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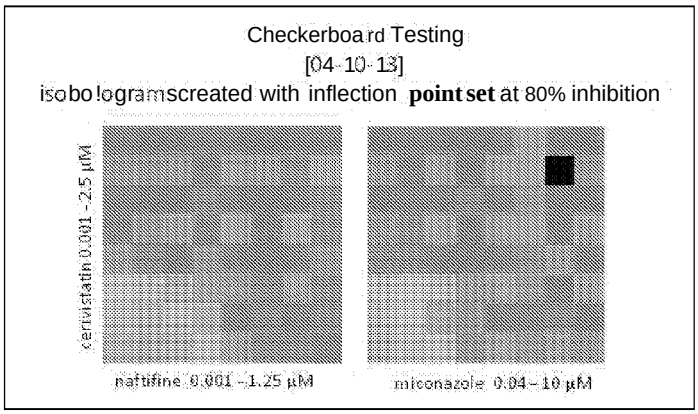
FIG. 1



(57) Abstract: A composition and method for the prophylaxis and treatment of topical fungal infections is provided. Generally, the composition includes an HMG-CoA reductase inhibitor and a carrier. In some forms, the composition further includes an anti-fungal agent. The method generally includes the steps of applying the composition topically once or multiple times. The composition and method can be used in combination with another form of fungal treatment, such as oral medications.

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DERMATOPHYTOSIS PROPHYLAXIS AND TREATMENT

FIELD OF INVENTION

The present disclosure is related to an HMG-CoA reductase (also referred to as a 'statin') composition for the prophylaxis and treatment of fungal infections of the hair and/or skin. More specifically, the present disclosure is related to a statin composition for the prophylaxis and treatment of fungal infections of the hair and/or scalp. A statin composition is provided for reducing the severity of a fungal infection, reducing the number of fungal cells, minimizing or eliminating spore shedding, decreasing the spread of fungal infections in a population, decreasing acquisition of fungal infections, decreasing susceptibility to fungal infections, decreasing the infection potential including preventing the spread of fungal infections to other children as well as further spreading on the same child, and preventing fungal infections or re-infections. The present disclosure also provides methods related to the treatment and prevention of fungal infections, specifically related to tinea capitis caused by *T. tonsurans.*

BACKGROUND OF THE INVENTION

Tinea capitis is a fungal infection of the scalp where dermatophytes in the Trichophyton and Microsporum genera invade the hair shaft and cause infection. Symptoms of tinea capitis generally present as a single or multiple patches of hair loss, sometimes with a "black dot" pattern that can be accompanied by additional symptoms such as inflammation, scaling, pustules, and itching. *Trichophyton tonsurans* (*T. tonsurans)* is one of the causes of tinea capitis, where this species of fungal infection is prevalent among school-aged children in the United States.

Tinea capitis is found to have become integrated into metropolitan communities having a striking presence and infection rate. Studies have shown that infection rates are higher than previously thought and two large scale studies of over 10,000 preschool and primary school-aged children showed schools had infection rates as high as 30%. (Abdel-Rahman, et al., Tracking *Trichophyton tonsurans* Through a Large Urban Child Care Center: Defining Infection Prevalence and Transmission Patterns by Molecular Strain Typing; Pediatrics, December 2006, Vol. 118, No. 6, pp. 2365-2373; Abdel-Rahman, et al.; The Prevalence of Infections With

Trichophyton tonsurans in School children: the CAPITIS Study; Pediatrics; May, 2010; Vol. 125, No. 5, pp. 966-973). These studies also showed a large degree of genetic heterogeneity among the fungal isolates and a very low response rate to oral medicines administered for treatment. (Id.; Abdel-Rahman, et al., Tracking *Trichophyton tonsurans* Through a Large Urban Child Care Center: Defining Infection Prevalence and Transmission Patterns by Molecular Strain Typing; Pediatrics, December 2006, Vol. 118, No. 6, pp. 2365-2373; Abdel-Rahman et al., Griseofulvin has only a modest impact on eradicating carriage of *Trichophyton tonsurans.* Journal of Pediatric Pharmacology and Therapeutics, April 2009, Vol. 14, No. 2, pp. 94-99).

While oral medications for treating tinea capitis are known, these treatments face challenges. Often the infection is prevalent within a community of children, leading to vast opportunities for re-infection. Additionally, objects, such as bed sheets, pillows, hair brushes, stuffed toys, etc. carry the fungus and provide a means for re-infection. Objects in a classroom environment also have an impact on the prevalence of infection for the children in the classroom. Further, current oral medications used to treat tinea capitis have side effects such as liver toxicity and/or interactions with other drugs. This is in addition to the challenge presented when administering oral medication to a child, such as a child being unwilling to take a medication, ensuring enough of the medication was received, etc.

Several studies have investigated the antimycotic effect of statins, both alone and in combination with known antimycotic agents. As summarized in PCT/HU2009/000043 (the '043 application), no reference discussed therein found a generally valid antimycotic effect when using statins alone; no general synergistic antimycotic interaction between statins and known antimycotic agents can be detected; the presence or absence of a synergistic effect of statins and known antimycotic agents was different from species to species; and the fact that a combination of a statin and an antimycotic agent showed some synergistic effect does not mean that the effect could be achieved using clinically acceptable dosage ranges. The '043 application showed an additive effect for most combinations of fluvastatin and ketoconazole in *Candida albicans,* an additive effect for most combinations of pravastatin and miconazole in *Candida glabrata,* an additive effect for most combinations of simvastatin and primycin in *Candida glabrata,* a synergistic effect for most combinations of atorvastatin and itraconazole in *Aspergillus fumigatus,* an additive effect for most combinations of fluvastatin and miconazole in *Aspergillus*

flavus, and a synergistic effect for most combinations of atorvastatin and ketoconazole in Rhizopus oryzae. However, in addition to the summary of the antimycotic effect of statins provided in the '043 application, it can be appreciated that the organisms studied in the '043 application are not dermatophytes.

SUMMARY OF THE INVENTION

The present disclosure overcomes the problems present in the prior art and provides a topical composition incorporating a statin for preventing and treating fungus. The topical composition of the present disclosure generally comprises an amount of an agent and an amount of a vehicle or carrier suited for topical administration. The topical composition of the present disclosure is effective for at least one of the prophylaxis and/or treatment of a topical fungal infection, reducing the number of fungal cells, minimizing or eliminating spore shedding, decreasing the spread of fungal infections, decreasing acquisition of fungal infections, decreasing susceptibility to fungal infections, decreasing the infection potential including preventing the spread of fungal infections to other children as well as further spreading on the same child, preventing fungal infections or re-infections, and combinations thereof. In terms of a population of individuals, the topical composition described herein is effective at reducing the incidence of fungal infections, decreasing acquisition of fungal infections, decreasing susceptibility to fungal infections, decreasing the infection potential including preventing the spread of fungal infections to other children as well as further spreading on previously infected children, preventing fungal infections or re-infections, and combinations thereof, in the population. The topical composition of the present disclosure is generally applied to a topical fungal infection or applied to an area where topical fungal infections occur. The topical composition of the present disclosure may also be applied to articles that come in contact with a topical fungal infection, such as, but not limited to, a pillow, bed sheets, stuffed toys, clothing, furniture, automobiles, a classroom environment, and the like.

Methods for reducing the incidence of or severity of a topical fungal infection and for preventing a topical fungal infection are also provided for by the present disclosure. One method

for reducing the severity of a topical fungal infection generally comprises the steps of applying the topical composition of the present disclosure to the fungal infection. Preferably, the topical fungal infection is a fungal infection of the head or scalp. The method for preventing or treating topical fungal infections generally comprises the steps of applying the topical composition to areas of the body where topical fungal infections occur, most preferably on the scalp. The method for prophylaxis or treating a fungal infection provided by the present disclosure may also include application of the topical composition to articles that come into contact with a topical fungal infection, such as, but not limited to, a pillow, bed sheets, stuffed toys, clothing, furniture, automobiles, a classroom environment, and the like.

The present disclosure provides for an effective way to treat, manage, eradicate, and prevent topical fungal infections. Preferably, the fungal infection is tinea capitis, caused by *Trichophyton tonsurans (T. tonsurans)*, however, other fungal infections are also envisioned. The compositions and methods provided by the present disclosure preferably treatment and/or prophylaxis of a topical fungal infection, reducing the number of fungal cells, minimizing or eliminating spore shedding, decreasing the spread of fungal infections, decreasing acquisition of fungal infections, decreasing susceptibility to fungal infections, decreasing the infection potential including preventing the spread of fungal infections to other children as well as further spreading on the same child, preventing fungal infections or re-infections, and combinations thereof. Preferably, the number of fungal cells is decreased by at least 50% after the statin composition of the present disclosure is applied.

The topical composition of the present disclosure preferably comprises an agent in an effective amount for the treatment and/or prevention of topical fungal infection. The effective amount of the agent, in some embodiments, can be combined with or incorporated into known lotion products, shampoo products, topical sprays, and the like. Alternatively, the topical composition of the present disclosure includes an effective amount of an agent and an amount of a carrier or vehicle. The amount of carrier or vehicle will depend on the route of administration of the topical composition. Components in addition to the agent may be present in the topical composition such as, but not limited to, fragrances, colors, foaming agents, and the like.

When compositions in accordance with the present disclosure are applied to articles that come into contact with a topical fungal infection, it is preferred that such compositions are environmentally safe and do not damage the article by discoloring it, modifying its appearance, or modifying its physical characteristics or integrity. Compositions that are sprayable are especially preferred for application to such articles.

Preferred agents of the disclosure are selected from the group consisting of HMG-CoA reductase inhibitors or statins, plant oils and/or extracts, and combinations thereof. Preferred statins include cerivastatin, itavastatin, pitavastatin, simvastatin, simvastatin acid, mevastatin, 3'-hydroxy simvastatin acid, 6'-hydroxymethyl simvastatin acid, lovastatin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, active metabolites of any of the listed statins, or combinations thereof. In a most preferred embodiment, the statin is selected from the group consisting of cerivastatin, pitavastatin, and/or simvastatin acid. Preferred plant oils and/or extracts are selected from the group consisting of allspice *(Pimenta dioica)*, anise *(Pimpinella anisum)*, arachis *(Arachis hypogaea)*, baobab *(Adansonia digitata)*, basil *(Ocimum basilicum)*, clove *{Ocimum gratissimum)*, beach cabbage *(Scaevola sericea)*, cassia bark, Chinese *{Cinnamomum cassia)*, celery seed *(Apium graveolens)*, chives, garlic *{Allium tuberosum)*, cinnamon *(Cinnamomum verum)*, citronella *(Cymbopogon nardus)*, citronella *(Cymbopogon winterianus)*, clove *(Syzygium aromaticum)*, coriander *(Coriandrum sativum)*, eucalyptus *(Eucalyptus obliqua)*, fennel *(Foeniculum vulgare)*, fish poison tree *(Barringtonia asiatica)*, garlic *(Allium sativum)*, geranium *(Pelargonium hortorum)*, juniper *(Juniperus communis)*, kava kava *(Piper methysticum)*, kopiko ula *(Psychotria hawaiiensis)*, lavender *(Lavandula angustifolia)*, lemon grass *(Cymbopogon citratus)*, mamaki *(Pipturus albidus)*, morning glories *(Ipomoea sp.)*, mustard seed *(Brassica juncea)*, myrtle *(Eugenia umbelliflora)*, myrtle *(Pimenta racemosa)*, olive *(Olea europaea)*, orange *(Citrus sinensis)*, oregano *(Origanum vulgare)* palmarosa *(Cymbopogon martini)*, patchouli *(Pogostemon cablin)*, peppermint *(Mentha piperita)*, perilla *(Perilla frutescens)*, rose apple bark *(Syzygium jambos)*, rose apple, malay *(Eugenia malaccensis)*, rosemary *(Rosemarinus officinalis)*, shikakai *(Acacia concinna)*, tea tree, lemon scented tea tree *(Leptospermum petersonii)*, thyme *(Thymus vulgaris)*, turpentine *(Pinus palustris)*, and combinations thereof.

Carriers and vehicles useful with the present disclosure are preferably selected from the group of serum, cream, and ointment, and combinations thereof. Preferred serums include an ingredient selected from the group consisting of Alkyl Benzoate, Butylene Glycol, Cyclopentasiloxane, Cyclohexasiloxane, Dimethicone, Dimethiconol, Ethylhexyl Methoxycinnamate, Isodecyl Neopentanoate, Phenoxyethanol, and combinations thereof. Preferred creams include an ingredient selected from the group consisting of Aluminum Stearate, Acetamide MEA, Behentrimonium Methosulfate, Caprylyl Glycol, Cetyl Alcohol, Cetyl Esters, Cetearyl Alcohol, Glycerin, Hydroxyethylcellulose, Imidazolidinyl Urea, Isopropyl Lanolate, Lanolin, Methylparaben, Methylisothiazolinone, Mineral Oil, Phenoxyethanol, Peg-75, Polyquaternium 11, Polysorbate 20, PPG 10 Cetyl Ether, Propylparaben, Petrolatum, Polisorbate-60, Sodium Borate, Stearic Acid, Stearalkonium Chloride PA, and combinations thereof. Preferred ointments include an ingredient selected from the group consisting of Aluminum Stearate, Beeswax, Benzyl Alcohol, Benzyl Salicylate, Bis-Diglyceryl Polyacyladipate-2, Calcium Oxide, Carbomer, Caprylyl Glycol, Cetearyl, DMDM Hydantion, Glyeryl Stearate, Glycerin, Glycine, Imidazolidinyl Urea, Linalool, Mineral Oil , Oleth-5, Petrolatum, Peg-75, Polysorbate 80, PEG-40, Phenoxyethanol, Phenoxyethanol, Propylparaben, Shea butter, Stearic Acid, Sodium Cocoyl Glutamate, Triethanolamine, and combinations thereof.

DESCRIPTION OF FIGURES

Figure 1 is a representation of isobolograms depticting the synergistic activity of cerivastatin in combination of naftifine or miconazole at varying concentrations.

DETAILED DESCRIPTION

The topical composition of the present disclosure preferably includes an amount of a statin or HMG-CoA reductase inhibitor, or the active metabolites thereof. Preferred statins include, but are not limited to, cerivastatin, itavastatin, pitavastatin, simvastatin, simvastatin acid, mevastatin, 3'-hydroxy simvastatin acid, 6'-hydroxymethyl simvastatin acid, lovastatin,

atorvastatin, fluvastatin, pravastatin, rosuvastatin, any of the active metabolites of these preferred statins, or combinations thereof. In a most preferred embodiment, cerivastatin, pitavastatin, and/or simvastatin acid are used. The statins are preferably utilized in any form available for a statin, such as, but not limited to the acid or an active metabolite of a statin.

Preferably, the statin is present in the statin composition in an amount of from about 0.001% to 10% of the composition, more preferably from about 0.002% to 8% of the composition, more preferably from about 0.003% to 7% of the composition, still more preferably from about 0.004% to about 6.5% of the composition, still more preferably, from about 0.005% to about 6% of the composition, more preferably, from about 0.006% to about 5%, still more preferably from about 0.007% to about 4%, even more preferably, from about 0.008% to about 3%, still more preferably from about 0.009% to about 2% and most preferably from about 0.01% to about 1%, where values including, but not limited to, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, and 1% are also envisioned.

When the topical composition includes a statin, the topical composition is at least 5% more effective, more preferably at least 10% more effective, still more preferably at least 20% more effective, still more preferably at least 30% more effective, still more preferably at least 40% more effective, even more preferably at least 50% more effective, more preferably at least 60% more effective, still more preferably at least 75% more effective, even more preferably at least 80% more effective, more preferably at least 85% more effective, still more preferably at least 90%, even more preferably at least 95, 96, 97, 98, 99, or even 100% more effective at reducing the severity of a fungal infection, reducing the number of fungal cells, minimizing or eliminating spore shedding, decreasing the spread of fungal infections in a population, decreasing acquisition of fungal infections, decreasing susceptibility to fungal infections, decreasing the infection potential including preventing the spread of fungal infections to other children as well as further spreading on the same child, and preventing fungal infections or re-infections, wherein the increased effectiveness is in comparison to an individual that has not received a topical composition in accordance with the present disclosure. Further, 100% more effective means that the condition was completely eliminated or prevented. For example, spore

shedding would be eliminated, fungal infections would not spread, fungal cells would be eliminated, and the like.

In a further aspect of the present the statin composition of the present disclosure further comprises an anti-fungal agent. The anti-fungal agent can be any agent known to have anti-fungal properties, or any agent that was determined by the present disclosure to have anti-fungal properties including polyene antifungals, allylamines, echinocandins, amphotericin B, benzoic acid, ciclopirox, flucytosine, haloprogin, tolnaftate, candicicin, filipin, hamycin, rimocidn, squalene epoxidase inhibitors, the agents found below in Table 1, azoles, nystatin, griseofulvin, terbinafine, primycin, and combinations thereof. Preferred azoles include ketoconazole, fluconazole, and itraconazole. Plant oils and/or extracts, as described above, can also be used as an anti-fungal agent. In a preferred embodiment, the anti-fungal agent is selected from, but not limited to, plant oils and/or extracts, griseofulvin, terbinafine, naftifine, miconazole, or combinations thereof.

Preferably, the anti-fungal agent is present in the statin composition in an amount of from about 0.001% to 10% of the composition, more preferably from about 0.002% to 8% of the composition, more preferably from about 0.003% to 7% of the composition, still more preferably from about 0.004% to about 6.5% of the composition, still more preferably, from about 0.005% to about 6% of the composition, more preferably, from about 0.006% to about 5%, still more preferably from about 0.007% to about 4%, even more preferably, from about 0.008% to about 3%, still more preferably from about 0.009% to about 2% and most preferably from about 0.01% to about 1%, where values including, but not limited to, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, and 1% are also envisioned.

In an embodiment where a statin and an anti-fungal agent are present in the composition, the topical composition is preferably more effective than when the topical composition includes a statin but does not include an anti-fungal agent. Preferably, the topical composition including a statin and an anti-fungal agent is at least 5% more effective, more preferably at least 10% more effective, still more preferably at least 20% more effective, still more preferably at least 30% more effective, still more preferably at least 40% more effective, even more preferably at least

50% more effective, more preferably at least 60% more effective, and most preferably at least 75% or more effective at reducing the severity of a fungal infection, reducing the number of fungal cells, minimizing or eliminating spore shedding, decreasing the spread of fungal infections in a population, decreasing acquisition of fungal infections, decreasing susceptibility to fungal infections, decreasing the infection potential including preventing the spread of fungal infections to other children as well as further spreading on the same child, and preventing fungal infections or re-infections, wherein the increased effectiveness is in comparison to a topical composition that includes a statin, but does not include the anti-fungal agent.

In another embodiment of the present disclosure, the topical composition of the present disclosure includes a statin that is incorporated into a pre-existing product. Preferably, the pre-existing products are selected from, but not limited to, serums, creams, ointments, lotions, gels, shampoo products, conditioners, soaps, sprays, oils, and combinations thereof. Creams, serums, and ointments are particularly preferred.

In another embodiment of the present disclosure, the topical composition includes a statin, as described above, in combination with plant oils and/or extracts, as described above. Such compositions are preferably included in the pre-existing products, as described above. Such an embodiment may further comprise an anti-fungal agent, as described above.

In an embodiment where the topical composition of the present disclosure includes a statin incorporated into a pre-existing product, the statin is present in an amount of from about 0.001% to 10% of the composition, more preferably from about 0.002% to 8% of the composition, more preferably from about 0.003% to 7% of the composition, still more preferably from about 0.004% to about 6.5% of the composition, still more preferably, from about 0.005% to about 6% of the composition, more preferably, from about 0.006% to about 5%, still more preferably from about 0.007% to about 4%, even more preferably, from about 0.008% to about 3%, still more preferably from about 0.009% to about 2% and most preferably from about 0.01% to about 1%, where values including, but not limited to, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, and 1% are also envisioned. Similarly, if an anti-fungal agent is included, it is also present in an amount of from about 0.001% to 10% of the composition, more preferably from about 0.002% to 8% of the

composition, more preferably from about 0.003% to 7% of the composition, still more preferably from about 0.004% to about 6.5% of the composition, still more preferably, from about 0.005% to about 6% of the composition, more preferably, from about 0.006% to about 5%, still more preferably from about 0.007% to about 4%, even more preferably, from about 0.008% to about 3%, still more preferably from about 0.009% to about 2% and most preferably from about 0.01% to about 1%, where values including, but not limited to, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, and 1% are also envisioned. When plant oils and/or extracts are included in a composition that includes a statin and/or an anti-fungal agent, the plant oil and/or extract is present in an amount from about 0.001% to 50% of the composition, more preferably from about 0.01% to 40% of the composition, more preferably from about 0.1% to 30% of the composition, still more preferably from about 1% to about 20% of the composition, still more preferably, from about 1.5% to about 15% of the composition, and most preferably from about 2% to about 12%, where values including, but not limited to, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, and 11% are also envisioned.

In yet a further embodiment, the statin composition of the present disclosure additionally comprises a carrier or vehicle. Any carrier or vehicle suitable for topical administration will work for purposes of the present disclosure. Serums, creams, and ointments are preferred carriers or vehicles. As noted above, preferred serums include an ingredient selected from the group consisting of Alkyl Benzoate, Butylene Glycol, Cyclopentasiloxane, Cyclohexasiloxane, Dimethicone, Dimethiconol, Ethylhexyl Methoxycinnamate, Isodecyl Neopentanoate, Phenoxyethanol, and combinations thereof. Preferred creams include an ingredient selected from the group consisting of Aluminum Stearate, Acetamide MEA, Behentrimonium Methosulfate, Caprylyl Glycol, Cetyl Alcohol, Cetyl Esters, Cetearyl Alcohol, Glycerin, Hydroxyethylcellulose, Imidazolidinyl Urea, Isopropyl Lanolate, Lanolin, Methylparaben, Methylisothiazolinone, Mineral Oil , Phenoxyethanol, Peg-75, Polyquaternium 11, Polysorbate 20, PPG 10 Cetyl Ether, Propylparaben, Petrolatum, Polisorbate-60, Sodium Borate, Stearic Acid, Stearalkonium Chloride PA, and combinations thereof. Preferred ointments include an ingredient selected from the group consisting of Aluminum Stearate, Beeswax, Benzyl Alcohol, Benzyl Salicylate, Bis-Diglyceryl Polyacyladipate-2, Calcium Oxide, Carbomer, Caprylyl Glycol, Cetearyl, DMDM Hydantion, Glyeryl Stearate, Glycerin, Glycine, Imidazolidinyl Urea, Linalool, Mineral Oil , Oleth-5, Petrolatum, Peg-75, Polysorbate 80, PEG-40, Phenoxyethanol,

Phenoxyethanol, Propylparaben, Shea butter, Stearic Acid, Sodium Cocoyl Glutamate, Triethanolamine, and combinations thereof. Preferably, the carrier or vehicle is present in the statin composition in an amount of from about 1% to 99.999% of the composition, more preferably from about 10% to 99.99% of the composition, more preferably from about 20% to 99.9% of the composition, still more preferably from about 30% to about 99.8% of the composition, still more preferably, from about 35% to about 99.7% of the composition, more preferably, from about 40% to about 99.6%, still more preferably from about 50% to 99.5%, more preferably from about 60% to 99.4% of the composition, still more preferably from about 70% to about 99.3% of the composition, still more preferably, from about 80% to about 99.2% of the composition, more preferably, from about 85% to about 99.1%, and most preferably from about 90% to 99%.

In another aspect of the present disclosure, a method for the reduction of the severity of a fungal infection is provided. The method of the present disclosure preferably includes the step of administering the topical composition of the present disclosure to a subject in need thereof. Preferably, the method additionally includes the step of administering the topical composition at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, or more times. This administration can be done more than once per day, or once every 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days. Preferred administration schedules include a daily to weekly application for months, or even years. Preferably, the administration will continue until the individual is out of primary school. The method preferably includes the step of administering the topical composition to a location where it can contact a fungal infection or an area of the body susceptible to fungal infections. Most preferably, the method includes the step of applying the topical composition of the present disclosure to the head of a subject in need thereof. Additionally, the topical composition may be applied to articles that may come into contact with the fungal infection. The administration schedule for the article may be the same or different than the administration schedule to the location on the body. Further, the form of the topical composition may vary depending on whether the application is to an article or to a location on the body. For example, the topical

composition for article administration might be in a sprayable form while the topical composition for the body might be in a cream.

In another aspect of the disclosure, the topical composition is administered in conjunction with or as an adjunct to existing treatment. In such situations, the individual has already been diagnosed with a topical fungal infection and is receiving some other form of treatment, such as oral medications, to combat the active infection. The topical composition is administered as described above in order to help with the treatment aspect. After the active infection is minimized or eliminated, the other treatment regimen can be discontinued while the topical composition of the present disclosure can be administered for its prophylactic benefits.

The methods of the present disclosure and topical composition of the present disclosure preferably reduce the severity of a fungal infection, reduce the number of fungal cells, minimize or eliminate spore shedding, decrease the spread of fungal infections in a population, decrease acquisition of fungal infections, decrease susceptibility to fungal infections, decrease the infection potential including preventing the spread of fungal infections to other children as well as further spreading on the same child, and prevent fungal infections or re-infections, wherein the increased effectiveness is in comparison to an individual or population that has not received a topical composition in accordance with the present disclosure. Preferably, each of these are improved by at least 10%, more preferably by at least 20%, more preferably by at least 30%, still more preferably by at least 40%, more preferably by at least 50%, still more preferably by at least 60%, even more preferably by at least 70%, more preferably by at least 80%, more preferably by at least 90%, and most preferably by 100%. One of skill in the art can determine appropriate methods of comparison in order to determine the percentage of improvement. For example, for reducing the number of fungal cells, an improvement of 10% would mean that the individual being administered the topical composition of the present disclosure had 10% fewer fungal cells than an individual not receiving an administration of the topical composition. Similarly, for decreasing the spread of fungal infections in a population, populations receiving the administration of the topical composition of the present disclosure would preferably have at least 10% fewer fungal infections than a population that did not receive the administration of the topical composition.

In another aspect of the disclosure, use of the topical composition on individuals taking another form of treatment, such as oral medications, for the treatment of fungal infections will permit lower amounts or dosages of the other treatment to be administered and maintain the same level of effectiveness as the higher dosage. Preferably, the amounts or dosages of the other treatments will be able to be decreased by at least 10%, more preferably by at least 20%, more preferably by at least 30%, still more preferably by at least 40%, more preferably by at least 50%, still more preferably by at least 60%, even more preferably by at least 70%, and most preferably by at least 80%.

In another aspect of the disclosure, use of statins and an anti-fungal agent in the topical composition will permit lower amounts of at least one of the individual active ingredients (i.e. the statin and the anti-fungal) to be used but still maintain the effectiveness of the higher dosage when the statin or anti-fungal agent are used alone. Preferably, the amount or dosage of at least one of the active ingredients will be able to be reduced by at least 10%, more preferably by at least 20%, more preferably by at least 30%, still more preferably by at least 40%, more preferably by at least 50%, still more preferably by at least 60%, even more preferably by at least 70%, and most preferably by at least 80%.

In yet another aspect of the present disclosure, a method for preventing fungal infections is provided. The method preferably includes the step of administering the topical composition of the present disclosure to a subject in need thereof. Preferably, the method additionally comprises the step of administering the topical composition multiple times, as described above. The method preferably includes the step of administering the topical composition to a location where fungal infections generally occur or to an area of the body susceptible to fungal infections. Most preferably, the method includes the step of applying the topical composition of the present disclosure to the head of a subject in need thereof. In an alternate embodiment, the method additionally includes the step of administering the topical composition to areas that may contact a topical fungal infection, such as, but not limited to, a pillow, hat, hairbrush, bed sheets, clothing, stuffed toy, furniture, car seat, classroom environment, and the like.

Embodiments of the present disclosure can be used to treat, reduce the incidence of, or prevent fungal infections. In preferred forms, the methods and compositions of the present

disclosure can be used to treat, reduce the incidence of, or prevent dermatophyte infection. Preferably, the methods and compositions of the present disclosure can be used to treat, reduce the incidence of, or prevent Tinea barbae, Tinea captitis, Tinea corporis, Tinea cruris, Tinea manuum, Tinea pedis, Tinea unguiuum, Onychomycosis, Tinea corporis gladitorum, Tinea faciei, Tinea imbricate, Tinea incognito, Favus or the organisms *Epidermophyton floccosum, Microsporum canis, Microsporum audouinii, Trichophyton interdigitale, Trichophyton mentagrophytes, Trichophyton tonsurans (T. tonsurans), Trichophyton schoenleini, Trichophyton rubrum, Trichophyton equinum.* Of these, Tinea capitis and *T. tonsurans* are preferred targets for the composition and methods described herein.

Preferably, the method of the present disclosure and topical composition of the present disclosure preferably prevent fungal infection noted above or caused by the dermatophytes described herein. In preferred forms, the dermatophytes are selected from those listed above. In the case of Tinea capitis and *T. tonsurans,* the method prevents *T. tonsurans* from growing on the scalp. In a group or, by way of example, in a classroom setting, *T. tonsurans* infection is decreased by at least 10%, more preferably by at least 20%, more preferably by at least 30%, still more preferably by at least 40%, more preferably by at least 50%, still more preferably by at least 60%, even more preferably by at least 70%, more preferably by at least 80%, more preferably by at least 90%, and most preferably by 95% of the individuals in a group or classroom. This decrease or reduction is in comparison to a group or classroom that is not being treated as described herein.

The present disclosure also provides for a method of reducing the fungal cells on the scalp of an individual in need thereof. Such a method reduces the overall fungal burden and/or decreases the amount or number of growing spores. The method generally includes the steps of administering the topical composition of the present disclosure to the scalp of an individual in need thereof. The method preferably reduces the number of fungal cells on the scalp by at least 10%, more preferably by at least 20%, more preferably by at least 30%, still more preferably by at least 40%, more preferably by at least 50%, still more preferably by at least 60%, even more preferably by at least 70%, more preferably by at least 80%, more preferably by at least 90%, and most preferably by 100%.

The present disclosure further provides a topical composition effective for reducing the severity of fungal infections to a point below where symptoms are evident and the infection does not develop or progress to the point of exhibiting symptoms of fungal infection.

EXAMPLES

EXAMPLE 1

This example illustrates the mechanism by which statin activity is tested.

Materials and Methods

Isolation of spores:

Materials Used:

- 10mm x 100mm petri plate of dermatophyte culture grown to confluency (>14days) on Sabouraud's dextrose agar (Becton Dickinson, Sparks MD) containing 50mg/L chloramphenicol and 500mg/L cycloheximide (Sigma Chemical Company, St. Louis MO) (see appendix A for recipe).
- 1x sterile Phosphate Buffered Saline (Sigma Chemical Company, St. Louis MO).
- (2) 15mL sterile disposable conical tubes (Thermo Fisher Scientific, Rochester NY).
- Disposable sterile inoculating loop (Fisher Scientific, Hanover Park IL).
- Disposable sterile transfer pipette (Fisher Scientific, Hanover Park IL).
- Sterilized 2" x 2" 4 ply gauze (Medline Industries, Mundelein IL)
- 30mL sterile disposable syringe (Becton Dickinson, Franklin Lakes NJ).
- Hemocytometer (Fisher Scientific, Hanover Park IL).

Spore Prep Procedure (performed aseptically in a biosafety cabinet):

- The fungal plate was flooded with lOmL of sterile lx PBS and with a sterile disposable inoculating loop, then the surface was gently scraped until all the fungal material (hyphae and spores) was liberated into the PBS.
- Using a disposable transfer pipette, the entire volume of PBS/spores was transferred from the plate into a sterile 15mL conical tube.
- Next, 2mL of sterile lx PBS was added to the plate and swirled to rinse.
- Using the transfer pipette, the remaining volume of PBS/spores was transferred from the plate to the 15mL conical.
- Then, the 15mL tube was capped and vortexed at max speed for 10-15 seconds, set aside.
- The plunger from the 30mL syringe was then removed and the barrel was packed with 1 square of sterile 2" x 2" gauze.
- Using the plunger, the gauze was firmly packed at the bottom of the barrel then the plunger was removed.
- The syringe barrel was placed into a new sterile 15mL conical tube and the entire contents of the 15mL PBS/spore suspension was poured directly onto the gauze in the syringe barrel.
- The plunger was then gently inserted into the barrel and depressed all the way down to filter the spore/hyphal suspension through the gauze.
- The plunger was gently removed and additional 2mL of sterile PBS was added back to the original 15mL conical tube. The contents was vortexed briefly and poured into the syringe barrel.
- The filtering process was then repeated and flow collected through into the "filtered" 15mL conical.
- The spores were then counted using standard methods with the hemocytometer.
- They were then diluted to make lOmL of a 1 x 106 spores/mL.
- The tubes were then stored at 4°C and used within 24 hours.

Screening (384 well format):

This procedure assumed the library of compounds to be tested had been pre-spotted into the 384 well plates. Note: final concentration of DMSO was not to exceed 0.5%.

Materials Required:

- A fresh dermatophyte spore preparation @ 1 x 106 spores/mL
- 1x sterile Phosphate Buffered Saline (Sigma Chemical Company, St. Louis MO).
- 2x Sabouraud's Dextrose Broth (Becton Dickinson, Sparks MD) - Sterile (see appendix A).
- 384 well sterile black culture plate(s) with optically clear bottoms (Thermo Scientific, Rochester NY) spotted with compounds to be tested.
- Automated fluid dispenser
- Microplate reader capable of reading at 600nM.
- Sterile glass Erlenmeyer flask.
- EDGE® seals (EDGEbio, Gaithersburg, MD).

Procedure:

- For each 384 well plate to be tested, 4mL of the spore suspension was mixed with lOmL of 1x PBS (this resulted in an absolute number of 104 spores in 35µL dispensed per well). NOTE: there was residual spore suspension, the calculations above allowed for overage to ensure enough suspension is made for each plate.
- Using the peristaltic pump, the automated dispenser was programmed to deliver 35µL of 2x SabDEX broth to each well in the 384 well plate. The pump was then purged of growth media and re-primed with the spore suspension. The dispenser was then programmed to deliver 35µL of spore suspension to each test well (to include + growth controls).
- Negative growth controls were made by manually pipetting 35µL of sterile 1x PBS from a sterile multi-channel boat into each (-) control well using a IOOµE pipette.
- Each plate was given a numerical designation, dated, sealed with an EDGE® seal and placed in a 32°C incubator for 48 hours.
- After incubation, the seal was carefully removed and the plate read at 600nM using a single point read on a microplate reader.
- If more time was required, the plate was re-sealed and incubated an additional 24 hours.

MIC Testing (96 well format):

Materials Required:

- Dermatophyte spore prep @ 1 x 106 spores/mL (see above).
- Sterile 96 well flat bottomed clear culture plate (Falcon 1172, Becton Dickinson Labware, Franklin Lakes NJ).
- 2x Sabouraud's Dextrose Broth (Becton Dickinson, Sparks MD) - Sterile (see appendix A).
- 2x RPMI-1640 Culture Media (Sigma Chemical Company, St. Louis MO) - Sterile
- 2x Keratin Media.
- 2x Culture Medium - Sterile, containing 1.0% DMSO.
- 1x sterile Phosphate Buffered Saline (Sigma Chemical Company, St. Louis MO).
- Drug to be tested (identified from previous screening) dissolved in 100% DMSO (Sigma Chemical Company, St. Louis MO).
- Sterile 1.5mL disposable microfuge tubes (Midwest Scientific, St. Louis MO).
- Multichannel pipette capable of delivering IOOμL volumes.
- Sterile liquid reservoirs for holding spore/PBS solution (Midwest Scientific, St. Louis MO).
- IOOμL manual pipetteman.
- 15mL conical tubes (Thermo Fisher Scientific, Rochester NY).
- EDGE® seals (EDGEbio, Gaithersburg, MD).

General Procedure for MIC testing of compounds ranging from 10μM (high standard) to O.OIμM (low standard) (this may require modification based on media used, concentration ranges of compounds being tested and/or solvents used).

To make the spore suspension:

Combined 0.4mL of a 1 x 106 spore preparation with 3.6 mL sterile IX sterile PBS in a 15mL conical tube and vortexed to mix well.

To make drug dilutions:

- A2mM stock of the compound to be tested was made in 100% DMSO in a sterile 1.5mL microfuge tube.
- Vortexed the tube vigorously for 1 minute, then protected the compound from light and rocked or shook for 1 hour at room temperature to fully dissolve.
- NOTE: Because the 2x culture media was diluted with an equal volume of spore/PBS solution to achieve a lx final media concentration, the high standard for the range of compound to be tested was made at 2x the highest concentration desired and contain a final DMSO concentration of 0.5%.

To generate the range of compound to be tested, the following dilution protocol was performed:

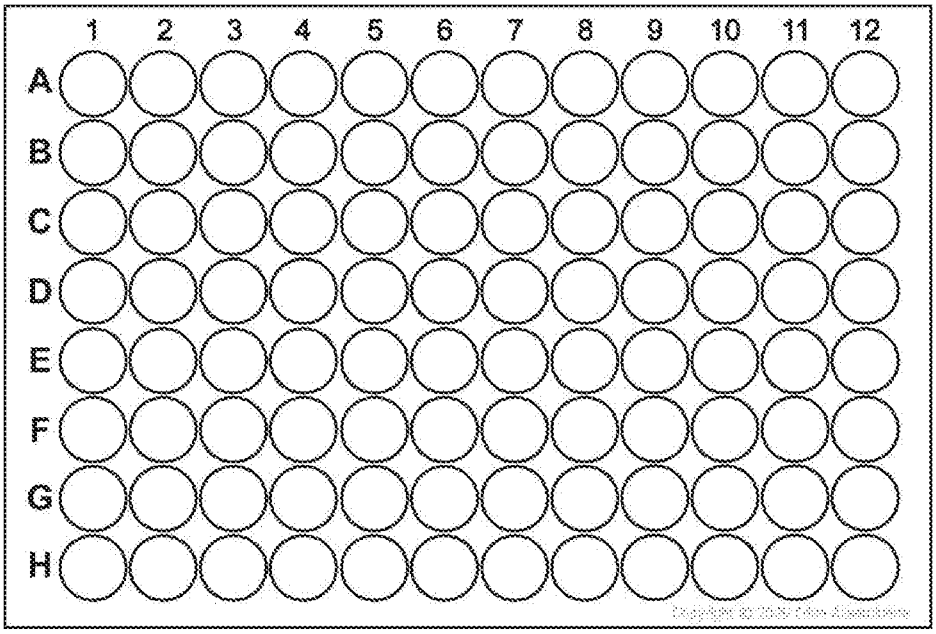
(a) The high standard was made:

20μM * IOOOμI =	10μL of the 2μM drug stock
2000μM	990μL 2x Culture Medium

The result was IOOOμI ، of a 20μM stock in 2x Culture Medium with a final [DMSO] of 1%.

(b) The drug dilution range to be tested was made by serially diluting the high standard 1:1 with 2x Culture Medium/1% DMSO.

Aseptically added IOOμL of the drug/media manually to each well according to the following plate map:



Al, Bl, CI = 100 µï of the 20µM high standard

A2, B2, C2 = IOOµI, of the IOµM

A3, B3, C3 = IOOµI- of the 5µM

A4, B4, C4 = IOOµI, of the 2.5µM

A5, B5, C5 = IOOµI- of the 1.25µM

A6, B6, C6 = IOOµL of the 0.625µM

A7, B7, C7 = 100µE of i1e 0.3125µM

A8, B8, C8 = IOOµL of the 0.156µM

A9, B9, C9 = IOOµL of the 0.078µM

A10, BIO, C10 = 100µE of i1e 0.04µM

All, Bll, Cll = 100µE of i1ε 0.02µM

A12, B12, C12 = IOOµL of the OµM (this serves as no drug + growth controls)

G1-G6 = IOOµL of 2x Culture medium containing 1% DMSO

• At this point, if more than (1) compound was being tested, a second MIC series was added to rows D, E, and F in the same format as done for rows A, B, and C.

- Manually added IOOμL of sterile IX PBS to wells G1-G6 to generate the (-) growth controls.
- Vortexed the spore suspension for 10 seconds and then added IOOμL to rows A, B, and C using a multichannel pipette man.
- Sealed the plate with an EDGE seal and incubated @ 32°C for a minimum of 48 hours.
- After 48 hours of incubation, carefully removed the plate seal and read the absorbance at 600nM using a 5X5 area scan protocol on a plate reader.

Checkerboard Testing (96 well format):

Materials Required:

- Dermatophyte spore prep @ 1 x 106 spores/mL (see above for protocol).
- Sterile 96 well flat bottomed clear culture plate (Falcon 1172, Becton Dickinson Labware, Franklin Lakes NJ).
- 2x Sabouraud's Dextrose Broth (Becton Dickinson, Sparks MD) - Sterile (see appendix A).
- 2x RPMI-1640 Culture Media (Sigma Chemical Company, St. Louis MO) - Sterile (See appendix A).
- 2x Keratin Media (see appendix A).
- 2x Culture Medium - Sterile, containing 1.0% DMSO (see appendix A).
- 1x sterile Phosphate Buffered Saline (Sigma Chemical Company, St. Louis MO).
- Drug to be tested (identified from previous screening) dissolved in 100% DMSO (Sigma Chemical Company, St. Louis MO).
- Sterile 1.5mL disposable microfuge tubes (Midwest Scientific, St. Louis MO).
- Multichannel pipette capable of delivering IOOμL volumes.
- Sterile liquid reservoirs for holding spore/PBS solution (Midwest Scientific, St. Louis MO).
- IOOμL manual pipetteman.
- 15mL conical tubes (Thermo Fisher Scientific, Rochester NY).
- EDGE® seals (EDGEbio, Gaithersburg, MD).

To make the spore suspension: Combined 0.4mL of a 1 x 106 spore preparation with 3.6 mL sterile IX sterile PBS in a 15mL conical tube and vortex to mix well.

To make drug dilutions:

- A 4mM stock of the compound to be tested in 100% DMSO was made in a sterile 1.5mL microfuge tube.
- The compound was then vortexed in the tube vigorously for 1 minute, then protected from light and rocked or shook for 1 hour at room temperature to fully dissolve.

NOTE: Because the 2x culture media is diluted with an equal volume of spore/PBS solution to achieve a lx final media concentration and 2 drug concentrations are being tested, the high standard for the range of compound to be tested must be made at 4x the highest concentration desired and contain a final DMSO concentration of 0.5%.

To generate the range of compound to be tested, the following dilution protocol is performed:

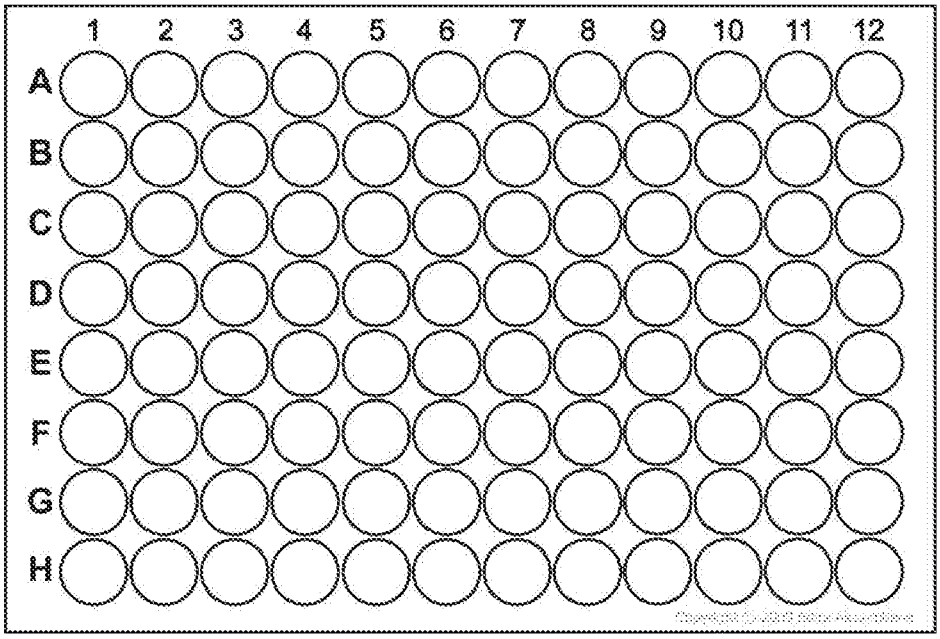
(a) The high standard was made for each drug in the combination being tested:

40μM * IOOOμI	=	IOμL of the 4μM drug stock
2000μM		990μL 2x Culture Medium

The result was IOOOμI, of a 40μM stock in 2x Culture Medium with a final [DMSO] of 1%.

(b) The drug dilution range to be tested was then generated by serially diluting the high standard 1:1 with 2x Culture Medium/ 1% DMSO.

- Aseptically, 50μL of each drug/media was manually added to each well according to the following plate map:



Al-8 = 50 µï of the 20µM drug A, 1 A-H 50 µï of the 20µM drug B

Bl-8 = 50µL of the IOµM drug A, 2 A-H 50 µï of the 10µM drug B

Cl-8 = 50µL of the 5µM drug A, 3 A-H 50 µï of the 5µM drug B

Dl-8 = 50µL of the 2.5µM drug A, 4 A-H 50 µï of the 2.5µM drug B

El-8 = 50µL of the 1.25µM drug A, 5 A-H 50 µï of the 1.25µM drug B

Fl-8 = 50µL of the 0.625µM drug A, 6 A-H 50 µï of the 0.625µM drug B

Gl-8= 50µL of the 0.3 125µM drug A, 7 A-H 50 µï of the 0.3 125µM drug B

Hl-8 = 50µL of the 0.156µM drug A, 8 A-H 50 µï of the 0.156µM drug B

11 A-H = IOOµL of the .OOµM (this serves as no drug + growth controls)

12 A-H = IOOµL of 2x Culture medium containing 1% DMSO

- Next, IOOµL of sterile IX PBS was manually added to wells G1-G6 to generate the (-) growth controls.
- The spore suspension was vortexed for 10 seconds and then IOOµL was added to rows A, B, and C using a multichannel pipette man.

- The plate was sealed with an EDGE seal and incubated @ 32°C for a minimum of 48 hours.
- After 48 hours of incubation, the plate seal was carefully removed and the absorbance was read at 600nM using a 5X5 area scan protocol on a plate reader.

Results and Conclusions :

Table 1. Rank order of the activity of selected HMG-CoA reductase inhibitors against a reference strain of *T. tonsurans* among the top 1% compounds from a preliminary screen of 7,676 compounds.

Compound	DR Plate	Row	Prelim H ratio	Prelim L ratio	upper asymptote	rMIC50 uoM
Liranaftate	DR14	A	1.01	2.00	98.3	<0.01
Itraconazole	DR13	B	1.00	1.85	96.4	<0.01
Adefovir dipivoxil	DR16	F	1.06	2.18	94.9	<0.01
Sulconazole nitrate	DR14	F	1.01	2.00	94.6	<0.01
Oxiconazole Nitrate	DR13	H	1.01	2.00	94.1	<0.01
KU0163477 Synthesized by J. Aube	DR7	D			91.6	<0.01
Cerivastatin	DR7	F	1.06	2.28	91.3	<0.01
Oxiconazole	DR8	E	0.93	1.75	90.4	<0.01
Butoconazole nitrate	DR12	D	1.02	1.88	88.6	<0.01
Econazole nitrate	DR12	B	1.05	2.06	88.5	<0.01
Terbinafine	DR7	G	1.04	2.25	88.1	<0.01
Posaconazole	DR16	E	1.00	2.04	86.1	<0.01
Phenylmercuric acetate	DR2	G	1.06	2.17	84.1	<0.01
Butenafine Hydrochloride	DR13	G	1.00	1.85	83.9	<0.01
Tolnaftate	DR11	C	1.01	1.99	87.8	0.013
Miconazole	DR11	B	1.07	2.09	92.5	0.014
Thimerosal	DR14	C	1.03	2.03	90.4	0.017
Itavastatin (Pitavastatin) Ca	DR10	B	1.04	2.00	97	0.018
Tioconazole	DR10	H	1.03	2.02	95.1	0.018
Ketoconazole	DR12	H	1.00	1.85	91.9	0.019
Sertaconazole nitrate	DR15	E	1.00	2.01	71.9	0.019
Isoconazole	DR11	A	1.05	2.06	100	0.022
Atovaquone	DR7	E	0.44	0.95	64.8	*0.033
Bifonazole	DR16	B	1.06	2.12	97.6	0.038
Fluvastatin sodium salt	DR15	B	1.03	2.03	93.4	0.043
Enilconazole	DR15	D	0.97	1.95	92.5	0.046
Hexachlorophene	DR16	C	1.02	2.05	92.7	0.056
Clotrimazole	DR11	G	1.03	2.02	85.3	0.070
Tetrachloroisophthalonitrile	DR5	D	1.10	2.21	95.1	0.073
Naftifine hydrochloride	DR15	F	1.02	2.05	91.7	0.075
Broxyquinoline	DR3	H	0.77	1.40	94.6	0.082
Clioquinol	DR14	G	0.98	1.93	84.9	0.083
Voriconazole	DR13	D	1.00	1.85	95.5	0.084
KU0044883 Synthesized by C. Spelling	DR5	F	1.14	2.29	99.1	0.088
Flutrimazole	DR5	A			100	0.089

Temsirolimus	DR16	D	0.39	0.80	73.3	0.091
Niclosamide	DR10	F	1.08	2.13	95.6	0.113
KU0157581 Synthesized by J. Aube	DR6	C	1.03	2.00	100	0.117
Ebselen	DR14	B	0.54	1.07	95.2	0.179
Triclabendazole	DR9	B	1.07	2.14	96.2	0.212
Chloroxine	DR11	E	1.01	1.99	89.7	0.220
Disulfiram	DR10	E	0.46	0.91	100	0.227
Simvastatin	DR15	C	1.01	2.00	85.7	0.248
Bleomycin	DR4	G	0.40	0.74	93.1	0.263
Flavokawain B	DR4	B	0.45	0.95	57	*0.290
Dequalinium dichloride	DR12	G	1.02	1.88	80.7	0.334
Deguelin	DR4	A	0.48	0.87	100	0.335
Haloprogin	DR12	C	1.04	1.91	89.3	0.345
Closantel	DR13	A	0.61	1.13	100	0.368
Cetrimonium bromide	DR5	B	1.04	1.91	97.7	0.390
Pyrvinium pamoate	DR15	G	0.88	1.77	87	0.415
Alexidine dihydrochloride	DR14	D	1.04	2.07	96	0.435
Digitonin	DR3	D	1.10	1.99	94.8	0.458
Tomatidine HC1	DR3	B	0.45	0.92	97.1	0.486
Mitotane	DR15	H	0.82	1.65	100	0.506
Mycophenolic acid	DR3	E	0.45	0.82	93.7	0.517
Anethole-trithione	DR8	A	0.79	1.70	100	0.529
Griseofulvin	DR12	A	0.71	1.40	96.5	0.532
Miltefosine	DR7	H	1.08	2.32	88.2	0.535
Myclobutanil	DR8	D	0.76	1.43	100	0.537
Auranofin	DR14	H	0.92	1.82	94.3	0.580
Ampicillin trihydrate	DR10	G	0.40	0.78	91.8	0.585
Climbazole	DR8	B	0.80	1.51	100	0.634
Thonzonium bromide	DR15	A	1.06	2.11	95.1	0.637
Terconazole	DR13	C	0.69	1.28	100	0.644
mevastatin	DR10	C	0.45	0.86	86.4	0.650
Triclosan	DR16	A	1.04	2.08	100	0.656
Lovastatin	DR13	E	0.75	1.39	90.7	0.708
Dichlorophene	DR3	A	1.08	2.21	100	0.709
Honokiol	DR9	A	0.49	0.98	100	0.737
Pterostilbene	DR9	D	0.71	1.42	100	0.826
Dihydrotenone	DR3	C	0.53	1.08	100	0.855
Ipriflavone	DR9	E			100	0.866
Homidium bromide	DR4	H	0.87	1.59	91	0.885
Chlorhexidine	DR11	D	0.95	1.86	100	0.912

Table 2. Investigation of the activity of selected HMG-CoA reductase inhibitors and their metabolites against a reference strain of T. tonsurans.

	IC_{50} (mcM) [range]
cerivastatin	0.01 [0.003-0.058]
pitavastatin	0.03 [0.003-0.032]
simvistatin acid	0.03 [0.024-0.062]

atorvastatin	0.14
rosuvastatin	0.19
fluvastatin	0.26
mevastatin	0.65
lovastatin	0.71
simvistatin	1.14
3"-hydroxy simvistatin acid	1.92
6'-hydroxymethyl simvistatin acid	2.07
pravastatin	>10
3"-hydroxy simvistatin	NA
3',5'-dihydrodiol simvistatin	NA
6'-hydroxymethyl simvistatin	NA

Table 3. Investigation of the activity of selected HMG-CoA reductase inhibitors/metabolites against 5 genetically distinct strain of *T. tonsurans.*

IC_{50} (mcM)	cerivastatin	pitavastatin	simvistatin acid
1119-0616	0.010	0.027	0.062
0924-1093	0.005	0.018	0.050
0924-1456	0.015	0.024	0.052
0924-0254	0.003	0.003	0.029
0924-1669	0.005	0.025	0.052

Table 4. Investigation of the activity of selected HMG-CoA reductase inhibitors/metabolites against different Trichophyton species.

IC_{50} (mcM)	cerivastatin	pitavastatin	simvistatin acid
T. rubrum	0.068	0.147	0.303
T. equinum	0.021	0.054	0.086
T. mentagrophytes	0.019	0.035	0.071

What is claimed is:

1. A topical composition comprising:

an HMG-CoA reductase inhibitor; and

a carrier selected from the group consisting of serum, cream, ointment, lotion, gel, shampoo, hair conditioner, soap, oil, and combinations thereof.

2. The composition of claim 1, further comprising an anti-fungal agent.

3. The composition of claim 1, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of cerivastatin, itavastatin, pitavastatin, simvastatin, simvastatin acid, mevastatin, 3'-hydroxy simvastatin acid, 6'-hydroxymethyl simvastatin acid, lovastatin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, active metabolites of any of the listed HMG-CoA reductase inhibitors, and combinations thereof.

4. The composition of claim 3, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of cerivastatin, pitavastatin, simvastatin acid, and combinations thereof.

5. The composition of claim 2, wherein the anti-fungal agent is selected from the group consisting of polyene antifungals, allylamines, echinocandins, amphotericin B, benzoic acid, ciclopirox, flucytosine, haloprogin, tolnaftate, candicicin, filipin, hamycin, rimocidn, squalene epoxidase inhibitors, liranaftate, adefovir dipivoxil, KU0163477, phenylmercuric acetate, butenafine hydrochloride, tolnaftate, thimerosal, atovaquone, hexachlorophene, tetrachloroisophthalonitrile, naftifine hydrochloride, broxyquinoline, clioquinol, KU0044883, temsirolimus, niclosamide, KU0157581, ebselen, chloroxine, disulfiram, bleomycin, flavokawain B, dequalinium dichloride, deguelin, closantel, cetrimonium bromide, pyrvinium pamoate, alexidine dihydrochloride, digitonin, tomatidine HC1, mitotane, mycophenolic acid, anethole-trithione, miltefosine, myclobutanil, auranofin, ampicillin trihydrate, thonzonium bromide, triclosan, dichlorophene, honokiol, pterostilbene, dihydrotenone, ipriflavone, homidium bromide, chlorhexidine, azoles, nystatin, griseofulvin, terbinafine, primycin, plant oils and/or extracts, and combinations thereof.

6. The composition of claim 5, wherein the anti-fungal agent is selected from the group consisting of plant oils and/or extracts, griseofulvin, terbinafine, naftifine, miconazole, and combinations thereof.

7. The preferred composition of claim 6, wherein the plant oil or extract is derived from a plant selected from the group consisting of allspice *(Pimenta dioica)*, anise *(Pimpinella anisum)*, arachis *(Arachis hypogaea)*, baobab *(Adansonia digitata)*, basil *(Ocimum basilicum)*, clove *(Ocimum gratissimum)*, beach cabbage *(Scaevola sericea)*, cassia bark, Chinese *{Cinnamomum cassia)*, celery seed *(Apium graveolens)*, chives, garlic *{Allium tuberosum)*, cinnamon *{Cinnamomum verum)*, citronella *(Cymbopogon nardus)*, citronella *(Cymbopogon winterianus)*, clove *(Syzygium aromaticum)*, coriander *(Coriandrum sativum)*, eucalyptus *(Eucalyptus obliqua)*, fennel *(Foeniculum vulgare)*, fish poison tree *(Barringtonia asiatica)*, garlic *(Allium sativum)*, geranium *(Pelargonium hortorum)*, juniper *(Juniperus communis)*, kava kava *(Piper methysticum)*, kopiko ula *(Psychotria hawaiiensis)*, lavender *(Lavandula angustifolia)*, lemon grass *(Cymbopogon citratus)*, mamaki *(Pipturus albidus)*, morning glories *(Ipomoea sp.)*, mustard seed *(Brassica juncea)*, myrtle *(Eugenia umbelliflora)*, myrtle *(Pimenta racemosa)*, olive *(Olea europaea)*, orange *(Citrus sinensis)*, oregano *(Origanum vulgare)* palmarosa *(Cymbopogon martini)*, patchouli *(Pogostemon cablin)*, peppermint *(Mentha piperita)*, perilla *(Perilla frutescens)*, rose apple bark *(Syzygium jambos)*, rose apple, malay *(Eugenia malaccensis)*, rosemary *(Rosemarinus officinalis)*, shikakai *(Acacia concinna)*, tea tree, lemon scented tea tree *(Leptospermum petersonii)*, thyme *(Thymus vulgaris)*, turpentine *(Pinus palustris)*, and combinations thereof.

8. The composition of claim 1, wherein the carrier is a serum including an ingredient selected from the group consisting of Alkyl Benzoate, Butylene Glycol, Cyclopentasiloxane, Cyclohexasiloxane, Dimethicone, Dimethiconol, Ethylhexyl Methoxycinnamate, Isodecyl Neopentanoate, Phenoxyethanol, and combinations thereof.

9. The composition of claim 1, wherein the carrier is a cream including an ingredient selected from the group consisting of Aluminum Stearate, Acetamide MEA, Behentrimonium Methosulfate, Caprylyl Glycol, Cetyl Alcohol, Cetyl Esters, Cetearyl Alcohol, Glycerin, Hydroxyethylcellulose, Imidazolidinyl Urea, Isopropyl Lanolate, Lanolin, Methylparaben, Methylisothiazolinone, Mineral Oil, Phenoxyethanol, Peg-75, Polyquaternium 11, Polysorbate 20, PPG 10 Cetyl Ether, Propylparaben, Petrolatum, Polisorbate-60, Sodium Borate, Stearic Acid, Stearalkonium Chloride PA, and combinations thereof.

10. The composition of claim 1, wherein the carrier is an ointment including an ingredient selected from the group consisting of Aluminum Stearate, Beeswax, Benzyl Alcohol, Benzyl Salicylate, Bis-Diglyceryl Polyacyladipate-2, Calcium Oxide, Carbomer, Caprylyl Glycol, Cetearyl, DMDM Hydantion, Glyeryl Stearate, Glycerin, Glycine, Imidazolidinyl Urea, Linalool, Mineral Oil , Oleth-5, Petrolatum, Peg-75, Polysorbate 80, PEG-40, Phenoxyethanol, Phenoxyethanol, Propylparaben, Shea butter, Stearic Acid, Sodium Cocoyl Glutamate, Triethanolamine, and combinations thereof.

11. The composition of claim 1, wherein the HMG-CoA reductase inhibitor is present in an amount from about 0.001% to 10% by weight of the composition.

12. The composition of claim 1, wherein the carrier is present in an amount from about 1% to 99.999% by weight of the composition.

13. The composition of claim 2, wherein the anti-fungal agent is present in an amount from about 0.001% to 10% by weight of the composition.

14. A method for the prophylaxis and/or treatment of a topical fungus comprising the steps of applying the topical composition of claim 1 to the topical fungus.

15. The method of claim 14, wherein said topical fungus is *T. tonsurans.*

16. The method of claim 14, wherein the topical composition is applied to an area where topical fungal infections occur prior to fungal spores being present on said area.

17. The method of claim 14, wherein the topical composition is applied more than once.

18. The method of claim 14, wherein application of the topical composition reduces the number of growing spores of the fungus by at least 10%.

19. The method of claim 14, wherein application of the topical composition results in a benefit selected from the group consisting of reducing the severity of a fungal infection, reducing the number of fungal cells, minimizing or eliminating spore shedding, decreasing the spread of fungal infections in a population, decreasing acquisition of fungal infections, decreasing susceptibility to fungal infections, decreasing the infection potential including preventing the

spread of fungal infections to other children as well as further spreading on the same child, preventing fungal infections or re-infections, and combinations thereof.

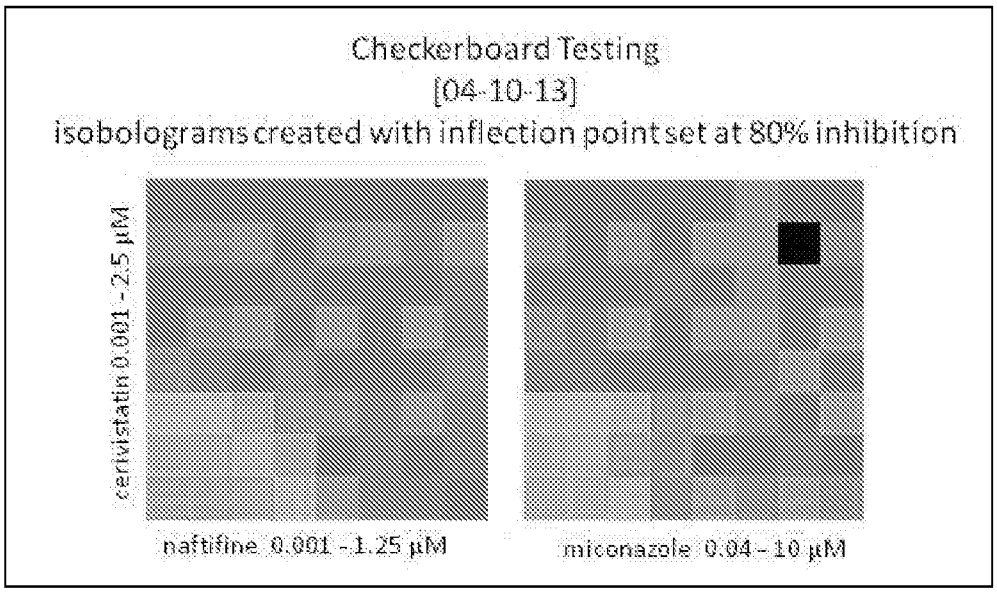
20. The method of claim 14, wherein the application of the topical composition is occurring at the same time as another form of treatment of an active fungal infection.

21. The method of claim 20, wherein the other form of treatment is oral medication.

22. The method of claim 20, wherein the amount of the other form of treatment is reduced by at least 10% when the topical administration and the other form of treatment are used together.

23. The method of claim 20, wherein the other form of treatment is in the form of an oral medication having an active ingredient therein, and wherein the amount of the active ingredient in the oral medication can be reduced by at least 10% while maintaining the same level of effectiveness.

FIG. 1


Checkerboard Testing
[04-10-13]
isobolograms created with inflection point set at 80% inhibition
certistatin 0.001 - 2.5 µM
naftifine 0.001 - 1.25 µM
miconazole 0.04 - 10 µM

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/021406

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/22; A61K 31/351; A61K 31/4402; A61K 31/4704; A61K 31/7048; A61K 36/00 (2016.01)
CPC - A61K 31/22; A61K 31/351 ; A61K 31/4402; A61K 31/4704; A61K 31/7048; A61K 36/00 (2016.02)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/22; A61K 31/351 ; A61K 31/4402; A61K 31/4704; A61K 31/7048; A61K 36/00 (2016.01)
CPC - A61K 31/22; A61K 31/351 ; A61K 31/4402; A61K 31/4704; A61K 31/7048; A61K 36/00 (2016.02)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/725; 424/773; 514/158; 514/703 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google Scholar.
Search terms used: statin, fungal, topical, tonsuran.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0183944 A1 (ASHTON et al) 28 July 2011 (28.07.2011) entire document	1-4, 9-13
Y		5-8, 14-21
Y	US 2009/0258098 A1 (ROLLING et al) 15 October 2009 (15.10.2009) entire document	5-7
Y	US 2012/0164087 A1 (CARTER) 28 June 2012 (28.06.2012) entire document	8
Y	US 2012/0276182 A1 (BAKER JR et al) 01 November 2012 (01.11.2012) entire document	14-21
Y	US 2003/0032578 A1 (JACKSON el al) 13 February 2003 (13.02.2003) entire document	20, 21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
28 April 2016

Date of mailing of the international search report
17 MAY 2016

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