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Human infections caused by plant pathogen fungi: an overview

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ABSTRACT

Plant pathogenic fungi causing human infections belong to several groups, *viz., Hyalohyphomycetes* and *Phaeohyphomycetes,* both of them including several orders and families of fungi in the phyla of *Deuteromycota* (*Fungi Imperfecti*), *Ascomycota,* and *Basidiomycota*. Important genera containing human pathogenic fungal species include *Fusarium, Phialemonium, Phaeoacremonium, Curvularia, Alternaria Cladosporium, Macrophoma,* and *Pseudozyma.* While the genus *Exerohilum* is the only important one in the *Ascomycota*, *Schizophyllum* represents *Basidiomycota* the same way. During the past six decades, numerous cases of human infections caused by plant pathogenic fungi have been described from several countries on all the continents and several reviews of human infections caused by these specific groups of plant pathogens have been published. The number of plant pathogenic species infecting humans continues to grow, most of them being of opportunistic behaviour. Socio-economic, geo-ecological characteristics and the increasing number of populations at risk are the main determinants of variations on the incidence and prevalence of fungal diseases around the world, including diseases caused by plant pathogens. The aim of this study is to present an overview of human infections caused by some selected plant pathogenic fungi representing different taxonomic groups.

Keywords : Human infections, plant pathogenic fungi, India, other countries, update

INTRODUCTION

Fungi are diverse groups of heterotrophic organisms with an estimated number of 2.2 to 3.8 million species out of which little over 1, 48,000 are currently described (Hawksworth and Lucking, 2017). They occupy various niches, play a diverse ecological role, and are of immense economic importance. While only several hundred cause diseases in immune-compromised humans, very few are actually able to affect healthy people. More than 600 fungal species are associated with humans as commensals, or as members of our microbiome. These species frequently or infrequently cause some of the most lethal infectious diseases (Brown *et al.,* 2012). Global mortality due to fungal infections exceeds that for malaria or breast cancer and is comparable to tuberculosis and HIV (Brown *et al.,* 2012; Fischer *et al.,* 2012). Human fungal infections range from superficial skin and nail infections (1.7 billion infections/year worldwide) to mucocutaneous candidiasis (>85 million infections/year worldwide) to invasive fungal infections (>2 million infections/year worldwide) (Brown *et al.,* 2012). Human invasive fungal infections typically affect persons with impaired immunity such as those undergoing solid organ or hematopoietic stem cell transplantation (Pappas *et al.,* 2010). The burden of invasive fungal infections (IFI) has been increasing during the past two decades.

Out of 270,000 species of fungi associated with plants, only a small subset can infect humans (Gauther and Keller, 2013). The first report of human infection due to a plant pathogenic fungus was from Hungary manifesting as skin lesions due to *Mycosarcoma (Ustilago) maydis* (Preininger and Durch, 1937-1938). The patient was a 31-year-old corn farmer with infiltrated, hyperpigmented patches on the chest, back, arms, inguinal region, and legs, scaly plaques in the axillae, on the neck, elbows, and dorsum of the feet and scattered red papules on the chest, legs, and buttocks. A microscopic examination of scrapings from the lesions disclosed spores, which were similar to those seen in the black smutty rain. The second case of *M. maydis* infection was from the USA in a patient with leptomeningitis (inflammation of the meninges-the tissues that surround the brain or spinal cord) and epididymitis, meaning an infection of central ventricular system (Moore *et al.,* 1946). The patient, a 55 years-old male corn farmer had symptoms of staggering, nausea, slight headaches, and attacks of vomiting of 2 years' duration; cerebral craniotomy without biopsy led to a diagnosis of "chronic cystic arachnoiditis" (meaning chronic compression of the spinal cord with cyst formation), following which the patient felt well and returned to doing his chores including husking of corn. The third was a culturally proven case of brain tumor (meaning a mass of abnormal cells in the brain) from India (Randhawa *et al.,* 1959) caused by the same fungus. The patient was a 13 years-old girl with chief symptoms of headache, loss of vision and sense of smell; histological examination of biopsy from the brain lesion revealed 6.0-8.5µm x 1.5-4.8µm septate hyphae, branching below the septa, occasionally dichotomously with the occasional presence of round and oval fungal bodies, leading to a diagnosis of brain mycosis. Cultures of the nasal blood originating from the brain yielded *Mycosarcoma* (then known as *Ustilago*) *maydis* (Randhawa *et al.,* 1959).

During the past six decades, numerous cases of human infections caused by a great variety of plant pathogenic fungi belonging to many taxonomic groups have been reported from several countries from across the globe. Also, several reviews of human infections caused by specific groups of plant pathogens including dematiaceous fungi have been published (Nucci and Anaissie, 2007; Pastor and Guarro, 2008; Pappas *et al.,* 2010; Revankar and Sutton, 2010; Queiroz-Telles *et al.,* 2011; Brown *et al.,* 2012; de Hoog *et al.,* 2019). Many species of *Aspergillus* are known to cause human infections of the ear, eye, nose, lung, central nervous system, and other sites (Bennet, 1990). There are far too

numerous reports of human infection of varying types due to *Aspergillus*. As a very limited number of *Aspergillus* species are known to invade living plant tissue (Bennet, 1990; de Hoog *et al.,* 2019), thus human infections caused by plant pathogenic aspergilli have not been included in this review. The present study aims to present an overview of human infections caused by some selected plant pathogenic fungi representing different taxonomic groups. The data presented should serve as a good source for plant pathologists for updating their knowledge of human infections caused by plant pathogenic fungi, risk factors involved in infections, and their therapy.

SEARCH CRITERIA

An exhaustive search of the literature was conducted using PubMed, MEDLINE, Biomedlib, Med Facts data bases to identify and download relevant publications using several sets of key words, *viz., Fusarium*, *Phialomonium, Phialoacremonium, Cladosporium, Curvularia, Alternaria, Exsorhilum, Scytalidium, Phoma, Macrophomina*, *Schizophyllum* plant infections, human infections etc. Cross references in the publications were also checked for information relevant to the review.

HUMAN INFECTIONS DUE TO *FUSARIUM* SPECIES

Fusarium species are widely distributed in soil, subterranean and aerial plant parts, plant debris, and other organic substrates (Nelson *et al.,* 1994). The genus *Fusarium* has been commonly associated with many crop diseases such as ear and kernel rot of corn, scab of rice and wheat, and stalks rot and grain mold infection of sorghum (Williams and McDonald, 1983). To date, approximate 15 species of *Fusarium* are known to cause human infections (fusariosis). The prominent among these are *F. verticillioides, F. chlamydosporum, F. dimerum, F. incarnatum* and other species (included in the *Gibberella fujikuroi* species complex) *viz., F. napiforme, F. nygamai, F. vorticoides F. anthophilum, F. proliferatum,* and *F. sacchari* are also reported to cause human infections (Nelson *et al.,* 1994; Nucci and Anaissie, 2007, Tortorano *et al.,* 2014). These species have been associated with different types of mycosis, particularly keratomycoses (mycotic infection of the cornea of the eye) and other ocular infections (de Hoog *et al.,* 2019) and with disseminated infections, particularly in immunocompromised patients (Summerbell *et al.,* 1988; Kumar *et al.,* 1997; Austen *et al.,* 2001; Nucci *et al.,* 2007; Hayashida *et al.,* 2018; de Hoog *et al.,* 2019). Hayashida *et al.* (2018) reported successful treatment of six patients of disseminated *F. solani* with hematological neoplasia with amphotericin B, liposomal amphotericin B, and voriconazole. The conidia of *Fusarium solani*, a frequent cause of keratitis (inflammation of the cornea), can adhere to the basement membrane of the cornea following damage of the epithelial layer (Thomas, 2003). The characteristic signs of disseminated *Fusarium* infections are skin nodules, fungemia, and involvement of multiple organs, myalgia may be frequently present. Salient clinical and demographic features of cases of human infections (excluding keratitis) due to *Fusarium* species selected to be representative of different countries and the treatment aspects are presented in **table 1**.

Table 1: Infections caused by *Fusarium* species

Fungal species	Type of infection	Country	Reference
Fusarium solani	Skin infections in cement factory workers, all adults	Nigeria	Oyeka and Gugnani, 1992
F. solani	Tender ulcerated swelling (4x 3 x 2 cm) on the medial side of the right breast with axillary adenitis, 55/F	India	Anandi *et al*., 2005
F. solani	Cutaneous erythematous (appearing red) lesion appeared on the first toe in a patient with ALL, 44/F	Switzerland	Josi *et al*., 2009
F. solani	Subcutaneous firm, violaceous nodule (2×2 cm) in a renal transplant recipient, 45/M. The patient was successfully treated with surgical excision of the lesion and oral voriconazole.	India	Banerji and Singh, 2011
F. solani	Cutaneous papulo-nodular erythematous plaques, with multiple discharging sinuses over the right knee joint, h/o renal transplant and diabetes, 42/M	India	Mohanty and Sahu, 2014
F. solani (6 cases with age and hematological neoplasia type (HNT) 1) 53-AML 2) 37-ALL 3) 42- ALL 4) 24-CLL 5) 49-Multiple Myeloma 6) Age and HNT not known	Disseminated infection with cutaneous nodules, six cases: 1. Erythematous, subcutaneous, slightly painful nodules on the upper limbs; 2. Diffuse erythematous nodules on the upper and lower limbs; 3. Violaceous nodule with a necrotic center in the region of the right metatarso-phalangeal joint; 4. Erythematous ulcerated nodules on the upper and lower limbs; 5. Erythematous and subcutaneous nodules on the knee; 6. Violaceous and diffuse nodules, with ulcerated centers covered by necrotic crusts, distributed across the face, trunk and upper and lower limbs.	Brazil	Hayashida *et al*., 2018

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F. solani	Multiple, tender papules and nodules with central crusting and necrosis on face, both arms, thighs and knees in a HIV infected patient, 40/M	India	Kumari *et al.,* 2018
F. solani	4 cases, leukonychia, distil subungual hyperkeratosis with yellowish brown discoloration, 73/F, 33/F, 45/F, 48/F	Brazil	Godboy *et al*., 2004
F. oxysporum	4 cases with distal subungual hyperkeratosis with yellowish brown discoloration in 4 patients, 11/M, 44/F, 58/F, 59/F	Brazil	Godboy *et al*., 2004
F. dimerun	Soft-tissue infection of the foot and possible pulmonary infection in a patient with STCR following allogenic, PBSCT, 19/F. The patient was successfully treated with oral voriconazole (200 mg twice daily) for nearly five weeks.	United Kingdom	Bigley *et al*., 2004
F. chlamydosporum	Catheter-associated fungemia in a patient with lymphocytic lymphoma and lymphadenopathy, 33/F	USA	Kiehn *et al*., 1985
F. concentricum	Onychomycosis-infection started as thickening of the nail in the distil end 4 years earlier; later forming a longitudinal streak in the middle of the nail and splitting it and turning it light yellow, 11/M	India	Sharma and Sumbali, 2020
F. proliferatum	Onychomycosis started from the proximal end of the left hand middle finger 3 years earlier progressing to the distil end with the nail becoming rough and appearing creamy white.	India	Sharma and Sumbali, 2020

HUMAN INFECTION DUE TO *PHIALEMONIUM* AND *PHAEOACREMONIUM*

Phialemonium genus is intermediate between the genera *Acremonium* and *Phialophora*. Pathogenic species of Phialemonium are opportunistic and most human infections have been caused by *P. curvatum*. Species of *Phaeoacremonium*, pathogenic to plants include *P. parasiticum, P. Itialicum,* and *P. sicilianum* causing discoloration, necrotic wood, and death of shoots of olive trees (Mosteri *et al.,* 2005; Carlucci *et al.,* 2015). Some other species of *Phaeoacremonium* cause Petri disease and esca on *Vitis vinifera, Phoenix dactylifera, Prunus armeniaca* (Armenian plum), *P. aviaum* (sweet cherry), *Quercus virginiana* (living oak) (Carlucci *et al.,* 2015). The species reported causing human infection include *Phaeoacremonim parasiticum, P. obovatum, P. venezuelense* (Tummidi *et al.,* 2020). Infections due to these species are known to involve skin, nails, subcutaneous tissue, anterior chamber of the eye (endophthalmitis), central nervous system, and the heart. Most of these infections have occurred in solid organ transplant recipients. In plants, out of the numerous species of *Phaeoacremonium, P. parasiticum* is the most common (Kelvin *et al.,* 2012; Tummidi *et al.,* 2020). In humans, the species commonly causing infections include *P. parasiticum, P. inflatipus, and P. rubrigenesi* (Mosteri *et al.,* 2005). Brief data on some selected cases of human infection due to *Phialemonium* and *Phaeoacremonium* in some countries are presented in **table 2**.

Table 2: Infections caused by species of *Phialemonium* and *Phaeoacremonium*

Fungal species	**Symptoms and histopathology of affected organs**	**Country**	**Reference**
Phialemonium curvatum	Disseminated infection with spondylodiscitis. The patient was treated with oral voriconazole (400 mg/12 h the first day and 200 mg/12 h after that) for 16 months and was also placed in a custom-made thoracic lumbosacral orthosis, 46/M, h/o alcohol abuse	Spain	Rivero *et al*., 2009
P. obovatum	Spondylodiscitis with low-back pain and a small soft tissue mass in the paravertebral region, 41/M, h/o alcohol abuse. Treated successfully with voriconazole for 16 months, but the patient still required a stiff brace for low-back pain.	USA	Magnon *et al*., 1993
P. obovatum	Mycetoma in RTR	USA	King *et al*., 1993
P. obovatum	Severe burn on several parts of the body followed by infection, 4.5 months old male child	USA	McGinnis *et al*., 1986
Phaeoacremonium infalitipes	Large lump with pain on the right foot which had been enlarging over the past 6 months. Patient treated by surgical debridement and amphotericin B for 2 weeks, later discharged on oral itraconazole for 2 months, 36/M, farmer	India	Baradkar *et al*., 2011

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P. parasiticum	Subcutaneous firm slightly tender (4x3 cm) nodule of 10 years' duration with restricted mobility on the medial aspect of the right knee; ultrasonography reveled two well defined oval thick-walled lesions below the anteromedial aspect of knee joint, 67/M, no h/o trauma. The lesions subsided with oral itraconazole, 200 mg twice daily for one month.	India	Tummidi *et al*., 2020
P. griseorubrum	Subcutaneous firm erythematous nodule of 3 yrs. duration on the left elbow with no h/o trauma, 55/M	India	Arora *et al*., 2018
P. aleophilum	Painful nodule on the surface of his left ankle, 19/M. The lesions healed with surgical intervention and use of itraconazole.	Brazil	Guarro *et al.,* 2003
P. rubrigenum	Nonpainful multiple nodules discharging pus on his left ankle and foot in renal transplant recipient, 55/M. Treatment with itraconazole failed to resolve the infection.	Brazil	Guarro *et al*., 2003
Phaeoacremonium parasiticum and *Paraconiothyrium cyclothyrioides*	Disseminated infection involving the skin, lungs and brain in renal transplant recipient 71/M, regular gardener. h/o of a painless non-pruritic nodule on the internal edge of the right middle finger for the last seven years. Chest X-ray and CT scan showed two bilateral opacities in the upper lung, and cranial MIR revealed a focal lesion in the right parietal lobe, both considered to represent fungal metastasis. Despite the use of antifungal drugs, voriconazole and amphotericin B, the patient died of bacterial sepsis and refractory septic shock.	Guadeloupe (French Caribbean)	Colombler *et al*., 2015
Meaning of medical terms	Spondhyloscitis- Primary infection of the intervertebral disc with secondary infection of neighboring vertebral disc; Mycetoma- A tumorous mass; h/o-History of; RTR-Renal transplant recipient; Subcutaneous mycosis-Fungal infection of the subcutaneous tissue (tissue below the skin); CGD-Chronic granulomatous diseases; CT-Computed tomography; MRI-Magnetic Resonance Imaging.		

HUMAN INFECTION CAUSED BY DEMATIACEOUS FUNGI

Dematiaceous fungi characterized by the presence of melanin in their cell walls are ubiquitous in the environment, many species in several genera are phytopathogenic. They frequently cause superficial and deep local and disseminated infections Infection results from traumatic inoculation of fungal elements into the skin, their inhalation, or their dissemination from a distant subacute infection (Revankar *et al.,* 2010). A brief account of human infections caused by common phytopathogenic species of some genera of dematiaceous fungi representing different geographic locales are described under specific subheads.

Human infections due to *Curvularia* and *Alternaria*: *Curvularia* is related to its sexual anamorph *Cochliobolus* and its species are common in soil and vegetation, and its spores are airborne (Sandhu and Randhawa, 1979; Karmarkar *et al.,* 2020). In human infections, the cornea is the commonest site infected, other ocular infections include conjunctivitis, dacryocystitis (infection of the tear (lacrimal) sac usually due to a blockage in the tear (nasolacrimal) duct), sino-orbital cellulitis (inflammation of the soft tissue of the nasal sinuses, and orbit of the eye), and endophthalmitis (inflammation of the anterior chamber of the eye) (Wilhelmus and Jones, 2001). Out of the 233 cases of *Curvularia* keratitis reviewed by these authors, and 40 cased investigated by them, *C. lunata* was the predominant infectious agent. Other species are known to cause keratitis include *C. senegalensis, C. pallescens, C. geniculata, C. brachyspora, C. prasadii,* and several unidentified *Curvularia* species. An analysis by these authors showed that one-fourth of the total number of cases came from the United States. Nearly half of the reports and two-thirds of the cases were from India and surrounding Asian nations (Wilhelmus and Jones, 2001). Besides India (n=109) and the United States (n=89, including their series), other regions reporting patients with *Curvularia* keratitis were from other countries in Asia (n=24; from Bangladesh, Taiwan, Thailand, Nepal, Sri Lanka, Korea, Singapore, and the Philippines), Africa (n=6; from South Africa and Ghana), South America (n=4; from Argentina, Brazil, Paraguay, and Venezuela), and one from Israel in the Middle East (Wilhelmus and Jones, 2001). Human infections other than keratitis caused by *Curvularia* range from onychomycosis to skin ulcers, mycetoma, and abscesses of lung, liver and connective tissue (Revankar and Sutton, 2017).

Alternaria species are ubiquitous in their occurrence and

cause disease in several plants mainly carrot, potato, crucifers, broccoli, tomato, and pepper. Generally, the aerial part of the plants is attacked forming small dark spots on the leaves, which gradually enlarge and become black. *Alternaria* infections on the roots, tubers, and fruits produce dark sunken lesions called cankers. Common plant pathogenic *Alternaria* species include *A. brassicae, A. brassicola, A. alternata, A. solani,* and *A. infectoria* (Mena *et al.,* 2010). Pastor and Guarro (2008) have mentioned most frequent clinical manifestations of human infections as cutaneous and subcutaneous infections (74.3%), followed by oculomycosis-fungal infection of the eye (9.5%), invasive and non-invasive rhinosinusitis-inflammation of the nasal sinuses (8.1%), and onychomycosis- a fungal infection of nails (8.1%). Revankar and Sutton (2017) have also extensively reviewed cases of phaeohyphomycosis caused by *Alternaria* species. Cases of keratitis caused by these fungi are excluded in the present account in view of far too numerous reports of this infection from all parts of the world. We present below in **table 3**, the brief clinical and demographic features of the types of invasive skin and deep-seated infections in humans caused by common species of *Curvularia* and *Alternaria*.

Table 3: Infections caused by *Cuvularia* species and *Alternaria* species

Fungal species	**Symptoms of affected organs**	**Country**	**Reference**
Curvularia lunata	Paranasal sinusitis, 5 cases	USA	Rinnaldi *et al*., 1987
C. lunata	Sternal wound infection in a neonate following cardiac surgery for congenital heart disease	Canada	Yau *et al.,* 1994
C. lunata	Mycetoma with swelling of right foot, multiple nodules, and sinuses discharging black-colored granules, 65/M, farmer	India	Garg *et al.*, 2008
C. lunata	Paranasal sinusitis, one case (non-invasive)	India	Chakrabarty and Sharma, 2000
C. lunata	ABPA with productive cough, 25/M, h/o bronchial asthma since childhood. The patient experienced spontaneous regression of Symptoms	Japan	Nasu *et al*., 2018
C. lunata	Fatal cerebral infection. Symptoms were headache in the parietal and occipital regions associated with double vision, dizziness, unsteady gate, anorexia, weight loss, low grade fever, chills and night sweats, h/o heavy smoking and occasional and marijuana. Denied intravenous drug use, 21/Male	USA	Carter and Boudreaux, 2004
C. pallescens	Irregularly marginated black, pruritic skin, and occasionally purulent lesions on the feet, thigh and thumb	India	Agrawal and Singh, 1995
Curvularia clavata	Skin lesions, 20/Female	Nigeria	Gugnani *et al*., 1990
Curvularia geniculata and *Pithomyces* sp.	Fungal peritonitis associated with 5 years' h/o vulvular cancer with diabetic nephropathy. Treated with 300 mg oral voriconazole, twice daily, gradually reduced to 50 mg twice daily till cured.	Japan	Terada *et al*., 2014
Curvularia sp.	Onychomycosis with a verrucose growth on the nail bed for 8 months, 57/Male, farmer, h/o nail pterygium	India	Ven eetha *et al*., 2016
Alternaria humicola and *A. pluriseptata*	Onychomycosis, 1 case each	India	Wadhwani and Srivastava,1985
Alternaria longipes and *Alternaria dianthicola*	Granulomatous cutaneous lesions on arms in patient with h/o chronic hepatitis B and heavy smoking, 60/Male. Treated with itraconazole (100 mg/12 hrly.) for 2 months but the patient died at home due to his neoplastic disease	Spain	Gene *et al*., 1995
A. dianthicola	Non-Inflammatory, circumscribed subcutaneous lesions on the chest wall	USA	Mitchell *et al*., 1983

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Alternaria sp.	Onychomycosis of the toe nails, multinodular, violaceous, mildly tender lesions over both lower extremities up to the level of knee in a 56-yr-old male with h/o end stage renal disease and renal and pancreatic transplant. There was complete resolution of lesions after treatment with posoconazole, 200 mg three times a day	USA	Bajwa *et al*., 2017
Alternaria alternata	Subcutaneous phaeohyphomycosis-two elevated, violaceos nodular swellings of about 6 months' duration: one near the wrist of the right arm and the other the left elbow. The patient could not recall any major trauma at the site of lesions, though he mentioned having minor bruises on the arms while working as road construction worker, 52/M	India	Sood *et al.,* 2006
Meaning of medical terms	CNS- Central nervous system, ABPM-Allergic bronchopulmonary mycosis; Fungal peritonitis-Fungal infection of the peritoneum - a silk-like membrane that lines the inner abdominal wall and covers the organs within the abdomen; Onychomycosis-Fungal infection of nails; Pterygium-Overgrowth of the proximal nail fold onto the nail bed		

INFECTIONS CAUSED BY SPECIES OF *CLADOSPORIUM*

Cladosporium comprises numerous species, most of them are found in soil or decomposing vegetation with some of them being found as contaminants of microbial cultures. Many species of *Cladosporium* cause animal and human infections, some of them *viz.*, *C. cladosporioides, C. oxysporum,* and *C. Sphaerospermum* are pathogenic to plants (de Hoog *et al.,* 2019). The salient feature of human infections caused by the phytopathogenic *Cladosporium* species are described in **table 4**.

Table 4: Human infections caused by *Cladosporium* species

Fungal species	Infection caused, Age/Sex	Country	Reference
Cladosporium cladosporioides	Pulmonary fungus ball in the upper lobe of right lung. Chest X-ray revealed a cavitary lesion in the right upper lobe 58/F, h/o treatment for diabetes and hypertension, and a cerebrovascular accident. The patient went into deep comma with decerebration and died.	USA	Kwon-Chung *et al*., 1975
C. cladosporioides	Red brown, firm slightly raised popular lesion on the anterior aspect of both knees and legs, 54/Male	Italy	Annessi *et al*., 1992
C. oxysporum	Papulo-nodular lesions on the right leg with Cushing syndrome, 66/Female, the lesions resolved by initial treatment with itraconazole, and later with ketoconazole	Italy	Romano *et al*., 1999
C. cladosporioides	Elevated scaly suppurating lesion with sinuses on the right leg, 25/M. The lesion healed completely with oral fluconazole therapy	India	Gugnani *et al*., 2000
C. cladosporioides	Brain infection. 30/M, h/o diplopia with stain on brain stem on CT scan and MRI	Turkey	Kantarcioglu *et al*., 2002
C. oxysporum	Cutaneous hyphyomycosis	India	Gugnani *et al.*, 2006
C. cladosporioides	A large non-healing suppurating ulcer with draining sinuses on the lateral aspect of right buttock. History of lesion starting as a small tender induration two years ago after receiving injection of glycorhizzin (a steroid) to treat pruritis of unknown origin.	China	Sang *et al*., 2011
C. sphaerospermum	Swellings over dorsum of right hand and one on the middle finger with a short h/o of non-Hodgkin's lymphoma and diabetic ketoacidosis, 65/F	India	Maduri *et al*., 2014
C. cladosporioides	Chronic verrucose nodules on the left foot and leg of 32 years duration, 55/M	India	Nath *et al*., 2015
C. cladosporioides	Cysts and nodules like acne on his face and neck for 5 years, 21/M	China	Zhou *et al*., 2016
C. oxysporum	Painless swelling over his left neck just below the angle of the mandible with enlarged multiple cervical lymph nodes, 16/M	Sri Lanka	Jayasinghe *et al*., 2017

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Meaning of medical terms	Decerebration- Elimination of cerebral brain function by removing the cerebrum, cutting across the brain stem, or severing certain arteries in the brain stem, Hodgkin's Lymphoma - A malignant lymphoma that is characterized by progressive enlargement of lymph nodes, spleen, and liver and by progressive anemia, ketoacidosis-A complication of uncontrolled diabetes characterized by accumulation of ketone bodies and acidity in the blood.

HUMAN INFECTIONS DUE TO *USTILAGINALES*

Ustilaginales in the phylum *Basidiomycota*, well known as 'smut fungi' are a vast and diverse group of fungi that cause significant losses to crops worldwide. Members of the *Ustilaginales* are also valuable models for the unraveling of fundamental mechanisms controlling important biological processes. *Mycosarcoma* (*Ustilago*) *maydis* is an important fungal model system and has been well studied with regard to mating, morphogenesis, pathogenicity, signal transduction, mycoviruses, DNA recombination, and recently genomics. (Martínez-Espinoza *et al.,* 2002). The corn smut fungus, M. maydis was the first plant pathogenic fungus known to cause human infection. The details of clinic-pathological feature of the first three cases of human infection caused by this fungus known in the period 1937 to 1969 have been mentioned in the introductory part of this paper. There are over twenty species of *Ustilaginales* implicated in human diseases. Salient clinical and demographic features of some cases due to phyto-pathogenic species of *Ustilaginales* selected to represent different geographic areas are described in the **table 5**.

Table 5: Infections caused *Mycosarcoma maydis, Pseudozyma aphidis, Pseudonymoua* species, mixed infection with *Pseudozyma* species and *Nocardia asteroides* and *Moesziomyces bullatus***.**

Fungal infection	**Age (in years)/sex of the patient**	**Country**	**Reference**
Mycosarcoma (*Ustilago*) *maydis*			
Dermatomycosis, skin lesion in a farmer	31/ Male	Hungary	Preininger and Durch, 1937-1938
Chronic leptomeningitis and ependymitis	55/ Male	USA	Moore *et al*., 1946
Brain tumor with intracranial pressure	13/ Female	India	Randhawa *et al*., 1959
Multifocal brain abscess	Child, Male	Egypt	Fogilo *et al*., 2013
Onychomycosis	Not known	Pakistan	Bokhari *et al*., 1999
Peritonitis with h/o end stage renal disease and hypertension	3/ Male	USA	Mcneil *et al*., 2012
CVC infection with a 1-week history of intermittent fevers, accompanied by chills, malaise and fatigue, h/o gastroschisis and ileocolonic resulting in short bowel syndrome. Treated with intravenous fluconazole (loading dose of 10 mg/kg followed 24 h later by a 5 mg kg^{-1} per day maintenance dose, replaced after 5 days by itraconazole (5 mg kg^{-1} per day) for 10 days.	7/ Female	USA	Lin *et al*., 2008
Pseudozyma sp Brain abscess with and with weakness of right leg for last 2 months MRI revealed a brain abscess. Histopathology suggested anaplastic astrocytoma. The poor general condition hindered initiation of antifungal therapy and the patient died.	78/ Male	Korea	Hwang *et al*., 2010
Pseudozyma aphidis and *Nocardia otitidiscaviarum* Chronic mycetoma of the leg with multiple discharging sinuses for 25 years in a farmer	51/ Male	China	Chen *et al*., 2011

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Pseudozyma antarctica, P. parantarctica , P. thialandica Fungaemia	Not known	Thailand	Sugita *et al*., 2003
Moesziomyces bullatus Disseminated infection in a neonate, second set of twins, at 32 weeks of gestation via an emergency cesarean section with low birth weight and anatomical abnormalities. The patient did not improve with empirical administration of fluconazole; in vitro antifungal susceptibility tests showed the isolate was resistant to fluconazole.		Nigeria	Okolo *et al*., 2015
Meaning of medical terms	CVC-Central Venous Catheter; AML -Acute Myeloid Leukemia; Leptomeningitis-Inflammation of the meninges-The tissues that surround the brain or spinal cord; ependymitis-Infection of central ventricular system; h/o- History of		

HUMAN INFECTIONS DUE TO *EXEROHILUM* SPECIES

The genus *Exerohilum* belongs to the family *Pleosporaceae*, class *Euascomycetes* of phylum *Ascomycota*. Several *Exserohilum* species are plant pathogens that cause distinct leaf spots and blights. *E. rostratum* is the most important species affecting a wide range of species, particularly grasses (family *Poaceae*) and also other monocotyledonous plant families, and is characterized as a cross-kingdom pathogen of plants and humans (Sharma *et al.,* 2014). However, under certain circumstances, *E. rostratum* can survive and thrive in human and animal hosts and therefore, it seems to be a versatile pathogen with an ability to jump from plants to animal and human hosts. A search of the literature in PubMed revealed only a dozen or so cases of human disease, the majority being keratitis and cutaneous infections. In October 2012, the CDC reported an outbreak of fungal meningitis associated with methylprednisolone injections, the majority of the patients having this infection due to *E. rostratum* (www.cdc.gov/hai/outbreaks/meningitis.html). The salient features of some selected cases of human infections caused by different species of *Exerohilum* are described in the **table 6.**

Table 6: Infections caused by *Exerohilum* species

Fungal species	Infection caused, Age (in years)/Sex	Count-ry	Reference
Exserohilum rostratum	Nasal polyps of 6 yrs. duration, preventing vision beyond the nasal vestibule with complaints of frontal sinus pain and occasional blood discharge, 27M. The patient's condition improved after Surgery	USA	Padhye *et al*., 1986
E. rostratum	Mycotic keratitis with pain, redness and decreased vision in the left eye, 42/M	India	Mathews and Maharajan, 1999
E. rostratum	Disseminated infection. Single painless necrotic lesion, 5 cm in diam. on left forearm in a three months old male child with ALL. CT scan of his sinuses revealed bilateral maxillary opacities	Canada	Saint-Jean *et al*., 2007
E. rostratum	Corneal ulcer with a greyish-white slough, feathery edges and diffuse cornea edema in right eye, 46 yrs. old farmer, h/o injury with vegetable matter while working in the field. Treated with topical natamycin (5%) applied hourly and itraconazole 200 mg twice a day for three weeks	India	Joseph *et al*., 2012
E. rostratum	Nodular discharging lesions on face, hands, axilla, groin and labia majora for last one month in an HIV-infected patient, 45/F. Treated successfully with itraconazole 200 mg and terbinafine 250 mg twice daily	India	Rajasekhar *et al*., 2013
E. rostratum	Bilateral nasal stiffness with nasal discharge for the last 12 months and left sided proptosis for the last 8 months, h/o bronchial asthma and recurrent allergic fungal sinusitis, since the age of 2 years, 11/F. The patient was given oral itraconazole and advised regular follow-Up	India	Gupta *et al*., 2014
E. rostratum	An outbreak infection in patients who received epidural injections of methyl-prednisolone acetate that was contaminated with environmental molds. *E. rostratum* was recovered twice from CSF in an index case (in the outbreak) of meningitis and vasculitis who had received a cervical spine epidural steroid injection for chronic pain a week before, the patient died	USA	Bell *et al*., 2013

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E. rostratum	Corneal ulcers 8 cases including 5 males aged 28, 56, 66, 75, 76 with h/o insect injury, chemical injury and trauma and unknown foreign body in one each. 3 females aged 36, 72 with h/o injury with an unknown foreign body in 2. Treated with topical application of natamycin (1%) and 2% miconazole cream	Sri Lanka	Jayasudha *et al*., 2018
E. mcginnisii	Corneal ulcer, one case, female aged 40, h/o injury with unknown foreign body. Treated with therapeutic keratoplasty	Sri Lanka	Jaisudha *et al*., 2018
E. rostratum	Mycotic keratitis with a feathery satellite lesion and brownish pigmented deposits in anterior surface of stroma and redness and blurred vision in the right eye, h/o insect bite, 48/M. The lesions healed with treatment by combined oral itraconazole and topical amphotericin B	Thailand	Chaidaroon *et al*., 2019
Mixed infection due to *Exserohilum rostratum* and *Candida parapsilosis*	Two superposed corneal infiltrate in the left eye, the larger infiltrate had gray interlaced braid-grid texture and irregular feathery margin, mainly involving the anterior corneal stroma. The smaller one, slightly elevated, gray in color with a rough surface was superimposing on the larger one, 40/F	China	Qiu and Yao, 2013
Meaning of medical terms	Nasal polyps-A growth or protrusion of tissue in the nose or nasal sinuses; Nasal vestibule-The area just inside the nostril (nose opening) that leads into the nasal cavity; mucus filling the largest sinuses near the nose; Keratitis- inflammation of the cornea of the eye, ALL- Acute lymphatic leukemia, CT- Computer tomography h/o-History of; Keratoplasty- Excision of corneal tissue and its replacement by a cornea from a human donor		

HUMAN INFECTIONS DUE TO *COELOMYCETES*

Some species like *Neoscytalidium dimidiatum* (syn. *Nattrassia mangiferae, Hendersonula toruloidea*), *Macrophomina,* and *Phom*a species, primarily plant pathogens (Punithalingam and Waterson, 1970: de Hoog *et al.,* 2019). *Neoscytalidium dimidiatum* is a dematiaceous mold and is well known to cause branch wilt, canker, and dieback of a wide range of trees, wood plants, and storage rot of plant tubers such as yams in tropical and subtropical regions worldwide (Punithalingam and Waterson, 1970). Infections caused by this coelomycetous fungus, which bears its conidia within fruiting bodies called 'pycnidia', are more likely acquired from plant/woody material or soil through abrasions, lacerations, or wounds in cutaneous and subcutaneous tissues, rather than by inhalation of conidia (Hay, 2002). Though it is known to be involved in skin and nail infections, deep infections caused by *N. dimidiatum* have been rarely reported and then most often in immuno-compromised hosts. A high prevalence of *N. dimidiatum* infection occurs in areas where the fungus is known to be endemic, including parts of West and Central Africa, the Caribbean, and Asia (Moore, 1986; Hay, 2002). Infections are often clinically indistinguishable from dermatophytic infections; mixed infections with dermatophytes have also been reported. Another species, *N. Hyalinum*, has hyaline hyphae and arthroconidia and is considered by some authors to be a melanin-deficient mutant of *S. dimidiatum* (Revankar and Sutton, 2010); most cases of infection have occurred in individuals) from the Caribbean or West Africa (Moore, 1986). *N. dimidiatum* is known as a wound-invading pathogen of a variety of woody hosts in tropical and subtropical countries worldwide (Revankar and Sutton, 2010). The natural habitat of *N. hyalinum* is not yet known. Bennet *et al.* (2018) have exhaustively reviewed human infections caused by *Phoma* species. *Lasiodiploidea theobromae* is known to cause dieback of mango (*Mangifera indica*) trees in Pakistan (Khanzada *et al.,* 2004), and bark canker and stem canker of shisham (*Dalbergia sisoo*) in India (Chandra *et al.,* 2014) and bot rot of grapevine in USA (Urbez-Torres, 2008). The salient features of some cases of human infections caused by *Coelomycetes* in different countries are presented in **table 7**.

Table 7: Infections caused by *Coelomycetes*

Fungal species	**Sites or type of infection**	**Age (in years) & Sex etc.**	**Country of resi-dence/ origin**	**References**
Neoscytalidium dimidiatum	Feet and nail in three patients	24 and 61/M	UK	Gentle and Evans, 1970
N. dimidiatum	Skin infection in coal miners	All adult males	Nigeria	Gugnani and Oyeka, 1989

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N. dimidiatum	Skin infection in coal miners	All adult males	Nigeria	Gugnani and Oyeka, 1989
N. dimidiatum and *N. hyalinum*	Skin infection in cement factory workers	All adult males	Nigeria	Oyeka and Gugnani, 1990
N. dimidiatum	Endophthalmitis in in right eye with painful corneo-scleral laceration in a farmer, h/o thorn injury. Treated with topical natamycin and amphotericin B following surgery and corneoscleral graft with administration of intravitreal miconazole and amphotericin B, and subconjunctival miconazole	M/40,	Saudi Arabia /Yemen	Al-Rajihi *et al.,* 1993
N. dimidiatum	Subcutaneous and invasive infection in a steroid diabetic patient with h/o COPD, congestive heart failure, and prior myocardial infarction	70/M	USA	Sigler *et al.,* 1997
N. dimidiatum	Onychomycosis	Adult male	Pakist-an	Bokhari *et al*., 1997
N. dimidiatum	Discharging lesion on left palm and on the dorsal aspect of right hand of 5 years duration following minor injury to right hand below wrist, h/o DLE. Therapy with ketoconazole was successful	24/F	India	Dhindsa *et al*., 1998
N. dimidiatum	Onychomycoses Case 1-dystrophic lesions on the nails of both hands, h/o HIV infection Case 2. dystrophic lesions on the nails of 1st, 2nd and 3rd toes of the right foot and on the 2nd and 3rd toes	38/M 32/F	Brazil	Lacaz *et al*., 1999
N. dimidiatum	Distil subungual Onychomycosis 2 cases in tea leaf pluckers. Case 1. Thickening and discoloration of the right thumbnail with occasional pain Case 2. Blackish discoloration of the right thumb nail with dystrophy and subungual hyperkeratosis in distil portion	44 and 55/F		Barua *et al..,* 2007
N. dimidiatum	Acute encephalomyelitis and cerebritis complaints of headache, low grade fever and vomiting of 10-day duration and weakness of the right side of the body for 3 days. The patient had received a total dose of 1500 mg of amphotericin B and 9600 mg of posaconazole, but he died due to complications of hydrocephalus with brain stem hypodensities	18/M	India	Mani *et al.,* 2008
N. dimidiatum	Small cutaneous lesions of 4 years' duration with grayish-green margin with slight central pitting on the sole and big toe of his right foot, mild scaling of the plantar surface. Successfully treated with topical application of 1% clotrimazole cream	25/M	Kuwait /Bang-ladesh	Khan *et al*., 2009
N. dimidiatum	Pulmonary infection with abdominal distension. Non-contrast CT of the chest multiple lung nodules, many of them cavitating, The patient was diagnosed to have diffuse large B cell lymphoma, h/o cirrhosis secondary to chronic hepatitis C virus infection. The patient was treated with antifungal drugs, liposomal amphotericin B, posaconazole and voriconazole, but the patient died	50/M	USA	Dionne *et al*., 2015
Scytalidium dimidiatum and *Lycthophora hoffmanii*	Intermittent productive cough, dyspnea with onset of facial pain and nasal discharged. Sinus X-ray confirmed maxillary sinusitis. later purplish, indurated weeping lesions were observed in the right inguinal regions, both feet and toes, h/o HIV infection and PCP	-	Austra-lia	Mariott *et al*., 1997
Macrophomi-na phaseolina and *Scyalidium dimidiatum*	Disseminated infection in a Sri Lankan borne LTR. Swelling, pain, and purulent discharge involving the left great toe	31/M	Canada	Tan *et al*., 2008

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Phoma hibernica	Skin and sub-cutaneous, raised, erythematous, nodular lesions on the upper surface of lower part of the left leg in a farm worker. Later the lesion spread to involve most of her anterior and median ankle areas. The patient was treated with griseofulvin 125 mg twice daily for over a 5 months.	22/F	Canada	Bakerspigel, 1969
P. oculo-hominis	Corneal ulcer, the fungus identified as a new species.	-	Sri Lanka	Punithalingam, 1976
P. cava	Violaceous nodules on the dorsum of right hand, h/o steroid therapy for pulmonary sarcoidosis. The patient healed after therapy with amphotericin B., followed by itraconazole.	53/M	Brazil	Zaitz *et al*.,1997
P. exigua	Fatal lung mass in a patient with acute myeloid leukemia and diabetes	-	Greece	Balis *et al*., 2006
P. herbararum	Onychomycosis and cutaneous lesion on foot	-	Italy	Tullilo *et al.,* 2010
Phoma sp	Persistent keratitis in a long term contact lens user	47/F	Greece	Adamopoulou *et. al*., 2019
Lasiodiploidea theobromae	Onychomycosis	40/F	Brazil	Restrepo *et al.,* 1976
L. theobromae	Subcutaneous ulcer on the anterior aspect of right leg following injury while stumbling on a wooden staircase in Jamaica	50/F	Canada	Summerbell *et al*., 2004
L. theobromae	Fugal sinusitis with intermittent bleeding and nasal discharge from the left side for I week, and complaint of headache, heaviness off and on left side for two months. The patient was treated by endoscopic surgery.	30/F	India	Kindo *et al*., 2010
L. theobromae	Corneal ulcer, h/o vegetable trauma	32/F	India	Saha *et al*. 2012
L. theobromae	Subcutaneous soft tissue swelling on the dorsum of right foot, h/o lacerating injury while walking in shallow ocean (diagnosed in Australia)	59/M	Kenya	Papacostas *et al.,* 2015
L. theobromae	Corneal ulcer extending to the superficial layers of stroma with complaint of pain, redness, photophobia and diminished vision, anterior chamber showed early nuclear sclerosis, h/o lacerating injury to the left eyebrow on medial aspect. Lesions resolved completely after 3 months of treatment with voriconazole 200 mg twice daily	50/M	India	Vanam *et al.,* 2019
Colletotrichum gloeosporioides	Tuberose-nodular erythematous violaceous lesions on his left forearm and elbow in a farmer, following injury by rotten wood h/o diabetes and hypertension. The fungal isolate was sensitive to flucytosine and azoles, but the patient could not be treated as he died of a car accident	56/M	Brazil	Guarro *et al*., 1998
C. gloeosporioides	Recurrent painful, necrotic ulcers covered by hemorrhagic crusts and purulent debris on the right lower leg, h/o recurrent stasis dermatitis and systemic corticosteroid therapy, and injury from orchid plants in her bedroom and balcony. She was successfully treated with oral itraconazole 100 mg twice daily for three months	70/F	Taiwan	Lin *et al*., 2015
Meaning of medical terms	Onychomycosis-Fungal infection of nails, Endophthalmitis -Inflammation of the anterior chamber of the eye, COPD-Chronic obstructive pulmonary disease, CLTR-Liver transplant recipient, h/o- History of, RTR-Renal transplant recipient, DLE-Discoid Lupus Erythematosus, PCP-*Pneumocystis carnii* pneumonia; Hematologic malignancies- Neoplastic (Cancerous) diseases of haematopoeic (blood forming) and lymphoid tissues.			

HUMAN INFECTION DUE TO *SCHIZOPHYLLUM COMMUNE*

The salient clinical and demographic features of some selected cases of human infection caused by *Schizophyllum commune* from several countries are presented in **table 8**. *S.commune*, a cosmopolitan macrofungal species belonging

Table 8: Infections caused by *Schizophyllum commune*

Type of infection	Age (in years) /Sex	Country	Reference
Ulceration of the palate with facial paralysis and ophthalmoplegia on right side, palpebral proptosis, anisocoria and bilateral hyporeflexia, and ophthalmoplegia	4/M	Brazil	Restrepo *et al*., 1973
Maxillary sinusitis with sudden nasal obstruction and purulent discharge. Computer tomography revealed extensive opacity of the maxillary sinus and also erosion of nasal wall and maxillary bone, h/o allergic rhinitis and dermatitis	36/F	Columbia	Sigler *et al*., 1997
Pulmonary infection, mucoid impaction of the bronchi manifesting as a component of ABPM. Chest X-ray showed bilateral, hilar band-like shadows. With mucous plugs in both B3 bronchi and consolidation, indicating atelectasis in the peripheral part of the mucous plugs	54/F	Japan	Ishiguro *et al*., 2007
Bronchopneumonia with a h/o gastric carcinoma and quiescent Hodgkin's disease. Chest X- ray revealed an abnormal infiltrative shadow	59/M	Italy	Tullilo *et al*., 2008
Maxillary sinusitis with nasal obstruction, purulent nasal discharge from right side of the nose, cough, headache, and sneezing. CT showed extensive opacity of the right maxillary sinus as well as erosion of the nasal wall and maxillary bone	50/M	India	Premamalini and Ambujavalli, 2011
Chronic sinusitis in an immunocompetent, non-diabetic patient with h/o chronic sinusitis and discomfort over her left frontal and maxillary sinuses for last one year, X-ray of paranasal sinuses showed a nodular mucosal thickening. A bone density CT scan of her sinuses showed polypoidal soft tissue attenuation lesion completely filling bilateral ethmoidal sinuses, and mucosal thickening of left maxillary antrum.	46/F	India	Swain *et al*., 2011
Two cases: **Case 1**- ABPA with progressive cough, purulent expectoration for the last 3 years, h/o of exposure to passive tobacco smoke and bagasse smoke while using its biomass as fuel for cooking for 20 years. She had also been inhaling corticosteroids. Patchy soft opacities were seen in chest X- ray. **Case 2**- Pneumonia with complaints of occasional hemoptysis for 1 year, h/o of diabetes mellitus for 10 years, and treatment of TB. Her chest x-ray revealed non-homogenous opacity in the right upper lobe. CEHRCT showed air crescent sign in the apical segment of the right-upper-Lobe	35/F 42/M	India	Chowdhary *et al*., 2012
Keratitis one case-A central corneal ulcer with greyish-white slough, feathery edges, and diffuse corneal edema, pain, redness and watery discharge in the right eye, h/o trauma with vegetable matter while working as farmer treated with topical natamycin and oral itraconazole	46/M	India	Joseph *et al*., 2012
Keratitis five cases: **Case 1**-2x 2 mm infiltrate with hypopyon, h/o trauma by vegetable matter. **Case 2**- 5x5 mm infiltrate with feathery margin and hypopyon, h/o trauma by stalk of tree **Case 3**-No record of clinical features, h/o trauma by vegetable matter. **Case 4**- No record of clinical features, h/o trauma with stone. **Case 5**- Clinical features and h/o trauma not known	43/M 45/M 23/F 33/M 50/F	India	Reddy *et al*., 2016
Erythema, papules, nodules revealed (granulomatous in histopathology), and scales on sole of the left foot for the last two years	25/F	China	Tian *et al*., 2018
Chronic non-invasive fungal rhinosinusitis	Not known	Italy	Cavanna *et al.,* 2019
Meaning of medical terms	ABPM-Allergic broncho-pulmonary myosis, h/o-History of, CEHRCT- Contrast-enhanced high-resolution computed tomography.		

to the *Schizophyllaceae* family in the phylum *Basidiomycota*, is recognized as a plant pathogen that causes wood rot on living trees, and many plant species including fruit and ornamental trees (Takemoto *et al.,* 2010; de Hoog *et al.,* 2019). Human Infections due to this fungus are rare. Diverse clinical cases include chronic or allergic sinusitis, pulmonary disease, ulcerative lesions of the palate, atypical meningitis, cerebral abscess, allergic broncho-pulmonary mycosis (ABPM), fungus ball, and keratitis, which can occur in both immunocompetent and immunocompromised individuals. Reports of *S. commune* sinusitis and keratitis in immuno-competent hosts are rare (de Hoog *et al.*, 2019). Maximum number of cases of ABPM and fungus ball have been reported from Japan with 33 cases (46%) and 1.4 to 7% in several other countries (Ishiguro *et al.,* 2007; Chowdhary *et al.,* 2012).

CONCLUSIONS

To the best of our knowledge, this review article presents for the first time a comprehensive review of various types of human infections caused by a great number of plant pathogenic fungi representing diverse taxonomic groups in several countries. The data provided here related to fungi pathogenic to humans should serve as a very good source of authentic information on human infections for medical mycologists and also plant pathologists in India, and other countries. A noteworthy finding in the review is the diverse types of human infections caused by plant pathogenic fungi as well as in some cases a combination of a plant pathogenic fungus and a fungal species not pathogenic to plants. The data presented mentions the therapy of many cases with antifungal drugs, and also the treatment of some cases by surgery alone. It is proposed that plant pathologists should carry out surveys of fungal infections acquired from infected plants in persons including the farm workers and suggest precautionary measures for such infections.

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