



Dermatophytosis caused by *Nannizzia nana* (*Microsporum nanum*): a comprehensive review on a novel pathogen

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Abstract

Keratinophilic fungi are mostly soil-inhabiting organisms with occasional infections in humans and animals. Even though most dermatophytes are host-adapted, cross-species infections are common by zoophilic and geophilic dermatophytes. *N. nana* is considered an etiological agent of ringworm in pigs but has also been isolated from other animals, including humans. However, it also possesses many characteristics of geophilic dermatophytes including the ability to grow in soil. *N. nana* produces characteristic pear-shaped macroconidia and usually exhibits an ectothrix pattern of hair infection. It has been isolated from dermatitis lesions as well as from soil. *N. nana* infections in pigs are not of much concern as far as economy or health is concerned. But it has been associated with onychomycosis and gonathritis in humans, which are significant in human medicine. The shift in the predominance of dermatophytes in humans and the ability to evolve into a potential tinea pathogen necessitates more understanding of the physiology and genetics of *N. nana*. In this review, we have attempted a detailed analysis of the studies about *N. nana*, emphasizing growth and cultural characters, physiology, isolation, infection in humans and animals, molecular characterization and antifungal susceptibility.

Keywords *Microsporum nanum* · *Nannizzia nana* · Dermatophytes · Cross-species infection · Ringworm · Skin disease

Introduction

Dermatophytes are molds that are keratinophilic and keratinolytic in nature and are associated with tinea or ringworm in humans and animals, respectively. Dermatophytes are

thought to be evolved into facultative or obligatory parasites from soil-inhabiting keratinophiles [1]. Earlier, dermatophytes were classified into three genera: *Microsporum*, *Trichophyton*, and *Epidermophyton*. Recently, based on a multilocus phylogenetic analysis dermatophytes are divided into seven genera: *Trichophyton*, *Epidermophyton*, *Nannizzia*, *Paraphyton*, *Lophophyton*, *Microsporum*, and *Arthroderma* [2]. They are also classified based on their ecological preferences: zoophiles, anthropophiles, and geophiles. Zoophilic dermatophytes like *M. canis*, *T. verrucosum* mainly affect animals, and anthropophilic dermatophytes like *T. rubrum*, *T. tonsurans* have an affinity toward humans. Geophilic dermatophytes such as *N. gypseae* can grow and multiply in the soil without any host preference but occasionally produces diseases in both humans and animals. The anthropophiles and zoophiles are considered to be evolved from soil-dwelling geophiles [3]. Dermatophytes are present throughout the globe, including regions with harsh climatic conditions [4], and have been isolated from animals [5, 6], humans [7], and soil [8]. The presence of dermatophytes in the soil can be interpreted in two ways: soil-inhabiting geophilic dermatophytes with the ability to propagate in the

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soil [9] or those shed from the host animal and remaining dormant in the soil within the tissue debris for a particular period [10]. In both ways, soil can act as a source of infection to the host with spores of actively multiplying geophilic dermatophytes and dormant spores of zoophilic/anthropophilic dermatophytes [11, 12]. Certain species of dermatophytes can infect humans through contact with animals and soil [13]. *N. nana* is one such dermatophyte that can infect humans from soil and their preferred host, pigs [14–16]. Even though the occurrence and severity of ringworm infection due to *N. nana* is not a matter of serious concern in the current scenario, it has the potential to evolve into a predominant pathogen due to its geophilic and zoophilic nature [17, 18].

The present review aimed to analyze the studies about *N. nana*, emphasizing growth and cultural characters, physiology, isolation, infection in humans and animals, molecular characterization, and antifungal susceptibility.

***Nannizzia nana*—geophile or zoophile?**

Microsporium nanum was first isolated from an inflammatory lesion of the scalp of an 8-year-old boy. The isolate was initially identified as a dwarf form of *Microsporium gypseum* and named *M. gypseum* var *nanum* [19]. Later, a second isolate showing similar properties to the first one was isolated and thus, a separate species from *M. gypseum* named *M. nanum* was accepted [20]. A recent phylogenetic study has reclassified *M. nanum* into *Nannizzia nana* [2]. Earlier, the genus *Nannizzia* was introduced to include only the teleomorphs or sexual states of dermatophytes. But based on molecular studies, it has now considered as a separate clade and the genus *Nannizzia* includes several geophilic and zoophilic species, namely *N. gypsea*, *N. fulva*, *N. aenygmaticum*, *N. corniculata*, *N. duboisii*, *N. incurvata*, *N. persicolor*, and *N. praecox* [21]. In contrast, the genus *Microsporium*, in which *N. nana* was earlier grouped, includes three species namely *M. canis*, *M. audouinii*, and *M. ferrugineum* [2].

The ecological preference of *N. nana* is still debated and has been classified both as a geophile and pig-adapted zoophile in various literatures [17, 18]. Even though it is known that certain dermatophytes have developed an affinity towards a particular host, the mechanism associated with host adaptability is not clearly understood. However, the species of dermatophyte involved, the host, and the environment may play a role in the process of developing affinity or adaptability. Dermatophytes were initially soil saprophytes, and during the evolutionary course, some species started utilizing keratin from the living host. Thus, species such as *N. nana* and *Trichophyton quinckeanum* started colonizing and utilizing the keratin substrate of pigs and mice, respectively living close to the soil [18]. Otčenašek and Dvořák,

1975 [17] categorized *N. nana* as a ‘species strongly specialized (susiophilic) paratrophic (pathogenic)’ dermatophyte. However, *N. nana* can also survive in the soil as a saprophyte, not as a contaminant. Macroconidia of *N. nana* have been isolated from the supernatant of soil collected from pig lots [22] which indicate that *N. nana* can multiply and sporulate in the soil as a saprophyte and thus can be considered a geophilic dermatophyte that has a specific affinity for swine and swine habitats [22]. In addition, the abundance of macroconidia production decreases in the order of geophilic, zoophilic, and anthropophilic dermatophytes [18]. *N. gypsea* produces abundant ellipsoidal macroconidia with rounded ends [23]. *N. nana* produces a large number of pear-shaped macroconidia in cultures, a characteristic feature of geophilic dermatophyte.

Geophilic dermatophytes can utilize the keratinous substrates present in the soil and propagate through various modes of reproduction. Zoophilic dermatophytes exhibit poor saprophytic growth and remain in the soil in a dormant state on the contaminated hair or scabs from the host. Whole genome sequence analysis has revealed that geophilic dermatophytes have their genome enriched with genes of virulence and metabolism, many of which have been lost in the zoophilic and anthropophilic dermatophytes during the course of adaptation to their respective hosts [24]. Since *N. nana* can survive both in soil and host body, the genome repertoire will be between a zoophile and geophile to maintain the genes required for survival in both soil and host body. Even though most dermatophytes exhibits variations in their ecological preferences, most of them secrete similar types of enzymes; however, the amount of enzyme production varies with each species [25]. The enzyme production can vary with the ambient temperature also. The maximum keratinase production in geophiles occurs at around 30 °C whereas zoophiles and anthropophiles exhibit maximum keratinase production at a temperature range of 35–40 °C, which indicates the host adaptation [26]. So, it can be assumed that *N. nana*, which can survive in both soil and pigs, may have different enzyme production profiles while propagating as a saprophyte and as a parasite.

The development of affinity towards a particular host keratin was considered a major reason for the host adaptability of dermatophytes [27]. Apart from the enzymes required for keratinolysis, dermatophytes also secrete a variety of other proteinases. The host skin and superficial structures will contain proteins other than keratin, which the dermatophyte will also degrade. Geophilic dermatophytes such as *N. gypsea* produce more enzyme elastase than zoophiles and anthropophiles, which will degrade the elastin present in human and animal skin [28]. This high elastase production can be attributed to the severe inflammation associated with geophilic dermatophytes. It should also be noted that *N. nana* produces severe inflammatory reaction in humans [14] while

producing mild inflammation in pigs indicating its geophilic nature and adaptation to pigs, respectively. Other than the enzyme production profile, the attachment of dermatophyte propagule to host tissue also plays a very important role in colonizing the host tissue. Dermatophytes may vary in the number and types of adhesion proteins present, which may also influence host adaptability [24]. Thus, in the course of evolution, dermatophytes developed an affinity towards particular host tissue determined by the keratin content and associated protein components and the binding ability of the dermatophyte propagule. The soil inhabitants may also have played some role in the evolution of the dermatophytes from geophilic to parasitic life [29, 30]. Soil-dwelling keratinophilic fungi like *Chrysosporium keratinophilum* produces anti-dermatophytic substances and might have influenced the evolution of dermatophytes into host-adapted zoophiles and anthropophiles [30]. In view of these facts, it can be assumed that *N. nana* has developed an affinity towards pig tissue while retaining the genes required for survival in the soil as a saprophyte. Since *N. nana* exhibits the properties of both geophiles and zoophiles it can be considered a link between these two classes of dermatophytes.

Isolation of *N. nana* from animals, humans, and soil

N. nana is considered to prefer pigs as their major host and infection in pigs has been reported in Europe [31], North America [32], and New Zealand [33]. It has also been attributed to the outbreaks of ringworm in Iberian pigs in Spain [34]. Apart from pigs, *N. nana* has been isolated from healthy and diseased domestic animals across the globe (Table 1). The isolation of *N. nana* from healthy animals indicates their ability to survive in a dormant form in the host body or the animal might have acquired it as a contaminant from the soil. Chances of acquiring *N. nana* infection

are higher in animals having close contact with soil, especially pigs inhabiting regions. This again underlines the dual nature of *N. nana* to propagate in the soil while maintaining a special affinity towards pig. Since *N. nana* can grow as a saprophyte, it can survive for an extended period once introduced into the soil. In general, the prevalence of *N. nana* infection is low in animals compared to other zoophiles and geophiles. Even in pigs the rate of isolation of *N. nana* is low. This reduced isolation rate of *N. nana* from pigs may be due to the less evident clinical signs that may go unnoticed. Hence, *N. nana* can be considered a low virulent pathogen in pigs.

Ringworm in humans due to *N. nana* has been reported in various countries like Brazil [35–38], Canada [39], Africa [40], South Australia [41], India [42, 43], Romania [44], and Victoria [16]. Pig rearing has been considered the major infection source in humans [45]. Close contact with the animals will help transmit *N. nana* from symptomatic and asymptomatic pigs. At the same time, cases of *N. nana* infection have been reported in humans with no contact with pigs, indicating the soil propagating ability of *N. nana* [15]. However, ringworm infection in humans from pigs or soil is rare compared to other dermatophyte infections. A survey for the prevalence of dermatophytoses in humans for a period of 3 years (1979–1981) in the USA could isolate *N. nana* only three times during the study period [46]. Similarly, the survey conducted in the USA from 1982 to 1984 and 1993 to 1995 in human patients isolated zero and one isolate of *N. nana* during the study period, respectively [47, 48]. A low prevalence of *N. nana* infection in humans has also been reported from other parts of the world. A study on the prevalence of dermatophytoses in humans over 9 months conducted in Sana'a, Yemen Republic, identified 157 out of 1100 patients exhibiting clinical signs of tinea corporis, tinea capitis, tinea cruris, tinea unguium, and tinea pedis as positive for dermatophytes [49]. However, only two patients suffering from tinea corporis yielded *N. nana* on culturing. In a 2-year study conducted in Southern Taiwan among 375 patients with onychomycosis, the etiological agents of onychomycosis were identified as dermatophytes (227), *Candida* species (1180), and non-dermatophytic molds (30) [50]. Two of the onychomycosis cases were found to be caused by *N. nana*. A retrospective study identifying the etiology of onychomycosis in humans detected 1 out of 4220 cases of onychomycosis due to *N. nana* [51]. Even though these two studies reported very low prevalence of *N. nana* in humans; it also indicates the ability of *N. nana* to affect nails. The low isolation rate of *N. nana* from humans cannot be attributed to a single reason. Misdiagnosis of *N. nana* infection can be a prime reason as the etiological agent is not well studied and characterized [15]. Restricted rearing of pigs and lack of exposure to pig habitat or soil due to better hygienic practices in modern society can also be a reason.

Table 1 Reports of *Nannizzia nana* isolated from animals

Country	Healthy animals or animals with skin lesions	No. of animals positive for <i>N. nana</i>	Reference
New Zealand	Skin lesions	4 pigs	[5]
Jordan	Healthy animals	1 cow, 2 rabbits and 1 cat	[108]
Jordan	Healthy animals	4 sheeps	[109]
Nigeria	Skin lesions	7 pigs	[110]
Western Turkey	Skin lesions	2 dogs 6 cats	[111]
Eastern Turkey	Healthy animals	3 van cats	[112]
Egypt	Skin lesions	4 camels	[113]

At the same time, there are reports of transmission of *N. nana* infection to humans from cows indicating the ability of *N. nana* as a potential pathogen to humans with multiple sources of infection [52].

N. nana has been isolated from the soil of different countries across the globe. But their prevalence as soil saprophytes is low as compared to other geophilic dermatophytes (Table 2). It has been isolated from various geographical regions such as glacier banks, valleys, and mountains stipulating its ability to survive in soil of different compositions and temperatures [4, 53]. In many studies, the presence of pigs has been attributed to the isolation of *N. nana* from the soil [53]. Limited information is available on the nutrient requirement and conditions required for the growth and development of *N. nana* in the soil. The presence of organic matter is inevitable for survival in the soil as *N. nana* has not been isolated from sandy soil and hot arid regions [54, 55]. Soil pH is major factor, which influences the growth of keratinophilic fungi, including dermatophytes. *N. nana* has been isolated from soil with a slightly alkaline pH (7.02–9.06) but not from acidic soil [10]. But *N. gypsea* has been isolated from soils with a pH range of 5.77–8.31, specifying its ability to survive in a wider range of pH unlike *N. nana*. The moisture content of the soil is another critical factor for the growth of geophilic dermatophytes. *N. gypsea* could grow in less than 5% moisture content, and soil with moisture content greater than 20% will not favor its growth [56]. Since *N. nana* can survive in the soil, and share characters of geophiles, it can be attributed that the moisture requirement will be more or less similar to *N. gypsea*. In general, dermatophytes capable of propagating in the soil are osmotolerant, have urease activity, are independent of the exogenous sources of vitamins and amino acids, and constitutively secrete protease enzymes [57]. Since *N. nana* survives and multiplies in soil, it might be harboring these intrinsic properties of a geophile, still extrinsic factors such as presence of pigs, pH, organic content, and moisture of the soil along with climatic conditions also significantly influence the survival of *N. nana* in the soil.

Table 2 Reports of *Nannizzia nana* isolated from soil

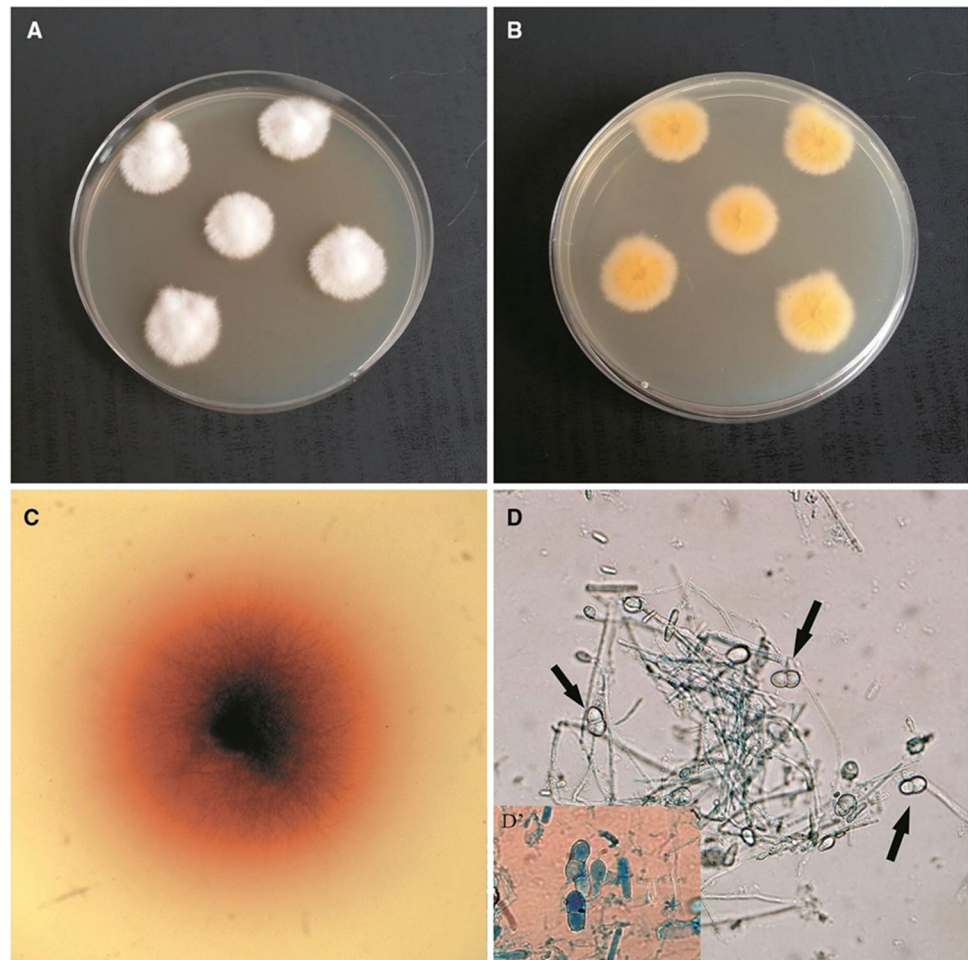
Country	Number of soil sample examined	No. of samples positive for <i>N. nana</i> out of total samples	Reference
India (Lucknow)	94	1	[8]
India (Madras)	45	3	[114]
India (Kashmir)	107	2	[4]
Jordan	30	3	[53]
Brazil	212	4	[10]

Growth and physiology

N. nana can be isolated from infected hair/ skin scrapings using Sabouraud's Dextrose Agar supplemented with cycloheximide and chloramphenicol. Penicillin and Streptomycin have also been used to prevent the growth of bacterial contaminants [19]. The growth usually appears around the 4th day of incubation [19]. The colonies will be initially whitish cottony with an orangish reverse side but later, around the 11th day, become granular and buff-colored with a brownish-red reverse side (Fig. 1A–C). Macroconidia are abundantly produced, but few microconidia are observed. Microscopically, the macroconidia (13–29 × 8–13 μm) are usually clavate to obovoid shaped with one or two septa and are thin verrucose walled with projections and truncate base [21] (Fig. 1D, D', Fig. 2). Many macroconidia may be borne on a single stalk. Spherical, elliptical and aseptate macroconidia may also be produced. Microconidia (3–7 × 2–3 μm) usually will be ovoidal or clavate in shape. The macroscopic and microscopic characteristics of the colonies do not alter with the agar used for isolation [19]. Racquet hyphae, pectinate hyphae, and intercalary chlamydospores can also be observed microscopically. *N. nana* can also be characterized by various laboratory and biochemical tests such as growth in dermatophyte test medium (DTM), ability to grow in the presence of cycloheximide and 5% NaCl, urease production, lipase activity in tween 80 opacity test medium, milk hydrolysis in bromocresol purple-milk solids-glucose agar (BCP-MS-G agar), beta-hemolysis in blood agar and ability to grow at 37 °C [21]. *N. nana* isolates produce reddish discoloration in DTM and can grow in presence of cycloheximide and 5% NaCl. Most of the isolates produce urease enzyme and exhibit lipase activity. They give variable results in milk hydrolysis and produce beta-haemolysis after 2 weeks of incubation. Most isolates can grow at 37 °C, depicting its thermo tolerance [15]. Thus, the colony morphology, abundance in macroconidia production, and the enzyme activity of *N. nana* classify it more towards the geophilic group. But, the ability to grow at 37 °C indicates their thermotolerance and infectivity towards mammalian skin as certain geophiles such as *Arthroderma uncinatum* grow well at 25 °C but are unable to grow at 34 °C or above [24].

The preferred substrate for the growth of dermatophytes is the keratinous structures present in the host body or the soil. Most zoophiles and anthropophiles degrade keratin slower than geophilic dermatophytes [58], indicating the ability of the geophiles to assimilate nutrients efficiently and grow faster. Keratin is a fibrous protein present in mammals, birds, and reptiles [59]. There are two types of keratin-alpha keratin (which contain alpha helix) and

Fig. 1 Micro- and macroscopic morphology of *Nannizzia nana*. **(A)** Obverse of *N. nana* culture. **(B)** Reverse of *N. nana* culture. **(C)** Reddish discoloration on Dermatophyte Test medium due to *N. nana* growth. **(D)** Micro-morphology of *N. nana*, arrows indicate characteristic macroconidia ($\times 400$) **(D')** Macroconidia stained with lactophenol blue ($\times 1000$). Reproduced from Gnat *et al.* 2020 [15] under a Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>)



beta keratin (which contains beta pleated sheets). Most of the keratinous structures are a mixture of alpha and beta keratin with varying proportions. Keratin also contains disulfide bridges providing rigid structure. There are variations in the amino acid composition of keratin in hair, epidermis, and epithelium [60]. Also, the degradability of the host keratin depends on the cystine content, which determines the hardness of the tissue. *N. nana* produces abundant growth in hair and fair growth in the toenails [19]. Even though both hair and toenails are made up of hard keratin, the difference in the affinity of *N. nana* towards both may be due to the presence of proteins other than keratin [61]. *N. nana* also exhibits differential preference toward nutrients as it can utilize aspartic acid, arginine, citrulline, alanine, ornithine, histidine, and proline but cannot utilize phenylalanine, cysteine, hydroxyproline, and methionine [62]. It can utilize a limited number of carbohydrates as a carbon source and will not grow in starch-containing media [62]. Thus *N. nana* exhibits selectivity in its nutrition. However, it can utilize keratin from different hosts apart from pig keratin. It was found that *N. nana* grew equally on human, horse, and pig hair [22]. Also,

N. nana can utilize keratin from chicken feathers [63]. So, it can be considered that *N. nana* retains the ability to utilize keratin from different hosts like geophiles, but has a slighter affinity toward pig tissue. As all recognized dermatophytes produce keratinases, the preference towards pigs may be due to the presence or absence of other proteins and the physiological conditions prevailing in the pig skin surface. This has to be validated by expression studies of proteases and analyzing the enzyme production profile both in the soil and host tissue.

Most recognized dermatophytes exist in two sexual states: anamorphic (asexual or imperfect) and teleomorphic (sexual or perfect). Adaptation to the host has a critical impact on the sexual dimorphism of dermatophytes. Most anthropophilic dermatophytes reproduce asexually as they now possess one mating type due to the selection pressure during the adaptation process [64]. Even though zoophiles have both mating types; particular mating type predominance indicates the gradual shift to asexual reproduction [64]. But geophiles possess both mating types in equal proportion and reproduce both by sexual and asexual methods [65]. Dawson and Gentles, 1962 [66] studied sexual reproduction in *N. nana*

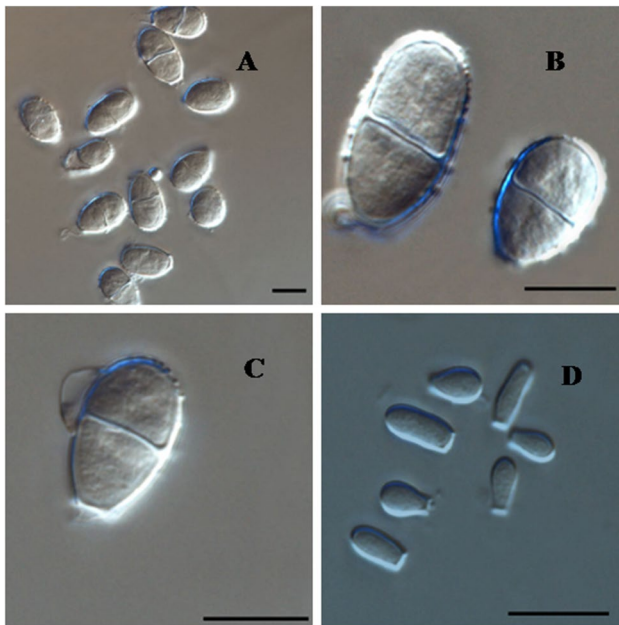
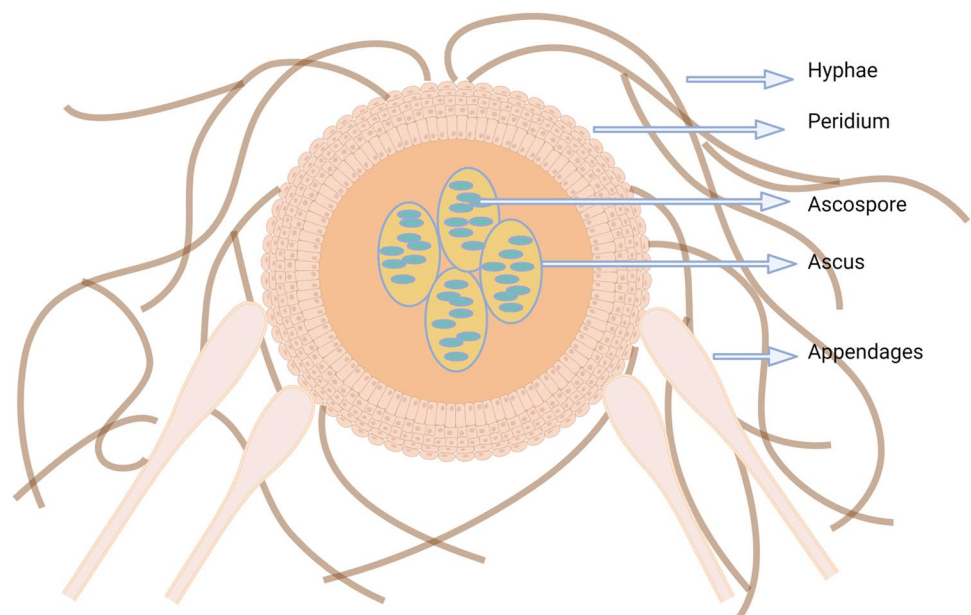


Fig. 2 Conidia produced by *N. nana*. (A–C) Macroconidia. (B) Microconidia. Scale bars = 10 μm . Reproduced from Dukik *et al.* 2020 [21] under a Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0>)

and proposed *Nannizia obtusa* as the perfect stage. They produced cleistothecia (Fig. 3) by crossing a Cuban and Korean isolate of *N. nana* and identified it as heterothallic. Fewer cleistothecia are produced and require a longer incubation period and lower temperature. The sexual stages are characterized by echinulate peridial cells, special appendages at terminal peridial cells, absence of disarticulation of peridial cells at maturity, dichotomous and verticillate

Fig. 3 Schematic representation of cleistothecia. Image created using Biorender.com



peridial hyphae, and obtuse angle between the branches and main hyphae. Asci are sub-globose with eight-spored, and ascospores are lenticular in shape [66]. The sex-determining region in the genome of dermatophytes is the mating type locus (MAT). There are two idiomorphs of MAT, namely MAT1-1 and MAT1-2 [67]. But the idiomorphs in *N. nana* have not been determined. The type and frequency of the idiomorphs among the *N. nana* population have to be studied to understand whether the distribution pattern is similar to that of geophiles or imbalanced, as in zoophiles.

Clinical signs and lesions

The inflammatory response associated with dermatophyte infection is mainly towards the proteases secreted by these fungi. However, a cutaneous immune response may also develop toward the cell wall components. Interestingly, the dermatophytes exhibit variations in the composition of their cell wall. The cell wall polysaccharide composition of geophilic dermatophytes was studied by Guarro *et al.* 1993 [68]. Glucomannan and glucan-chitin complex was identified as the major polysaccharide fraction of the cell wall of geophilic dermatophytes. *N. nana* exhibits a slight deviation in the cell wall composition compared to geophiles. Xylose was absent in the water-soluble fraction of the cell wall in *N. nana*, when compared to *N. gypseae*. Also, the galactose to glucose ratio in the water-soluble fraction was high in *N. nana* whereas the ratio was low in *N. gypseae*. These variations in the cell wall composition may reflect in the inflammatory response towards *N. nana* and *N. gypseae* in the host.

The pattern of hair infection varies with the species of dermatophyte involved. *N. nana* usually causes ectothrix

infection of hair, but favic and endothrix type of hair infection has also been reported [19, 69]. Electron microscopic examination of hairs infected with *N. nana* has revealed an ectothrix type of infection [70], which is the common mode of hair infection by *N. nana*. It gives variable results in Woods lamp analysis but majority being Woods lamp negative [19, 22, 71]. This may be due to the strain variations in the ability to metabolize tryptophan or false positive results. *N. nana* can produce wedge-shaped penetrations in human hair [45], signifying its ability to produce perforating organs, a characteristic feature of geophiles. But in an experimental infection on human models, the hairs were enmeshed with hyphae without any penetration [20]. These variations in the infection pattern of hair and tryptophan metabolism indicate heterogeneity among the population of *N. nana*.

The clinical course and lesions produced by *N. nana* depend on the host affected. In pigs, *N. nana* produces lesions mainly in the shoulder, flank, udder, neck, and behind the ears. Brownish crust formation without any signs of alopecia and pruritis is seen primarily in pigs [22, 72]. Lesions originate as small dark circles with crusts and progress in a circular fashion. Later, these lesions will coalesce and cover larger body regions [34]. Physiological status, sex, and age may influence the outcome of *N. nana* infection in swine [34]. Exudates formation is not common in *N. nana* infection but has been reported in pigs, suggesting the difference in the virulence pattern of *N. nana* strains [73]. In sows, ringworm infection due to *N. nana* can be complicated by acanthosis [74]. Unlike *N. nana* infection, other dermatophytes can evoke more severe inflammatory responses in pigs [75]. The pigs infected with *M. canis* exhibit alopecia and pruritis [76]. Roughening of the body surface can be seen in *Trichophyton mentagrophytes* infection in pigs [77]. The difference in clinical signs and inflammatory response produced in pigs by *N. nana* and other dermatophytes emphasizes the adaptation of *N. nana* towards swine. All known dermatophytes produce keratinases [78]. Even though the amino acid sequence of the proteases is conserved among the dermatophytes, they secrete variable amounts of the same enzyme [25]. The process of keratinolysis starts with sulfitolysis where the disulfide bonds are destroyed [79]. This is followed by keratin proteolysis carried out by the sequential action of endopeptidases such as fungalysin and subtilisins and exopeptidases such as aminopeptidases and carboxypeptidases [79]. Apart from the enzymes associated with keratinolysis, dermatophytes may vary in the secretion of other proteases such as elastase, which determines the inflammatory nature of dermatophytosis. It has been identified that dermatophytes produce less proteases in the host to which they are adapted but produce a large amount of enzymes in other host species [80]. The protein secretion profile will depend on the habitat of the dermatophyte, and it, in turn determines the level of inflammatory reaction in the host

[81]. Thus, *N. nana* qualitatively and quantitatively produces enzymes in pigs in such a way to avoid severe inflammatory reactions and thereby survive for a longer period.

N. nana can also infect hosts other than pigs but vary in the inflammatory response. In an experimental infection study, the human model exhibited erythematous pustular lesions, whereas in kittens and guinea pigs, scaly and crusty lesions were noticed [19]. Variation was also observed in the duration of regression of the lesions. The lesion started regressing after 5 weeks in humans, whereas the lesion lasted for only 2 weeks in kittens and guinea pigs. Histopathological study of *N. nana* infected guinea pig skin revealed hyperkeratosis of the epidermis, spongiosis, and excoriations with normal hair follicles, dermis, and subcutaneous tissue. Thus, even though *N. nana* can infect heterologous hosts more intense inflammation may be produced in species distantly related to pigs. But it was also found that *N. nana* was unable to infect monkeys [19], indicating the requirement of specific physiological conditions or protein adhesins to establish the infection in the host body. In humans, anthropophilic dermatophytes produce low-intensity inflammation, zoophiles produce moderate inflammation and geophiles produce high-intensity inflammation [82]. *N. nana* produces more intense skin infections in humans than in pigs. The common lesions in humans include erythema, pruritis, scale formation, and lustreless and brittle hair [19, 71]. But it has also been associated with more severe conditions such as mycoses of the submandibular region and associated exudative gonarthrtis in humans [52]. Pustules and hyperkeratotic crust were observed in the chin area, along with inflammation of submandibular lymphatic glands. The association of *N. nana* with these clinical signs was confirmed by isolating the organism from the clinical samples. *N. nana* can also be associated with tinea corporis [7] and inflammatory tinea faciei and tinea cruris [14]. Severe itching with a burning sensation has been reported in humans [15]. Even though nail infections are not common in *N. nana* it has been associated with total dystrophic onychomycosis and recurrent onychomycosis [15, 51]. Onychomycosis due to *N. nana* may be due to simple invasion by mechanical action [83] or the ability of certain strains to degrade nail tissue. Thus, the clinical spectrum of *N. nana* infection in humans is wider than that in pigs and has the potential to emerge as a major cause of tinea in the due course of time.

Molecular characterization

Most dermatophytes can be identified by their morphological and microscopic characteristics. But, the emergence of genotypes and strains associated with a particular geographical region and antifungal resistance has necessitated the molecular characterization of dermatophytes [84]. For

example, *N. nana* can be distinguished easily by the microscopic examination and identification of the characteristic pear-shaped macroconidia. But, certain non-dermatophyte fungi, such as *Trichothecium roseum*, also have morphologically similar macroconidia, often resulting in misidentification [85] (Fig. 4). Also, heterogeneity has been detected among the strains of *N. nana* [15], which further emphasizes the need for molecular characterization of *N. nana*.

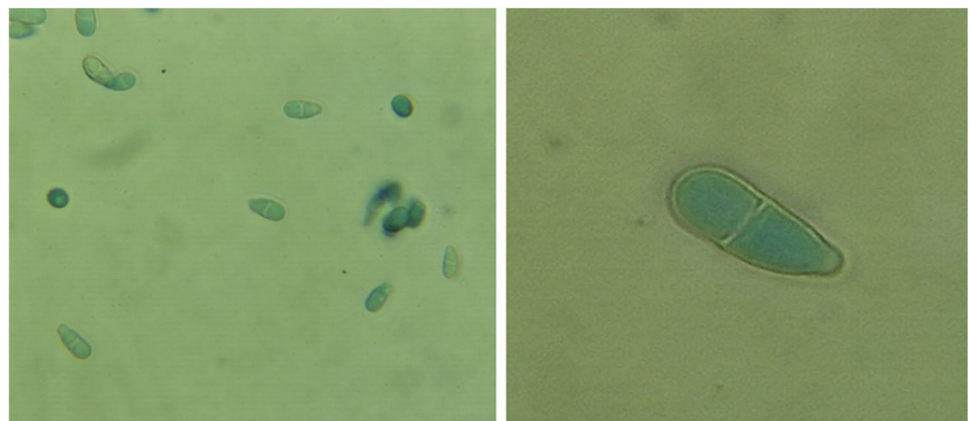
The polymerase chain reaction (PCR) is a highly sensitive molecular technique that can detect the presence of microbial genome in clinical samples even at very low concentrations. PCR has been standardized to detect the presence of dermatophytes from clinical samples such as nail and skin scrapings [86]. Compared to culture, the high sensitivity of PCR has made it highly useful in the fast and accurate diagnosis of dermatophytosis in conjunction with clinical signs [86]. PCR-based identification of *N. nana* is not commonly used, but it has been included as a study organism in assessing various types of PCR [87, 88] and PCR-based techniques [89, 90]. Restriction enzyme digestion of amplified products of ITS region and topoisomerase II gene produced *N. nana* specific band patterns [89, 91, 92]. Arbitrarily primed PCR (AP-PCR) or random amplified polymorphic DNA (RAPD) PCR which can be used for species and strain identification has also been found useful to distinguish *N. nana* from other common dermatophytes [90, 93]. Recently, PCR has been employed to detect the strain variations among *N. nana*. Melting profile PCR (MP-PCR) of 3 *N. nana* isolates detected two different electrophoretic profiles [15]. One isolate was obtained from a man (lesions were in the neck) and two from women (lesions were in the feet and nails, respectively). Interestingly, the isolate from the women shared a similar electrophoretic profile. This study indicates the presence of genetic diversity among *N. nana* isolates and the need to develop a molecular assay to identify those variants that may be associated with particular traits, host preference, virulence, or geographical distribution.

MALDI-TOF mass spectrometry is an advanced molecular technique that helps to identify organisms or biomolecules

based on the ions produced from the analytes. A small amount of fungal colony is needed for MALDI-TOF MS identification. Fungal identification can be made in 3 to 6 days, including the period required for the isolate to produce sufficient growth in the culture plate for protein extraction [94]. MALDI-TOF has been optimized for identifying dermatophytes by many researchers [95, 96]. However, limited studies have been done on the MALDI-TOF identification of *N. nana*. In one study, MALDI-TOF was able to correctly identify two clinical isolates of *N. nana* up to the genus and species level [97]. One of the major disadvantages of MALDI-TOF-based identification is the pre-requirement of a sufficient database [98]. Also, the mass spectra produced by the dermatophyte may show variations in individual peaks and peak intensity depending on the media in which they have grown [94, 99]. The requirement of costly sophisticated equipment and skilled personnel also limits the use of MALDI-TOF.

Some of the closely related dermatophyte species have been grouped into species complexes like *N. gypsea* complex (*N. gypsea*, *N. fulva*, and *N. incurvata*) [115], and *T. mentagrophytes* complex (*T. mentagrophytes*, *T. interdigitale*, *T. erinacei*, *T. quinckeanum*, and *T. benhamiae*) [100]. The members within the complexes are difficult to be distinguished by morphological or conventional laboratory tests. Sequencing genomic regions and subsequent phylogenetic studies will help us differentiate the species and strains. For example, members of *T. mentagrophytes* complex are difficult to differentiate morphologically but can be identified based on the sequence analysis of genomic regions such as ITS [100]. Earlier, *N. nana* was grouped in the *N. gypsea* cluster based on the ITS region analysis [101]. But when additional genomic regions were exploited, *N. nana* was found to be genetically distinct. A phylogenetic tree based on TEF-1 α and BT2 sequences positioned *N. nana* as a separate branch owing to interspecies diversity [102, 103]. Recently, a phylogenetic study based on the ITS, LSU, beta-tubulin, translation elongation factor, and 60S ribosomal protein L10 has identified five

Fig. 4 Conidia of *Trichothecium roseum* stained with lactophenol cotton blue



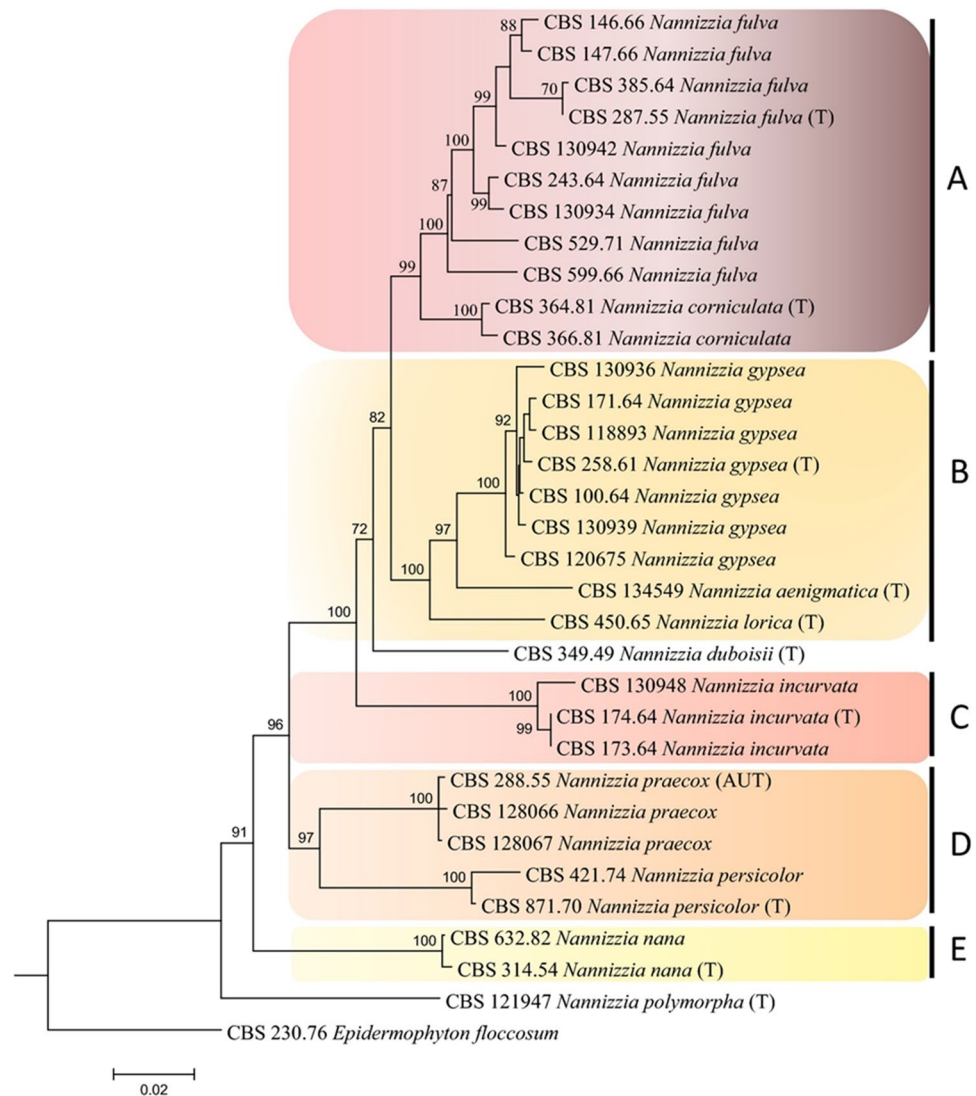
clades among *Nannizzia* species, with *N. nana* forming a separate clade with a sole member [21] (Fig. 5). Interestingly, *N. nana* took an ancestral position to all species of *Nannizzia* studied. This indicates *N. nana* is harboring the ancestral characteristics of dermatophytes even after developing host affinity towards pigs. Whole genome sequence analysis of *N. nana* isolates will give a clear picture of the genome repertoire. Also, identifying beta-tubulin and TEF genotypes indicates intra-species variation among *N. nana*, which warrants detailed genomic studies.

Antifungal susceptibility

Dermatophyte infections are characterized by their chronic nature and the requirement for prolonged antifungal therapy. They exhibit species variations in antifungal susceptibility, so susceptibility testing must be done before initiating

anti-dermatophytic treatment. A limited spectrum of antifungal drugs is available for the treatment of dermatophytosis. The most commonly used drugs are azoles such as ketoconazole, voriconazole, and itraconazole, allylamines such as terbinafine, echinocandins such as caspofungin and micafungin, polyene drugs such as amphotericin B, pyridinone derivatives such as ciclopirox and non-polyene drugs such as griseofulvin. These antifungal drugs vary in their mechanism of action and target enzyme/ cellular structure affected [104]. Azole drugs and allylamine interrupt the ergosterol synthesis by inhibiting the 14 α lanosterol demethylase and squalene epoxidase, respectively. Polyenes will increase cellular permeability by binding to ergosterol whereas griseofulvin will disrupt microtubule polymerization and depolymerization. Echinocandins inhibit the β -(1, 3)-D-glucan biosynthesis and ciclopirox acts by irreversibly binding to the cellular structures. Most of the antifungals are found to be effective against *N. nana* [105, 106]. In many

Fig. 5 Maximum likelihood concatenated tree of *Nannizzia* species based on ITS LSU, TUB2, TEF3, and RP 60S L1. AUT: authentic strain. T: type strains. A to E: different clades within genus *Nannizzia*. Reproduced from Dukik *et al.* 2020 [21] under the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>)



studies, the minimum inhibitory concentration (MIC) of the antifungal drugs has been determined for *N. nana*, and the values were in the normal range of susceptibility. Single isolate of *N. nana* was included in a study and the MIC for voriconazole and fluconazole was found to be 0.125 µg/ml and 4 µg/ml, respectively [105]. In another study, fluconazole exhibited higher MIC against different strains of dermatophytes but was highly effective against *N. nana* [106]. The MICs of the antifungal drugs for *N. nana* were voriconazole <0.125–0.25 µg/ml, itraconazole 0.03 µg/ml, terbinafine 0.125–0.01 µg/ml, fluconazole 4 µg/ml, ketoconazole 0.5–0.1 µg/ml, and griseofulvin 4–8 µg/ml. Perera *et al.* 2001 [107] studied the antifungal susceptibility of 19 species of dermatophyte to voriconazole, itraconazole, terbinafine, fluconazole, ketoconazole, and griseofulvin [107]. Two strains of *N. nana* were included into the study. The geometric mean MIC for *N. nana* were, voriconazole 0.18 µg/ml, itraconazole 0.03 µg/ml, terbinafine 0.03 µg/ml, fluconazole 4 µg/ml, ketoconazole 0.71 µg/ml, and griseofulvin 5.66 µg/ml. All these studies indicate the susceptibility of *N. nana* to the most common available antifungal drugs. This may be due to the low frequency of occurrence and limited exposure of *N. nana* isolates to these drugs. Clinically, *N. nana* infection has been treated with a high success rate. Enilconazole solution (0.2%) has been used to treat *N. nana*-infected lactating sows and disinfection of surroundings [34]. Total dystrophic onychomycosis due to *N. nana* has been treated successfully with itraconazole [51]. Three cases of *N. nana* infection were treated successfully with oral terbinafine and topical ketoconazole [15]. Even though the medication was the same, the duration was different in each case. Thus, the success of therapy may depend on other factors such as the patient's age and the region of infection.

Conclusion

Increased frequency of atypical tinea is being reported in humans. Zoophilic dermatophytes like *M. canis* and geophilic dermatophytes like *N. gypsea* are among those agents associated with atypical manifestations. The exact role of animals in transmitting dermatophytes to humans is still debated. *N. nana* having the characteristics of both geophiles and zoophiles with a special affinity towards swines can thus be considered a potential agent for human dermatophytosis. Limited studies on this pathogen are a setback in understanding its exact physiology and virulence. Whole genome sequencing of a few isolates will enable us to decipher its genomic repertoire and help us understand the genetic difference from other zoophiles, geophiles, and anthropophiles through comparative genomics technologies. Such studies will indisputably give hints on the host adaptation mechanism of dermatophytes also.

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