with the use of tea-tree oil. *Australas. J. Dermatol*. 1991; 32:177.

6) De Groot AC, Weyland JW. Systemic contact dermatitis from tea tree oil. *Contact Dermatitis*. 1992; 27:279-80.

7) Knight TE, Hausen BM. Melaleuca oil (tea tree oil) dermatitis. *J. Am. Acad. Dermatol*. 1994; 30:423-7.

Systematic Review – Tertiary Resource #1

Source:

Martin KW, Ernst E. Herbal medicines for treatment of fungal infections: a systematic review of controlled clinical trials. *Mycoses*. 2004;47(3-4):87-92. <http://onlinelibrary.wiley.com/doi/10.1046/j.1439-0507.2003.00951.x/pdf>. Accessed 07/07/12.

Study Objectives

To critically assess the evidence for herbal antifungal medicines tested in controlled clinical trials. .

Review Scope

Included studies compared tea tree oil to control for treatment of tinea pedis or onychomycosis (4 studies), *Solanun nigrescens* to control for treatment of vaginal candidosis (1 study), *Solanum chrysotrichum* Schldl. to control for treatment of tinea pedis (1 study) and oil of bitter orange to control for treatment of tinea infections (1 study). Outcomes of studies evaluating herbal medicines for tinea pedis included conversion to negative culture, clinical assessment and resolution of lesions and symptoms.

Review Methods

MEDLINE (via PubMed), EMBASE, CISCOR, and Cochrane Library were searched (from inception until August 2002) for controlled clinical trials. Primary search terms used were 'herb' OR 'plant' AND 'antifungal' AND 'clinical trials.' Trials included in the analysis had a control group and reported experimental use of a single herbal medicine for reduction or elimination of disease-producing fungal populations colonizing humans. Methodological quality of all trials was assessed according to a system developed by Jadad *et al*¹.

Main Results

Seven clinical trials met the selection criteria (see Table).

Tong et al. showed that although attention to foot hygiene probably contributed to some clinical improvement in all three groups, both tolnaftate and tea tree oil creams showed significantly greater improvement in symptomatology than placebo. However, only tolnaftate-treated patients showed significant conversion to negative culture (85% vs. 30%, 21%). The same group of researchers followed up this study with another RCT showing that mycological cure was achieved in significantly more patients in both tea tree oil groups than in those using placebo

Clinical trials of herbal antifungal medicines for tinea pedis

Reference	Sample Size	Condition Treated	Experimental Intervention	Control Interventions	Main Outcome Measure	Main Results
Ramadan <i>et al.</i>	70 patients (65 evaluable)	<i>Tinea pedis, corporis, cruris</i>	Bitter orange oil (a) 25% emulsion (b) 20% in alcohol 3x daily for up to 4 weeks (c) 100% 1x daily for up to 3 weeks	Imidazole derivative for up to 4 weeks	(a) Conversion to negative culture (b) Clinical assessment	(a) 80% cured after 2 weeks (b) 50% cured after 2 weeks (c) 93% cured after 2 weeks none of control group cured after 2 weeks, 80% cured after 4 weeks
Loyoza <i>et al.</i>	28 patients	<i>Tinea pedis</i>	Cream containing 5% extract of <i>Solanum chrysotrichum</i> Schldl. 2x daily for 4 weeks	Cream containing 2% miconazole nitrate twice daily for 4 weeks	Resolution of lesions and symptoms	45% of experimental group cured, none of miconazole group cured
*Tong <i>et al.</i>	121 patients (104 evaluable)	<i>Tinea pedis</i>	<u>10% w/w tea tree oil</u> , 2x daily for 4 weeks	(a) 1% tolnaftate cream, 2x daily for 4 weeks (b) Placebo cream, 2x daily for 4 weeks	(a) Conversion to negative culture (b) Clinical assessment	(a) Tea tree oil no better than placebo (b) Tea tree oil superior to placebo, comparable
*Satchell <i>et al.</i>	158 patients (120 evaluable)	<i>Tinea pedis</i>	<u>(a) 25% tea tree oil</u> <u>(b) 50% tea tree oil</u> 2x daily for 4 weeks	Placebo 2x daily for 4 weeks	(a) Conversion to negative culture (b) Clinical assessment	(a) Significantly higher cure rate in both tea tree oil groups (b) Significantly improved clinical score in both tea tree oil groups

*Controlled clinical trials evaluating tea tree oil

(55%, 64% vs. 31%) and that statistically significant improvement in clinical scores was also observed in the tea tree oil groups (72%, 68% vs. 39%). The other studies examining oil of bitter orange and *Solanum chrysotrichum* Schldl. for the treatment of tinea pedis were criticized by the authors for having small sample sizes and several other serious limitations.

Conclusions

Tea tree oil is the most thoroughly clinically tested herbal antifungal medicine and positive outcomes have been attributed to the intervention in all trials.

Comments:

It is difficult to locate controlled clinical trials comparing the efficacy of herbal medications to placebo. This may be due to the availability of other effective treatments (e.g. azoles), the desire to publish only studies with positive results or the inaccessibility of certain journals through electronic databases. The author mentioned that there may have been existing trials that were missed and these could have potentially been located had a more thorough search been completed using non-electronic resources. On the other hand, the inclusion criteria for this study were well established and the results provide us with useful information. All of the located studies evaluated one specific intervention in a particular medical condition, so direct conclusions may be drawn from each study. Additionally, all of the studies produced promising results and the review authors concluded that further clinical research should be conducted for all remedies; especially tea tree oil. Tea tree oil is the most clinically tested of all the herbal antifungals and further studies would further propagate wide-spread use of this agent.

This review focused specifically on high quality, placebo-controlled trials which can be viewed as an advantage as well as a disadvantage. The specific inclusion criteria of this study were advantageous as stated above, however, the study excluded several important remedies that have proven to be effective in tinea pedis. For example, Menendez *et al.* showed that Oleozon (ozonated sunflower oil) is just as effective as ketoconazole 2% cream for the treatment of tinea pedis². Since this study was a comparative trial and did not include a placebo, it was not included in the review; however, several more recent studies have shown that sunflower oil is an established therapy for the treatment of antifungal infections and should not be overlooked³⁻⁴. It is also the only natural agent considered to have good scientific evidence (grade B) by Natural Standard⁵.

References:

- 1) Jadad JR, Moore A, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996; 17:1–12.
- 2) Menendez S, Falcon L, Simon DR, Landa N. Efficacy of ozonized sunflower oil in the treatment of tinea pedis. *Mycoses*. 2002; 45:329-332. <http://onlinelibrary.wiley.com/doi/10.1046/j.1439-0507.2002.00780.x/pdf>. Accessed 07/08/2012.
- 3) Geweely NSI. Antifungal Activity of Ozonized Olive Oil (Oleozone). *Int. J. Agri. Biol.* 2006; 8(5):670-675. <http://www.ozonterapiklinigi.com/literatur/AntifungalActivityofOzonizedOliveOil.pdf>. Accessed 07/08/2012.
- 4) Menedez S, Falcon L, Maqueira Y. Therapeutic efficacy of topical OLEOZON in patients suffering from onychomycosis. *Mycoses*. 2010; 54(5):e272-7. <http://onlinelibrary.wiley.com/doi/10.1111/j.1439-0507.2010.01898.x/pdf>. Accessed 07/08/2012.

5) Natural Standard. Natural Standard Professional Monograph <Sunflower oil>. 2012. www.naturalstandard.com. Last updated 07/07/12.
Accessed 07/07/12.

Textbook – Tertiary Resource #2

Source:

McQueen CE, Orr KK. Chapter 51: Natural Products. In: Krinsky DL, Berardi RR, Ferreri SP, Hume AL, Newton GD, Rollins CJ, eds. *Handbook of Nonprescription Drugs – An Interactive Approach to Self-Care*. 17th ed. Washington, DC: American Pharmacists Association; 2012:990.

Summary:

The main therapeutic uses of tea tree oil are as an antiseptic and an anti-infective agent. The primary active ingredient thought to be active against pathogenic bacteria and fungi is terpinen-4-ol. The concentrations of the oil vary widely from 0.4-100% depending on the condition and area of treatment. For athlete's foot, it is recommended to be used in concentrations of 25% to 50% applied twice daily for 4 weeks. Although the oil is safe on oral mucosa, it should not be swallowed as it can cause confusion, ataxia and systemic contact dermatitis. In fungal infections, tea tree oil is an option for individuals not tolerating current therapies.

Comments:

The most up-to-date evidence suggests the use of tea tree oil as an alternative agent when other therapies are not tolerated. This may be due to the fact that it has been shown to be equivalent to other pharmacological therapies¹ and also superior to placebo for the treatment of tinea pedis². Nonetheless, there are no studies showing that tea tree oil appears to be superior to standard care for the treatment of tinea pedis. Therefore, this recommendation seems appropriate for the time being until further clinical trials are published.

References:

- 1) Tong MM, Altman PM, Barnetson RS. Tea tree oil in the treatment of tinea pedis. *Australas J Dermatol*. 1992; 33(3):145-9. <http://onlinelibrary.wiley.com.proxy.lib.uwaterloo.ca/doi/10.1111/j.1440-0960.1992.tb00103.x/pdf>. Accessed 07/07/2012.
- 2) Satchell AC, Saurajen A, Bell C, Barnetson RS. Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: a randomized, placebo-controlled, blinded study. *Australas J Dermatol*. 2002; 43(3):175-8. <http://onlinelibrary.wiley.com/doi/10.1046/j.1440-0960.2002.00590.x/pdf>. Accessed 07/07/2012.

Double-blinded RCT – Primary Resource #1

Source:

The following journal article was obtained using PubMed (Medline) database - Tong MM, Altman PM, Barnetson RS. Tea tree oil in the treatment of tinea pedis. *Australas J Dermatol*. 1992; 33(3):145-9. <http://onlinelibrary.wiley.com.proxy.lib.uwaterloo.ca/doi/10.1111/j.1440-0960.1992.tb00103.x/pdf>. Accessed 07/02/2012.

Study Objectives

To determine the efficacy of 10% w/w tea tree oil cream compared with 1% tolinaftate and placebo creams in the treatment of tinea pedis

Methods

Design: Randomized, double-blinded, placebo-controlled trial.

Allocation: Unknown.

Blinding: Blinded (patients and clinicians).

Follow-up period: 4 week treatment period, patient were seen 4 times over 5 weeks.

Setting: Department of Dermatology, Royal Prince Alfred Hospital, Camperdown, Australia.

Participants: 121 patients (ages 16-65 years, 76% male) with tinea pedis diagnosed clinically and by positive fungal culture. Exclusion criteria included systemic antifungal therapy drugs in the preceding 6 months, topical antifungal therapy in the preceding week, or medical conditions/medications that would predispose the individual to fungal infections (ie. diabetes mellitus, corticosteroid therapy). Patients with positive microscopy findings and negative dermatophyte culture findings were also removed from the study.

Intervention: Tea tree oil (10% w/w) in sorbolene cream, tolinaftate 1% cream, or placebo cream applied twice daily for four weeks.

Outcome: Effective treatment defined as mycological cure with clinical improvement. Clinical improvement was defined as 1) improvement by more than 2 points or 2) improvement by 2 or less points or deterioration. Participants were classified into four categories including 1) mycological cure (negative culture) and improvement in severity score (>2 points), 2) mycological cure and no improvement in severity score, 3) no mycological cure and improvement in severity score, and 4) no mycological cure and no improvement in severity score.

Patient follow-up: 104 of 121 patients completed the study (86%).

Main Results

Although only tolinaftate exhibited a statistically significant number of negative culture results ($p < 0.001$), both tolinaftate and tea tree oil showed a statistically significant improvement of clinical signs and symptoms ($p = 0.018$ and 0.022 respectively) compared to placebo (see Table). Overall skin tolerance was excellent and no patients dropped out of the study due to adverse effects.

Overall evaluation of clinical response for 3 treatment groups

Mycological cure?	Improvement in total severity <2 points?	# of patients Placebo	# of patients Tea tree oil	# of patients Tolinaftate
Yes	Yes	3 (9%)	8 (22%)	15 (46%)
Yes	No	4 (12%)	3 (8%)	13 (39%)
No	Yes	11 (32%)	16 (43%)	4 (12%)
No	No	16 (47%)	10 (27%)	1 (3%)
TOTAL		34 (100%)	37 (100%)	33 (100%)

Conclusion

Tea tree oil cream reduces clinical symptoms of tinea pedis as effectively as tolinaftate 1% cream.

Comments:

In this equivalence trial by Tong et al., tea tree oil (10% w/w) cream was shown to be an equally effective alternate for treating tinea pedis as tolinaftate 1% cream. Overall, the trial was well designed with the exception of controlling for gender (majority of participants were male). On the other hand, there were no differences in stratification for other important factors like age and history of recurrent infections. Theoretically, it may have been beneficial to collect data and further stratify patients based on treatment history since 97% of the patients were experiencing recurrent tinea. From this data, it could have been determined whether prior treatment regimens would have had any effect on the efficacy of treatment in any of the 3 groups. This study also re-iterates the lack of adverse effects seen with alternative treatments such as tolinaftate and tea tree oil.

The weaknesses of this study were the small sample size and the single center location. Ideally, future trials would take place in multiple centers with a larger study group. Also, clinical improvement of patients was assessed using a non-validated, subjective rating scale¹.

References:

1) Natural Standard. Natural Standard Professional Monograph <Tea tree oil>. www.naturalstandard.com. Last updated 07/07/12. Accessed 07/07/12.

Double-blinded RCT – Primary Resource #2

Source:

The following journal article was obtained using PubMed (Medline) database - Satchell AC, Saurajen A, Bell C, Barnetson RS. Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: a randomized, placebo-controlled, blinded study. *Australas J Dermatol.* 2002; 43(3):175-8. <http://onlinelibrary.wiley.com/doi/10.1046/j.1440-0960.2002.00590.x/pdf>. Accessed 07/02/2012.

Study Objectives

To determine whether 25% or 50% tea tree oil solutions are more effective than placebo for the treatment of intertriginous tinea pedis.

Methods

Design: Randomized, double-blinded, placebo-controlled trial.

Allocation: Unknown.

Blinding: Blinded (patients and clinicians).

Follow-up period: 4 week treatment period, patients reviewed at weeks 2 and 4.

Setting: Department of Dermatology, Royal Prince Alfred Hospital, Camperdown, Australia.

Participants: 158 patients (aged 14 years or older, 66% male) with typical clinical features of intertriginous tinea pedis and microscopy suggestive of a dermatophyte infection. Exclusion criteria included treatment with systemic antifungals within the preceding 6 months, topical antifungal treatment within the preceding 7 days, dermatitis, immunosuppression or a history of hypersensitivity to tea tree oil. Patients with positive microscopy findings but negative dermatophyte culture findings were not included in the evaluation.

Intervention: 25 or 50% tea tree oil solution or placebo solution applied twice daily for four weeks.

Outcome: Effective cure considered to be both a marked clinical response and mycological cure. A marked clinical response was considered to be reduction of three or more in the clinical score (scale of 0 to 4) to a final value less than three or a final value of zero.

Patient follow-up: 120 of 158 patients completed the study (76%).

Main Results

Both tea tree oil groups showed a statistically significant mycological cure rate ($p < 0.01$) as well as marked improvement in the clinical score (72% or 25% tea tree oil group, 68% of 50% tea tree oil group, $p < 0.005$). An effective cure was seen in 48 and 50% of the 25 and 50% tea tree oil groups, respectively ($p < 0.0005$). Four patients (1 was using 25% tea tree oil and 3 were using 50% tea tree oil) experienced dermatitis reactions and one patient was withdrawn from the study. However, there were no serious adverse events reported.

Conclusion

Tea tree oil solutions (25 or 50%) are effective for the treatment of tinea pedis, however, 25% tea tree oil is associated with fewer complications.

Comments:

In the trial by Satchell et al., tea tree oil solutions in high concentrations (25 or 50%) can eradicate fungal infections while also providing relief from clinical symptoms of tinea pedis. Overall, the trial was well designed and patients were recruited and stratified appropriately. The severity of the infections among study patients appeared to be similar, although no details were given regarding history of recurrent infections, duration of current infection or type of infecting organisms. An additional strength of this study was that each of the treatment and placebo groups were instructed to perform non-pharmacological measures in addition to taking medication and were asked not to use other antifungal treatments. It is fair to assume that most patients were compliant with non-pharmacological measures because of the 13% cure rate in the placebo group. With this assumption, we can attribute the results of this study directly to the intervention.

This study also had several weaknesses namely the small sample size and the use of a non-validated, subjective rating scale to assess clinical outcomes (similar to the previous study conducted by this group – see **Primary Resource #1**). Also, there was <80% follow-up rate for this trial¹ for various different reasons. Last, the authors mention that it could be argued that the study was single-blinded due to the distinctive odour of tea tree oil being identified by the patients.

References:

- 1) Crawford S, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. (Review). *The Cochrane Library*. 2009;(3):1-118. <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001434.pub2/full>. Accessed 07/07/2012.

Additional References

Mallin A. Chapter 52: Athlete's Foot. In: Patient Self-Care – Helping Your Patients Make Therapeutic Choices. 2nd ed. Ottawa, ON: Canadian Pharmacists Association; 2010:489-493.

Natural Medicines Comprehensive Database. <Tea tree oil>. <http://naturaldatabase.therapeuticresearch.com/>. Last updated 07/06/2012. Accessed 07/07/2012.