

# Natural Products that Exhibit Antifungal Activity

Can natural products fight the fungus among us?

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While there is a growing interest in using natural products to treat fungal skin infections, there is limited research on botanicals that exhibit antifungal activity *in vivo*, and fewer still using a proper randomized, double-blind, placebo-controlled clinical trial design. In this brief review, we explore the evidence of botanicals that may be effective for topical application against fungal species implicated in seborrheic dermatitis, tinea versicolor, tinea pedis, and onychomycosis, among others.

Current topical antifungals are largely safe and effective, but at times may be ineffective because of increasing resistance mechanisms, and some of these agents can cause irritant and allergic skin reactions.<sup>1-6</sup> Moreover, even when their use is successful, there is still a high rate of recurrence in superficial skin diseases. Therefore, it may be important to identify novel treatments that may be more appropriate for long-term use without risk of these side effects.

## SEBORRHEIC DERMATITIS

Seborrheic dermatitis (SD), with its erythematous and scaly patches,<sup>7,8</sup> is estimated to affect up to three percent of the adult population.<sup>9</sup> Causes of SD are multifactorial, but *Malassezia* species are believed to play a prominent role. In individuals with Parkinson's disease, a neurodegenerative disorder in which the prevalence of SD is much higher in some studies, there is a significantly increased yeast density on lesional skin sites as compared to SD individuals without Parkinson's disease.<sup>10</sup> Further, researchers have discovered an association between *Malassezia* density at lesional skin sites and increased severity of SD symptoms.<sup>11,12</sup> The mechanism of action is believed to be related to *Malassezia spp.* extracellular lipase activity. These extracellular lipases break down triglycerides on the skin into oleic and arachidonic fatty acids, causing desquamation of skin cells and triggering an inflammatory response that worsens itch and erythema.<sup>7,9</sup>

Many natural products show anti-fungal effects, but these effects may not always translate into clinical efficacy. The

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leaves of *Azadirachta indica* exhibited a minimum inhibitory concentration of 90 percent ( $MIC_{90}$ ) at 64 mg/mL for *M. sympodialis*, comparable to  $MIC_{90}$  of ketoconazole (KTZ) control.<sup>13</sup> The essential oil of *Melaleuca alternifolia* inhibited 80 percent of SD isolates at 1.112 mg/ml and 100 percent at 2.225 mg/ml.<sup>14</sup> In another study, the leaves of *Melaleuca alternifolia* exhibited an  $MIC_{90}$  of 64mg/mL for *M. furfur* as compared to KTZ control  $MIC_{90}$  of 16mg/mL.<sup>15</sup> Clinical studies have been conducted with these agents, among others, and we report the data below.

Tea tree oil (*Melaleuca alternifolia*) has been used by the indigenous people of Australia as a traditional remedy for wounds and skin infections, and numerous studies have reported its antiseptic properties due to disruption of bacterial membranes.<sup>16</sup> Satchell et al studied 5% tea tree (TT) oil to 63 patients with SD and observed a 41 percent improvement in symptom severity score compared to only 11 percent in the placebo group.<sup>17</sup> Practitioners should advise their patients, however, that tea tree oil has the potential to cause allergic and irritant dermatitis.

Bitter-ash (*Quassia amara L.*) is another medicinal plant widely used in Brazilian folk medicine. Its wood is purported to have antimicrobial, antimalarial, and analgesic properties.<sup>18</sup> One study had 20 patients apply a 4% bitter-ash gel, 20 received a 2% ketoconazole (KTZ) gel, and 20 received a 1% ciclopirox olamine (CIC) gel.<sup>19</sup> One month after treatment, the bitter-ash group had the lowest severity score of 5.1, compared to 6.7 and 6.8 in CIC and KTZ groups, respec-

tively. Further, two weeks after discontinuing treatment the bitter-ash group still has a significantly lower severity score of 3.8, compared to 5.6 and 6.4 in CIC and KTZ groups.

The neem tree (*Azadirachta indica*) is primarily cultivated in India. Its antimicrobial and antiviral properties have been used traditionally to clean teeth, treat skin disorders, and act as a tonic.<sup>20</sup> Ringworm shrub (*Cassia alata*) is native to the Americas, but also grows well in tropical areas. Its ethnomedicinal uses include mixing the root powder with lime juice and applying topically to act as an antiparasitic and astringent.<sup>21</sup> Krishnamoorthy, et al. formulated a poly-herbal oil containing Pala indigo (*Wrightia tinctoria*), Ringworm shrub (*Cassia alata*), and Neem Tree (*Azadirachta indica*) and had 10 volunteers with severe dandruff apply daily for three weeks.<sup>22</sup> At day 10, there was no evidence of scaling in all participants. At the end of the study, scale samples were cultured, but none of the cultures contained *M. furfur*, demonstrating clinical antifungal activity.

Lastly, *Aloe vera* is used widely throughout southeast Asia, especially in Ayurvedic medicine. The leaves and juice of the plant have been used to treat peptic ulcers, animal bites, and burns.<sup>23</sup> In a study with 44 adults with seborrheic dermatitis, an *Aloe vera* emulsion containing 30 percent crude extract was prescribed to 24 adults, while 20 patients were given a placebo emulsion.<sup>24</sup> After four weeks of use, there was a significant decrease in scaling (36.6 percent treatment vs. 17.6 percent placebo) and pruritus (21.5 percent vs. 5.3 percent) as compared to baseline; additionally, 58 percent of patients had complete resolution or significant improvement in their SD symptoms.

## TINEA VERSICOLOR

Tinea versicolor (TV) is a recurrent skin infection caused by *Malassezia* species. TV is estimated to affect as many as 60 percent of individuals in tropical and humid areas.<sup>12</sup> While the exact pathogenesis is not known, certain conditions, such as frequent antibiotic use, humid climate, and poor hygiene, seem to exacerbate prevalence.<sup>25</sup> Under these conditions, *Malassezia* species convert to the mycelial phase, invading the stratum corneum and causing inflammation and pigmentary alteration.<sup>25</sup>

Several studies have explored plant extracts for topical application against TV lesions. Dill seed (*Anethum graveolens*) is widely used in Ayurvedic medicine in India as a carminative, digestive aid, and diuretic.<sup>26</sup> One study prescribed a dill seed ointment to 10 patients to apply twice daily.<sup>27</sup> After two weeks of treatment, all patients had complete healing of skin lesions. Limitations to this study, however, include the small sample size, lack of blinding, and absence of a control group.

*Artemisia sieberi* is a desert plant found throughout central Asia and traditionally used as an insecticide.<sup>28</sup> Researchers

explored the efficacy of 5% *Artemisia sieberi* essential oil lotion on 51 TV patients (group 1), compared to 49 TV patients who received 1% topical clotrimazole (CL) (group 2) for two weeks.<sup>29</sup> At the end of two weeks, there was an 86.3 percent improvement in group one vs. 65.3 percent in group two. Further, lab examination at four weeks showed 96.1 percent clearance of fungal colonies in group one, compared to 65.3 percent in group two. Because of the high rates of recurrence with TV, further research should be conducted that explores the efficacy of these treatments long-term.

Lemongrass (*Cymbopogon citratus*) is a plant widely used throughout southeast Asia as a snake repellent, purgative, antispasmodic, and diuretic.<sup>30</sup> Its high terpene content is believed to contribute to its antimicrobial, anti-inflammatory, and antimalarial properties.<sup>30</sup> Thirty patients with TV received lemongrass essential oil shampoo and cream treatment, and 18 patients received KTZ control shampoo. The lemongrass treatment group had a 60 percent cure rate compared to an 80 percent cure rate for KTZ.<sup>31</sup> Although the KTZ group had a higher cure rate, the fact that a single botanical exhibited such a high cure rate shows promise that combined formulations could prove more effective. For example, Lone, et al. developed a poly-herbal formulation containing Ceylon leadwort (*Plumbago zeylanicum*), Black mustard (*Brassica nigra*), Sneezewort (*Dregea volubilis*), India madder (*Rubia cordifolia*), Radish (*Raphanus sativus*), and vinegar and had 20 TV patients apply it twice daily. Results were compared to those for 20 TV patients who received a 20% sodium thiosulphate lotion.<sup>32</sup> At 30-day assessment, all participants' cultures were negative for *Malassezia* colonization. Further, there was a significant improvement in scaling, itching, and symptom severity score as compared to baseline score for the poly-herbal treatment group. Overall, this evidence demonstrates a wide variety of botanicals implicated for the successful treatment of tinea versicolor.

## TINEA PEDIS

Tinea pedis (TP) is a dermatophytic infection of the feet and toes most often caused by the fungus *Trichophyton rubrum*.<sup>33</sup> Approximately 70 percent of the population will have tinea pedis during their life.<sup>33</sup> Infections are caused by asexually reproducing conidia.<sup>33</sup> Risk factors for development of TP include hot and humid temperatures, a less acidic pH, sporting activities, and excessive pedal sweating.<sup>33</sup>

In addition to its efficacy for SD, tea tree (TT) oil was also tested in individuals with interdigital TP. A randomized, controlled, double-blinded study looked at the efficacy and safety of 25% and 50% TT oil. One hundred fifty eight patients were randomized to receive either placebo, 25% or 50% TT oil solution. Clinical response was seen in 68 percent of the half-strength group, compared to 72 percent in the quarter-strength group and 39 percent in the placebo

group. Culture of skin scrapings also showed a mycological cure rate of 64 percent in the half-strength group compared to 31 percent in the placebo group.<sup>34</sup>

Snakeroot (*Ageratina pichinchensis*) is a perennial plant found throughout central America. In Mexican traditional medicine, the aerial parts of the plant are used for treatment of skin wounds.<sup>35</sup> A randomized, double-blinded clinical trial divided 160 patients into three groups: low concentration *A. pichinchensis* extract, high concentration *A. pichinchensis* extract, and 2% KTZ control. After applying the assigned solution topically for four weeks, mycological cure rate was 34.1 percent, 41.8 percent, and 39.53 percent in groups one, two, and three, respectively.<sup>36</sup>

Garlic (*Allium sativum*) has been used for thousands of years in folk medicine.<sup>37</sup> Garlic originated in central Asia and is one of the oldest plants to be cultivated.<sup>38</sup> The Ebers Papyrus, an Egyptian medical scroll that dates to 1600 BCE, mentions garlic in 22 formulas as an effective remedy for heart problems, headaches, bites, worms, and tumors.<sup>38</sup> The renowned ancient Greek physician Dioscorides recommended garlic as a purgative for helminthic infections.<sup>38</sup> Studies have demonstrated the multifarious properties of garlic, including antibacterial, antifungal, anthelmintic, anticancer, and antioxidant activity.<sup>39-43</sup>

One study evaluated the efficacy of ajoene, one of the primary bioactive compounds in garlic, on 47 patients with TP. The patients were divided into three groups: 14 patients were treated with 0.6% ajoene, 15 treated with 1% ajoene, and 18 in the control group treated with 1% terbinafine. After 30 days of treatment, mycological cure was achieved in 60 percent, 100 percent, and 88 percent of groups one, two, and three, respectively.<sup>44</sup> Another study using 0.4% ajoene cream achieved mycological cure in 79 percent (27/34) of patients after seven days of treatment. The remaining 21 percent achieved mycological cure after an additional seven days of treatment. At 90-day follow-up, the patients were evaluated for recurrence, and all yielded negative cultures for fungus.<sup>45</sup>

## ONYCHOMYCOSIS

Onychomycosis is a dermatophytic infection of the nails predominantly caused by the fungal agent *Trichophyton rubrum*.<sup>46</sup> It is estimated to affect up to 10 percent of the US population and can have negative consequences, such as pain and undermining a patient's work and social life.<sup>46</sup> It is difficult to treat because of the slow growth of the nail and subsequent long treatment times (three to 12 months).<sup>46</sup> Common risk factors include age, being immunocompromised, wearing tight shoes, exposure to gymnasiums and locker rooms, and having direct trauma to the nail.<sup>46</sup> The results of two botanical extracts previously discussed for their clinical efficacy in TP and SD are reported below.

In addition to its efficacy for SD and TP, TT oil also was tested in individuals with distal subungual onychomycosis (OM). A double-blind, multicenter, randomized controlled trial looked at the efficacy and safety of either 100% TT oil or 1% clotrimazole (CL) solution applied for six months. Debridement and clinical assessment were performed at 0, 1, 3, and 6 months. After six months of therapy, the two treatment groups were comparable based on culture cure (CL= 11%, TT= 18%), and clinical assessment, documenting partial or full resolution (CL=61%, TT=60%).<sup>47</sup> While the effect is somewhat modest, this suggests that the use of TT in conjunction with debridement of the nail may be a useful treatment for OM.

In addition to its efficacy for TP, *Ageratina pichinchensis* is also implicated for the clinical treatment of OM. A lacquer solution containing *A. pichinchensis* extract was given to 49 patients and a similar solution containing 8% ciclopirox was given to 47 patients in the control group. Seventy one percent of patients in the experimental group and 80.9 percent in the control group showed therapeutic effectiveness. Moreover, 59.1 percent and 63.8 percent from the experimental and control group, respectively, achieved mycological cure rates, without adverse side effects.<sup>48</sup>

## CONCLUSION

There are several botanicals with promising antifungal effectiveness in clinical trials. Future studies should continue to examine formulations of plant extracts that are safe and efficacious in the treatment of fungal infections. While tea tree oil demonstrated clinically-relevant antifungal activity in SD, OM, and TP, there remains a risk of developing contact dermatitis. Indeed, "natural" does not necessarily equate to "safe," and future trials must quantify the long-term safety and efficacy of botanical product formulations. Despite this, there is provocative evidence that there are natural products that may be of value for cutaneous fungal infections that may one day yield more mainstream therapies. ■

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