Nondermatophytic filamentous keratinophilic fungi and their role in human infection

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Summary

Keratinophilic fungi include a variety of filamentous fungi mainly comprising hyphomycetes and several other taxonomic groups. Hyphomycetes include dermatophytes and a great variety of nondermatophytic filamentous fungi. Most of the latter occur as saprophytes in soil, and some are plant pathogens. *Chrysosporium* species are the commonest nondermatophytic filamentous fungi and are predominantly recovered from soil and other natural substrata by hair-baiting technique. *C. tropicum* and *C. pannicola* have been frequently isolated from human and animal skin lesions but their etiological relationship has not been established. *Nattrassia mangiferae*, a coelomycete with its anamorph as *Scytalidium dimidiatum*, is a well known plant pathogen, and has been frequently reported during the last three decades as an etiological agent of human skin and nail infections. Another species of *Scytalidium*, viz. *S. hyalinum*, regarded as an albino mutant of *S. dimidiatum* has also been frequently known to cause similar infections. *Phoma*, another coelomycete, includes several species pathogenic to humans. Among other nondermatophytic filamentous keratinophilic fungi known to cause human infections are species of *Fusarium, Scopulariopsis, Aspergillus, Geotrichum, Alternaria, Curvularia, Onychocola, Microascus, Aphanoascus* and *Chaetomium*. Several species of gymnoascaceous fungi, viz. *Ctenomyces serratus, Gymnoascus reesii, G. intermedius* and *Gymnascella dankaliensis* are often isolated from soil by hair-baiting technique; they have also been occasionally recovered from human skin lesions but without any evidence of etiological relationship. The criteria considered important for evaluating the role of nondermatophytic filamentous fungi in skin infections are the demonstration of mycelial elements in direct microscopy of skin scrapings or biopsy compatible with those in culture, repeated positive cultures from clinical material, and the exclusion of infection due to a dermatophyte or a fungus other than the one in question.

Key words

Keratinophilic fungi, Nondermatophytic fungi, Filamentous fungi, Keratinolytic ability, Human infection

Keratinophilic fungi are a group of fungi that colonize various keratinous substrates and degrade them to components of low molecular weight. These include a host of filamentous fungi representing mainly hyalohyphomycetes and several other taxonomic groups, and some species of yeast-like fungi. Most of the keratinophilic fungi, viz. species of *Chrysosporium*, *Fusarium Aspergillus*, *Scopulariopsis*, *Curvularia* and *Alternaria* etc. are common saprophytes in soil and plant debris; some of them are often recovered as laboratory contaminants. Many keratinophilic fungi frequently parasitize keratinous tissue, viz. skin, nails and hair in man and animals; some of them share certain morphological features, constituting a special group called dermatophytes. The dermatophytes comprise three genera: *Microsporum*, *Trichophyton* and *Epidermophyton*. Most species of dermatophytes are anthropohilic or zoophilic in their natural habitat, while some occur in soil as saprophytes and are termed geophilic dermatophytes eg. *Microsporum gypseum* and *Trichophyton terrestre* [1,2]. Some species of keratinophilic fungi, like *Nattrassia mangiferae* (Syn. *Hendersonula toruloidea*) and *Phoma* species, are primarily plant pathogens [3,4]. Over the last three decades, an increasing number of nondermatophytic filamentous fungi have been recognized as agents of skin infections in humans and animals producing lesions clinically similar to those caused by dermatophytes [2-5]. Several investigators have demonstrated that, like dermatophytes, nondermatophytic filamentous fungi can also degrade keratin *in vitro* and produce proteolytic enzymes including keratinase [6,7]. This paper attempts to review concisely the present state of knowledge of the biology and ecology of different taxonomic groups of non dermatophytic filamentous keratinophilic fungi and their role in human infection. The yeast-like keratinophilic fungi are not included in the review.

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Chrysosporium spp.

Chrysosporium species are common soil saprophytes of world wide occurrence and are the predominant fungi recovered from soil by conventional hair-baiting technique [8]. The commonest *Chrysoporium* species are *C. indicum*, *C. tropicum* and *C. keratinophilum* [9-10]. *Chrysosporium* species have also been recovered from hair coats of rodents [11-13], laboratory and domestic animals [14], and foxes [15], from wool [16], feathers of migrant birds [17], wild birds and domestic fowl [18] and from hooves and horns of goats and sheep [19]. Over the last two decades many new *Chrysosporium* species have been reported [20-22]. The capacity of *C. tropicum* to utilize keratin has been proven by Deshmukh and Agarwal [23] by showing loss of dry matter in culture substrates. There have been some studies on the mechanisms of colonization of human hair and breakdown of keratin by *Chrysosorium* species [6] but the ultrastructural details of the process are not known. However, these mechanisms have been adequately studied in dermatophytes. A study by Fusconi and Filipello-Marchsio [24] on the ultrastructural aspects of the demolition of human hair *in vitro* by *C. tropicum* indicated that the mechanical and physiological processes involved were similar to that in dermatophytes. Like dermatophytes, *C. tropicum* has strong keratinolytic activity and can destroy both cuticle and cortex of the hair, producing big empty zones of lysis. In the cuticle the sequence of digestion is as follows: intercellular material, cytoplasmic membrane, endocuticle, exocuticle, layer A, and a thinner layer below the inner cytoplasmic membrane of the cuticle cells. In the cortex, the order was: cementing material, plasmelemma, intermacrofibrillar material, microfibrils and matrix of the microfibrils. A different mode of attack with radial penetration of the various layers in disregard of degree of keratinization was also observed [24]. Though some species of *Chrysosporium*, viz. *C. tropicum C. keratinophilum* and *C. pannicola* have been frequently isolated from human and animal skin lesions, the etiological relationship has not been conclusively established [3].

Nattrassia mangiferae and *Scytalidium hyalinum*

Nattrassia mangiferae (formerly known as *Hendersonula toruloidea*) is a well recognized plant pathogen causing branch wilt, canker and dieback disease of a wide range of trees, and storage rot of tubers of plants such as yam [4]. Its occurrence in soil has not been established. The species is classified in a coelomycete genus because of potential production of pycnidial fruiting bodies on special media. Pycnidia are spherical, uni- or multilocular, later becoming confluent. On routine media such as Sabouraud agar, it grows as hyphomycetous anamorph, *Scytalidium dimidiatum* characterized by black, fluffy mycelium rapidly expanding mycelium, which easily fragments into one or two celled segments called arthroconidia; pycnidia are mostly absent. Its importance as a human skin and nail pathogen was first established in 1970 by Gentles and Evans [25]. Later in 1977, Campbell and Moulder [26] described human skin and nail infection by a new species of *Scytalidium*, viz. *S. hyalinum*, a species showing some similarities to *S. dimidiatum* but not known from plants or soil. In the last three decades these species have been frequently reported in tropical countries as etiological agents of superficial skin and nail infections [27-33].

Earlier, most cases of *N. mangiferae* infection in the United Kingdom were detected in immigrants from tropical and subtropical countries of the Indian subcontinent, West Africa, West Indies and the Pacific islands, while those due to *S. hyalinum* were diagnosed in patients originating from the West Indies, Guyana and West Africa [29]. In the past fifteen years, numerous cases of human infections due to these two fungi have been reported in the known endemic areas [28,31-34]. Epidemic occurrence of foot infections due to these species has also been described in coalminers and cement factory workers in Nigeria [32,34]. In general, lesions are clinically indistinguishable from those caused by dermatophytes. Itching and soreness are the most common symptoms, followed by scaling, erythema and maceration. However, inflammation is less pronounced as compared than in dermatophytic infections. The high prevalence of mycotic foot infections in coal miners and cement factory workers is caused by certain occupational factors. The wearing of heavy protective shoes, for as long as 8-10 hours a day, by these occupational groups provides a warm environment conducive to the growth of fungi. Further highly acidic mine water in coal mines and calcium oxide content of the cement help to erode the feet thus aiding fungal invasion of the skin [32,34]. *N. mangiferae* and *Scytalidium hyalinum* also cause recalcitrant toe- and fingernail infections. Nails become darkly pigmented, striated, thickened and dystrophied, often with subungual hyperkeratosis [25,26,30].

The isolates of *S. dimidiatum* can be grouped in two distinct morphological types, viz. fast-growing type A with abundant aerial mycelium and arthroconidia, and relatively very slow growing type B with little aerial mycelium and sparse arthroconidia. Type A is widely prevalent in South America, the West Indies, West Africa and the Indian subcontinent. The type B is known from West Indies, the Indian subcontinent and West Africa [32,35-36]. The relationship between plants infected with *N. mangiferae* and human infection due to this species has not been definitely established. An anthropophilic mode of transmission in human infections due to *N. mangiferae* has been suggested [34]. *S. hyalinum* is characterized by whitish, cottony or smooth colonies with golden yellow or ochraceous reverse, and hyaline one- or two- celled arthroconidia. Moore and Hay [37] have suggested that *S. hyalinum* is a mere albino mutant of *S. dimidiatum*. Molecular taxonomic studies of *S. hyalinum* and *N. mangiferae* by Roeijmans *et al.* [38] showed that ARDRA of two species was identical, thus confirming that *S. hyalinum* is a melanin-less mutant of *N. mangiferae*. This explains why two species are regularly found in the same patient population groups as agents of dermatomycoses. A study of physiological characteristics of isolates of *N. mangiferae* and *S. hyalinum* demonstrated their ability to hydrolyze casein, gelatin, urea and olive oil but not hypoxanthine, collagen or esculin [39]. The isolates of these fungi were also able to utilize all the 13- carbon and 3- nitrogen sources tested, which indicates their nutritional versatility [39]. Oyeka and Gugnani [40] demonstrated a definite ability of *N. mangiferae* (*Scytalidium dimidiatum*) and *S. hyalinum* to degrade nail keratin although the extent of degradation was relatively less pronounced than in dermatophytes. These workers also demonstrated significant proteolytic activity in clinical isolates of *N. mangiferae* and *S. hyalinum* and suggested that proteases may play a role in the pathogenesis of infection caused by these fungi by hydrolyzing keratinized tissues such as stratum corneum and nails of humans [41]. Clinical isolates of *N. mangiferae* and *S. hyalinum* are sensitive *in vitro* to several azoles, viz isoconazole, clotrimazole, fluconazole, oxiconazole and bifinazole [42]. The clinical efficacy of 1% cream of isoconazole and clotrimazole in treating foot infections due to these two species was reported by Oyeka and Gugnani [43].

Fusarium spp.

The genus *Fusarium* includes 200 species known to occur as ubiquitous soil inhabiting organisms; some of them are able to cause disease in plants, insects, reptiles, turtles and humans. *Fusarium* species are occasionally recovered from soil by hair-baiting technique [9]. They are characterized by fusiform spores and hyaline hyphae, and belong to the group hyalohyphomycetes. These organisms are considered opportunistic pathogens and at least 15 species of *Fusarium* are able to cause infections in man and animals. *Fusarium* species can cause a variety of human infections, including onychomycosis and foot infections [34,44]. So far, nearly 100 cases of onychomycosis caused by *Fusarium* species, mainly *F. oxysporum*, *F. solani* and *F. moniliforme* have been reported. The typical clinical picture in Fusarium-induced onychomycosis, is the occurrence of white superficial lesions involving the big toenail; the fingernails are very rarely involved. There are frequent cases of proximal subungual onychomycosis associated with paronychia or a distal subungual onychomycosis [45]. Some researchers have observed that paronychia associated with a proximal leukonychia is suggestive of *Fusarium* infection [46,47]. Guarro and Gene [44] have described a simple scheme for identification of medically important *Fusarium* species. Oyeka and Gugnani [40] showed that *F. solani* can degrade nail keratin *in vitro* efficiently. Marked protease activity has also been demonstrated in clinical isolates of *F. solani* [48]. Sekhon et al. [49] showed that *Fusarium* species are susceptible *in vitro* to amphotericin B, itraconazole and ketoconazole while these are resistant to 5-flourocytosine and fluconazole.

Geotrichum candidum

This fungus is ubiquitous with world-wide distribution occurring in soil, air, water, sewage, milk and milk products. It occurs as a commensal in the mouth, gastrointestinal tract and on skin. It is an occasional etiological agent of superficial infection of skin and nails [2]. Though a hyalohyphomycete, it has a teleomorph called *Galactomyces geotrichum* [50].

Scopulariopsis spp. and *Aspergillus* spp.

Propagules of *Scopulariopsis brevicaulis* are frequently present in an indoor environment. This fungus is known to degrade keratin *in vitro* [51] and is often regarded as an opportunistic secondary invader in nails after a primary dermatophyte infection. The patients present show typical subungual heperkeratosis and lysis of the distil nail plate, and occasionally total dystrophy of the affected nails associated with painful periungual inflammation [52]. Occasionally *S. brevicaulis* can cause inflammatory ringworm-type lesions on the skin [53]. Other species of *Scopulariopsis* rarely reported as etiological agents of nail infections are *S. asperula, S. acremonium, S. fusca, S. fulva,* and *S. koningii* [50].

Aspergilli are widely distributed in nature i.e. in soil, decomposing matter, and in dust. It has been demonstrated that *Aspergillus* species can utilize sulphur containing amino acids and produce sulphate from cystine [54]; they are frequently recovered from soil by hair-baiting [9]. The species of *Aspergillus* involved in human skin infections are *A. flavus* [55], *A. glaucus*, *A. niger*, *A. unguis*, *A. nidulans* [50], *A. terreus* [56] and *A. chevalieri* [57]. Doncker et al. [58] reported success with itraconazole in the treatment of onychomycosis caused by moulds like *S. brevicaulis*, *Fusarium* spp. and *Aspergillus* spp., either by continuous dosing (100 or 200 mg/day) for 6-20 weeks or by one week pulsing dose (200 mg twice daily for one or two weeks).

Hortaea werneckii (Phaeoannelomyces wernecki)

This is a dematiaceous hyphomycete which causes superficial infections of the skin, mostly of the thickly keratinized sites such as palmar surface of the hands and plantar surface of the feet, rarely on other body sites viz., neck, chest and dorsum of the hand. The lesions are erythematous, dark macular with generally no scaling. The infection has been sporadically reported world-wide but is most common in tropical and subtropical areas [2]. Initially the growth is yeast-like comprising dark-coloured oval yeast cells with occasional septa. In older cultures mycelium and conidia predominate. The fungus occurs as halophilic saprophyte in soil, and is occasionally isolated from seafish [50].

Unusual keratinophilic moulds

Apart from the above mentioned filamentous fungi, many unusual moulds have been recognized to be keratinophilic and etiological agents of skin and nail infections. These include coelomycetes like *Phoma* spp. and ascomycetes like *Onychocola canadensis, Microascus cirrosus*, *Aphanoascus* spp., gymnoascaceous fungi like species of *Ctenomyces*, *Gymnosascus* and *Gymnascella* and dematiaceous fungus like species of *Alternaria* and *Curvularia*. A brief account of these species is given below.

Phoma spp.

Several species of the genus *Phoma*, a member of coelomcytes are recognized as keratinophilic. These fungi, usually soil dwelling saprobes or phytopathogens have rarely been reported to be associated or responsible for superficial or invasive skin lesions in man. The species involved have *been Phoma cruris-hominis, P. herbarum, P. eupyrena, P. minutella,* and *P. sorghina* [50,59-61]. The patients with skin infection due to *Phoma* spp. show discrete, chronic, scaly lesions; hyaline to pale brown broad filaments radiating from a central core of cells are focally present in the stratum corneum. Cultures produce grey, fluffy colonies with the formation of brown, rounded to ampulliform ostiolate pycnidia.

Onychocola canadensis

Onychocola canadensis and its teleomorph *Arachnomyces nodosetosus* were described by Sigler and Congly [62], and Sigler *et al.* [63] as a new fungus responsible for onychomycosis. The fungus has yet not been isolated from soil or plants. Thirteen confirmed cases of *O. canadensis* infection have been described so far: seven from Canada, three each from New Zealand and France [64]. The cases have generally occurred in elderly females largely involving the big toenail. Cultures on Sabouraud agar grow very slow and form very small colonies with white floccose aerial mycelium with a brown reverse.

Microscopic examination of 7-8 days growth on 2% water agar shows numerous chains of persistent arthroconidia. Cleistothecia of *A. nodosetosus* are spherical with 3 to 8 thick walled setae about 1 mm in length. Asci are subspherical, evanescent, containing pale brown, oblate ascsopores [50].

Microascus spp.

Several cases of onychomycosis due to *Microascus cirrosus* have been described [65]. The infected nails had dark greyish bands. Light and electron microscopic histology of the infected nail plate in one case revealed perforating fungal filaments, developing perpendicularly into the keratin layers and originating from the invaded hyponychium. The genus *Microascus* is characterized by the production of ostiolated, sometimes papillated, long-necked, superficial or immersed ascocarps, which are composed of thick-walled dark brown cells. The asci are obvate-ovate, evanescent, and the asymmetrical ascospores are extruded through the ostiole as a long copper brown cirrhus. The anamoph is a species of *Scopulariopsis* or *Wardomyces* [65]. Another species of *Microascus*, viz. *M cinereus* has been isolated from clinical sources such as cutaneous lesions and onychomycosis but its pathogenicity is questionable [50].

Aphanoascus spp.

The genus *Aphanoascus* includes two well defined groups of species, one with ellipsoidal ascospores with reticulated or verrucose walls, and another with lenticular or discoid ascospores with an equiatorial rim and reticulated or pitted walls. Several species of *Aphanoascus*, viz. *A. fulvescens* (*Anixiopsis stercoraria*), *A. keratinophilum* and *A. verrucosus*, representing the first group, and *A. terreus* representing the second group have been frequently isolated from soil all over the world [9,66]. These species are keratinolytic. A study of the invasion of human hair *in vitro* by *Aphanoascus* spp. by Cano *et al.* [67] showed that *A. fulvescens* and *A. verrucosus* invade the hair through cuticle without the presence of specialized erosive organs, while in case of *A. keratinophilum* keratinolytic activity is mainly confined to the cortex, and extends later to the cuticle. The anamorph is a *Chrysosporium*. Ascocarps (cleistothecia) are spherical, non-ostiolate, buff to light brown, with pseudoparenchymatous peridium and contain 8-spored, subspherical to ellipsoid asci. Ascospores are light brown to yellowish brown in mass, irregularly lens shaped [50]. *A. fulvescens* has been recovered on several occasions as an etiological agent of dermatomycosis in man and animals [67].

Chaetomium globosum

This species is a common soil saprophyte and an occasional laboratory contaminant. It is infrequently isolated from soil by hair-baiting technique [9]. A few cases of cutaneous infection and onychomycosis due to this fungus have been reported [50].

Gymnoascaceous fungi

Several species of gymnoascaceous fungi, *Ctenomyces serratus, Gymnoascus reesii, G. intermedius* and *Gymnascella dankaliensis* are often recovered from soil by hair-baiting technique. These species can degrade keratin. *C. serratus* (anamorph *Myceliophthora vellerea*) is found on feathers and in soil- harbouring feathers or other keratinaceous materials [68,69]. *G. reessii* and *G. intermedius* are coprophilous but they are frequently isolated from soil enriched with the dung of herbivores by hair-baiting technique [9,50]. None of these fungi has been proven to be an etiological agent of infection in man or animals.

Alternaria spp.

Alternaria species are ubiquitous soil saprophytes and common plant pathogens. A review of literature up to 1986 revealed 33 cases of human infections due to *Alternaria* spp. [70]. Cutaneous infections due to *Alternaria* species, *A. alternata, A. tenuissima* and *A. chlamydospora* have been reported from several parts of the world. These infections have often been associated with debilitating diseases or conditions [70,71]. After 1986, a few cases of human cutaneous infection due to *A. alternata, A. humicola*, and *A. pleuriseptata* have been reported [71,72]. The clinical appearance of skin lesions was similar to those caused by dermatophytes. In KOH preparations of scrapings from skin and nail lesions and in tissue sections of the lesions, dematiaceous septate hyphae were observed. Three cases of onychomycosis, one each caused by *Alternaria humicola, A. pluriseptata*, and *A. alternata* have also been described. The affected nails were dystrophic, black and raised with subungual hyperkeratosis. Cases of skin infection due to *Alternaria* spp. have also been described in cats [73] and equines [74].

Curvularia spp.

Curvularia species are ubiquitous species present in soil and on plant material. They are occasionally recovered from soil by hair-baiting technique [9]. They rarely cause superfical infections of skin and nails in man. The species involved are *C. lunata* [75] and *C. clavata* [76]. In the KOH preparations of skin lesions, pale brown, septate hyphae with slightly contorted branches are seen [76].

Conclusion

It is apparent that there are numerous nondermatophytic filamentous keratinophilic fungi belonging to diverse taxonomic groups. The ability of these fungi to invade and parasitize tissues is associated with and depends upon use and breakdown of keratin. However, it must be realized that the reverse is not true. A great variety of non-dermatophytic filamentous fungi can utilize keratin for their growth and are strongly keratinolytic with no concrete evidence of their pathogenic role; their mere isolation in culture from lesions on skin or other sites should not ascribe them any etiological significance. The spores of numerous species of fungi can be transient contaminants or residents in the skin lesions of nonspecific etiology, and can appear in pure culture in the scrapings from the lesions. Also, the spores of these fungi may occasionally be seen in KOH mounts of the skin scrapings. This often leads the inexperienced investigator to assign them a pathogenic role. Three important criteria should be used to evaluate the role of a nondermatophytic filamentous mold in skin infection. Direct microscopy of skin scrapings or biopsy from the lesion should demonstrate mycelial filaments compatible with those in culture. Multiple inocula, preferably at least three out of many should reveal the same organism on repeated culture of the clinical specimens from the lesions. Lastly infection due to a dermatophyte or another fungus other than the one in question should be ruled out. With time, many more nondermatophytic filamentous keratinophilic fungi with potential to cause skin infections in man and animals are likely to be discovered. Skin and nail infections due to certain nondermatophytic filamentous fungi are often recalcitrant to treatment; newly known antimycotics should be tried to treat such infections. Investigation of proteolytic enzymes including keratinases of these fungi is an area where further research is needed.

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