An in-sight analysis of molecular evolution of *Trichoderma* as emerging human pathogen

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Research Article

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Abstract

Due to climatic changes, anthropogenic activity and pollution, new variants of known species of human pathogens are emerging. Similarly, non-pathogenic *Trichoderma* spp are becoming pathogenic via molecular evolution. The literature survey provides us that some spp of *Trichoderma* (*T. longibrachiatum, T. viride*, T. *koningii, T, harzianum, T. citrinoviride, T. reesii, T. atroviride* and *T. pseudokoningi*) infected some organs of patients which were immune-compromised. These are the case of "cross-kingdom host jumps**".** The first case report was found in 1970. Latest case report was presented in 2019. So, after 50 years, 42 cases or episodes of *Trichoderma* infection to human have been recorded. In maximum cases *T. longibrachiatum* was involved. Proposed pathogenecity factors, molecular evolution and a hypothetical linage of evolution of clinical *Trichoderma* have been presented here. Although, this opportunistic pathogen is still not reported in COVID-19 patients, it may infect them as COVID-19 patients are with high risk factors.

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Introduction

Near about 50 years have passed since the first discovery or report of *Trichoderma* as opportunistic human pathogen which was surfaced in 1970. For this long year different species of *Trichoderma* have come in our close contact due to its manifold application in human society but how much it has acquired its pathogenecity or virulence via molecular evolutionary processes or adaptive evolution of gene sequence involving positive selection, is also a part of discussion in this review work. The systemic position of *Trichoderma* Pers., Fr includes genus *Trichoderma*, family Hypocreaceae, order Hypocreales and phylum Ascomycota but the taxonomy of *Trichoderma* is still rather incomplete, and the distinction of species in the genus *Trichoderma* remains problematic. Christiaan Hendri Persoon in 1794 (Römer's Neues Mag. Bot. 1: 92. 1794) introduced the genus *Trichoderma* in fungal taxonomy. Mukherjee et al. (1) noted more than 200 well-defined species of *Trichoderma* but about 260 species have been recognized and accepted by some scientists on the basis of phenotypic and phylogenetic analysis (2-5). According to Cai and Druzhinina6, validated spp of *Trichoderma* are 375 species. Many species of this genus yield bioactive compounds which have medical significance (1) and enzymes like cellulose,7 with huge industrial application (1). It plays a major role in ecology as decomposer of plant and animal residues in the soil. Several species of this genus have excellent antagonistic properties against plant pathogenic fungi and plant growth promoting agents (8- 15). Therefore, they are frequently being applied in agrifields for the biological control of several plant diseases (16,12). Most environmental opportunistic species of *Trichoderma* are generally abundant in agricultural habitat (17). Previously it has been regarded as nonpathogenic to humans or as a contaminant in organ site cultures in clinical study. But increase of case reports of *Trichoderma* infection in immune-compromised and immune-suppressed patients raised its clinical interest. These cases indicated that some spp of *Trichoderma* have acquired the ability of "cross-kingdom host jumps"18. van Baarlen et al. (18) highlighted a number of cross-kingdom pathogens including *Trichoderma*. The disease caused by *Trichoderma* sp is known as "hyalohyphomycosis", as the it exhibits the presence of hyaline septate hyphae in infected tissue under microscope (19). Now published case reports since 1970 are being reviewed in order to raise awareness of this emerging opportunistic pathogen. It has been noted that whatever the disease type and the therapy used, the prognosis for *Trichoderma* infection was usually poor, however, case reports on infections by this genus have increased due to increased number of immunocompromised patients like HIV/AIDS and the use of immune-suppressants for organ transplantation and cancer therapies (20 – 22). Other reasons behind increasing *Trichoderma* attack is the poor diagnostic tools. As this fungus has acquired resistant to commonly used antifungal agents (23,24), an effective control demands treatment with combination of different drugs(24,19). *Trichoderma* infections in human have been associated mostly with peritoneal dialysis, organ transplantation, and hematologic disorders. Other diseases attributed to members of this genus are allergic and acute invasive sinusitis, keratitis, otitis externa, skin and subcutaneous infections, peritonitis, deep pulmonary infections, endocarditis, and brain abscess. Even some spp of *Trichoderma* are pathogenic to plants. *T. viride* RF1 infects the seedlings of cucumber, pepper and tomato (25). *Trichoderma* has been reported to cause diseases of near about 32 genera of plants (26-30). In case of human, most infections are caused by *T. longibrachiatum*, but other species (*T. atroviride*, *T. citrinoviride*, *T. harzianum*, *T. koningii*, *pseudokoningii*, *T. reesei*, and *T. viride*) have also been reported occasionally (31,32,21). The sources of human and animal infections by *Trichoderma* species are still unclear (33,34) but agrifields may be one of main sources as members of this genus are cosmopolitan soil-inhabitation fungi and frequently found in the rhizosphere or as endophytes (33,34,30). Furthermore, its appearance has been noticed in damp walls of buildings (35,36). The opportunistic human infection nature of fungi relies on the ability to grow at 37°C temperature. So before using in agrifields isolates of *Trichoderma* must be tested *in vitro* for growth at 37°C which indicates a safety measurement for reducing our health risks (37). Furthermore, as the most frequent human pathogen within the genus *Trichoderma* is *T. longibrachiatum*, the random use of this species in agriculture and biotechnology must be restricted along with special care for handling (37). Under COVID -19 pandemic situation our society is already grappling with more cases and fatalities. For survival, COVID-19 patients are administered with steroids or glucocorticoids. On the other hand, administration of steroids results in a neutrophilic leukocytosis and steroids are also known to cause lymphopenia (T > B cells). Continuous use of glucocorticoids may increase the risk of the patient to infections of many opportunistic ones (38) including *Trichoderma* (39). Latter worker (39) reported a *Trichoderma* infected ottis externa induced by cortisteroid therapy and the use of steroids may be the cause of invasive fungal infection in post COVID-19 patients (40). Already mucormycosis is causing additional burden to our society (41,42). In this period, a great suspicion of increase of opportunistic cases of *Trichoderma* may increase like mucoromycosis which are on raising. Therefore, the main objectives of this work include searching and analysis

of the case reports of this fungus with management strategies, pathogenecity with molecular evolution, linage of evolution of this genus from saprophyte/ myco-trophy to human parasite.

Methodology

The database of PubMed, Google Scholar and other electronic data bases were attentively searched upto 30th June of 2021 putting *Trichoderma* associated mycoses, pathogenecity of clinical *Trichoderma*, antifungal therapy of clinical *Trichoderma*, evolution of *Trichoderma*, human fungal disease, evolution of human fungal pathogen, kingdom barrier jump of *Trichoderma* and keywords like *Trichoderma*, opportunistic fungi, etc. All original case study reports and reviewed works on this topic were downloaded and all were critically studied and this article was prepared on the basis of these information or data.

CASE STUDIES

T. longibrachiatum

It has been reported that *T. longibrachiatum* frequently causes lung and skin infections, allergic sinusitis, peritonitis, sinusitis sphenoidalis, as well as disseminated infections in the heart, stomach, liver and brain of immune-compressive patients (43–49). A fatal peritonitis by *T. longibrachiatum* complicating peritoneal dialysis was noted in a male patient of 48 year aged and he was treatment with amphotericin B but could not survived50. Similarly, a brain abscess patient of 17 year aged female was found due to infection by this pathogen and she was successfully cured after surgical resection and rigorous application of multi antifungal drugs (5-fluorocytosine, amphotericin B, itraconazole and ketoconazole)51. This fungus was recorded to infect a pediatric patient (11 year old male) with aplastic anemia and neuroanimia. He developed an invasive *T. longibrachiatum* infection which caused a lesion (2 cm diameter raised and round) on his wrist skin and subcutaneous tissue. The fungus was isolated from this infected zone. He was treated with amphotericin B for 3 months and recovered successfully (52). A liver and small bowel transplant recipient (29-year-old female) was suffering acute invasive sinusitis caused by *T. longibrachiatum* (53). The isolation of *T. longibrachiatum* was reported in a case from a HIV-positive patient54 but original paper was not available, it was noticed in the paper of Kedices et al. (21) . A male patient (44 year) who had received an allogenic bone marrow transplant for acute lymphoblastic leukemia was infected by *T. longibrachiatum*. The fungus was isolated from a perirectal ulcer biopsy and stool. The amphotericin B and itraconazole, were applied but patient failed to survive (55). A case of otitis externa infection by this fungal species in a child (39) and also a case of a fatal necrotizing stomatitis (oral) in a neutropenic patient with malignant lymphoma (56) were recorded. Chouaki et al. (23) presented of a case of *Trichoderma* infection on a 63-year-old woman liver transplant patient. The surgical removal and application of povidone iodine resulted the total recovery of the patient. The species was phenotypically identified as *T. pseudokoningii* but molecular (ITS1 5.8S ITS2 of r DNA) analysis showed it was *T. longibrachiatum*. Monitoring for 4 years showed no relapse of the infection (23). Same workers (23) reported another case report of *Trichoderma* infection in 11 year boy with pulmonary transplantation. The fungus was initially phynotypically identified as *T. koningii* but molecularly (ITS1 5.8S ITS2 of r DNA) it was *T. longibrachiatum*. The antifungal therapy was started with liposomal amphotericin B (5 mg/kg q.d.) along with itraconazole (5 mg/kg q.d.) but boy was expired. This fungus also has been found to cause invasive pulmonary infection in a neutropenic patient. The patient became infection free by treating with voriconazole combined with caspofungin (19). This fungus has been found to infect skin of a renal transplant recipient (46 year old male patient) in Tunisa. The patient was applied the immune-suppressive therapy. The fungal infection was successfully treated with voriconazole (57). A case of this fungal infection of stinitis and peritonitis in a patient (3 year old female) with congenital cardiac disease and asplenia has been recorded and initially she was administered with caspofungin alone and later on with a combination of caspofungin and voriconazole, and intraperitoneal amphotericin B but patient did not survived (58). Molnár-Gábor et al. (45) presented that infection of this fungus caused sinusitis sphenoidalis in an immune-competent patient with head ache. Rodríguez Peralta et al. (46) presented a case report of endocarditis of a male patient by this fungus. The removal of the infected catheter along with antibiotic therapy resolved the infection and patient was cured, and Tascini et al.*(*47) reported the case of endocarditis in a 30- year- old male patient (non-immunocompromised) that was due to the infection by *T. longibrachiatum*. The patient was cured after antifungal treatment (voriconazole and liposomal amphotericin B. Recently Akagi et al.(48) reported infection of a *T. longibrachiatum* in a 29-year-old man with severe aplastic anemia who underwent allogeneic stem cell transplantation. The latest case report associated with *T. longibrachiatum* is a constrictive pericarditis on a a 59-year-old farmer (male). After a pericardiectomy, unusual mould grew in the biopsy sample culture of the patient. He had received a lung transplant 2 months before, requiring immunosuppression with prednis one, tacrolimus, and mycophenolate mofetil. The contaminated fungus was confirmed as *T. longibrachiatum.* Although antifungal drugs were administered but the patient died (59) (Table 1).

T. viride

One female of 26 year age was infected from contaminated saline. The fungus was isolated from blood and she was treated by antibiotic amphotericin B and outcome of patient was disease free(60) . It was the first case study report on *Trichoderma* infection in human. *T. viride* was isolated from a pulmonary mycetoma in a patient (46 year old male) with chronic lung disease (61). The source of isolation was sputum and lung

biopsy. The treatment was surgery but outcome was not recorded. Peritonitis caused by *T. viride* were documented in 47 year old male patient undergoing continuous ambulatory peritoneal dialysis and patient was not survived (62). Warnock and Johnson63 presented another case study of peritonitis caused by *T. viride*. An infection of a perihepatic haematoma due to *T. viride* in a liver transplant recipient (44 year old female) was reported by Jacobs et al.(64) . Antifungal therapy was started by intravenously administration of amphotericin B (25 mg every other day) and later dose of this drug was increased (50 mg daily). Then it was switched to intravenous fluconazole with 200 mg daily for the first **4** days, then reduced to 200 mg. every other day because of renal insufficiency and later surgical removal of the infected haematoma was done, but, the patient died of unrelated complications (64). A case report of nonfatal pulmonary infection caused by *T. viride* in leukemia patient of 54 year old female came to surface. *T. viride* was isolated from pulmonary aspirate culture from the patient who had treated by chemotherapy for acute myeloid leukemia (65). After treatment by voriconazole and caspofungin, patient was cured from fungal infection (Table 1).

T. harzianum

This member of the genus also infected peritonitis patient of 82 year old male and killed the patient although he was treated with 5-fluorocytosine and ketoconazole (66) while a fatal systemic infection of *T. harzianum* in a renal transplant recipient (68 year old male) has been reported (67). Here patient was not treated with antifungal as fungus was identified phenotypically after postmortem examination. Another fatal *T. harzianum* infection in a leukemic pediatric patient of 9 year old boy was documented by Lu et al. (68) (Table 1).

T. koningii

This species of *Trichoderma* has been reported from peritoneal fluid of two patients. One of these two was 63year old female and she recovered from this infection by removal of Catheter (69) and another patient was 41year old female and treated with antibiotics (5-fluorocytosine, amphotericin Bandfluconazole) but did not survive (70) (Table 1).

T. pseudokoningii

Till now two cases have been reported. In one case this fungus infected a bone marrow transplant recipient (45-year-old female) and this infection was fatal (71). In another case peritonitis patient (33-year-old male) was infected by *T. pseudokoningii*. After removal of catheter, patient survived (72) (Table1).

T. citrinoviride

It has been isolated from blood cultures of a patient in aplasia associated with lymphoma. The original report was not available and it was mentioned in the paper of Kredics et al. (21). Kviliute et al. (73) reported a non-fatal pneumonia infected by this fungus in an acute myeloid leukemia patient.

T. reesei

A case of *Trichoderma* infection of a cerebrospinal fluid shunt device in a non- immune-compromised patient of 61-year-old male following two cerebrospinal fluid shunt placements for congenital hydrocephalus. The *Trichoderma* was identified as *Trichodenna reesei*. The patient was administered with 3 antifungal drugs for two months and improved. Later cysternal -ventriculostomy was done and the patient become disease free after stopping antifungal treatment (74) Table 1).

T. atroviride

A liver transplant patient (49-year-old man) with a hepatocellular carcinoma in the context of alcoholic cirrhosis was infected by this fungus (75) (Table1). The fungus was molecularly (PCR base ITSs Zone of r DNA) identified. A probabilistic treatment with 800 mg/day oral fluconazole was administered. Later on antifungal was switched to voriconazole (400 mg bid) on day-16. Patient died.

Trichoderma sp.

Keratitis by *Trichoderma* spp. was recorded by Venugopal et al. (76). Amato et al. (77) reported an AIDS patient with *Trichoderma* sp. The details of these two cases were not available. Bustamante-Labarta et al. (78) presented an embolic fungal endocarditis of an aortic conduit in a patient

(66-year aged male). The fungus was identified upto genus (*Trichoderma*). The patient was administered by antifungal drugs but antifungal drugs were not mentioned and survived. A case of peritoneal fluid infection by *Trichoderma* sp. in a patient (40 year old male) with continuous ambulatory peritoneal dialysis was recorded by Esel et al.(79). The catheter was removed and antifungal like itraconazole was applied for 28 days but the patient's condition became poor and patient expired within 10 days (79). A 64-year old female with metastatic carcinoma of the colon was infected with fungi. Bronchoalveolar lavage (BAL) was positive for *Aspergillus* species and an unknown fungus species. Later on, unknown species was identified as *Trichoderma*80. Recently a 45-year-old Caucasian male who was severely immune-compromised (a multiple myeloma patient), was reported to be infected by *a fungus* and it was a case of *Trichoderma* fungemia with pulmonary. He was recovered from this fungal infection by treatment with voriconazole81

Table 1. Different case study reports of infection in human by different species of *Trichoderma*

Trichodrma sp	Type or Infected organ of patient	Molecular identification of fungi (ITSs Zone)	Age(year)	Gender	Treatment	Outcome	Reference
T. longibrachiatum	A fatal peritonitis (peritoneal fluid infection) of renal transplantation, CAPD patient.	No	48	Male	AmB	Died	50
	A brain abscess infected by this fungus patient	No	17	Female	Surgical resection with 5-FC, AmB, Itraz. and ketoz.	Cured	51
	A lesion on wrist skin of the patient with aplastic anemia and neuroanimia	Yes	11	Male	AmB for 3 months	Cured	52
	An acute invasive sinusitis caused this fungus in a liver and small bowel transplant recipient.	No	29	Female	Surgical debridement and AmB followed by oral itraz	Cured	53
	Fungus isolated from a HIV-positive patient.	No; details of fungus is not found	NF	NF	NF	NF	54
	Fungus isolated from stool cultures and a perirectal ulcer biopsy specimen from an allogeneic bone marrow transplant patient. Probably it was the first report of acquisition of fungus through the gastrointestinal tract.	Yes	29	male	AmB and itracz.	Died	55
	Otitis externa (otomycosis) in a 12-year-old child with history of otitis and subjected to corticosteroid therapy	Yes	12	NF	A combination of nystatin, polymyxin B, and oxytetracycline	Cured	39
	A fatal necrotizing stomatitis (oral) in a neutropenic patient.	Yes	66	Female	Itraz. capsules and oral rinses with AmB syrup (100 mg/ml)	Died	56
	A case of Trichoderma infected pulmonary edema in pulmonary transplantation patient	Yes	11	Male	LamB (5 mg/kg q.d.) and itracz. at the same dosage	Died	23
	A case of Trichoderma infected liver transplant patient.	Yes	63	Female	surgical debridement and administration of povidone iodine	cured	23

	An invasive pulmonary infection in a neutropenic patient	yes	16	Male	Voriz. combined with caspof.	Cured	19
	A fungal infection in blood of neutropenic patient with pulmonary cancer and HIV patient	Yes	58	Male	Removal of catheter and AmB. and voricz.	Cured	82
	Skin infection of a renal transplant recipient	No	46	Male	Voricz.	Cured	57
	A case of *T longibrachiatum* post-operative media stinitis and peritonitis in a child with complex congenital cardiac disease and functional asplenia	Yes, and also D1/D2 region of the 28S rRNA gene	3	Female	Caspof. & Voriz. (systemic and topical) and AmB	Died	58
	A sinusitis sphenoidalis in an immune-competent patientwith head ache by infection of this fungus.	Yes	29	Female	surgery and AmB	Cured	45
	A case of endocarditis on a catheter of a patient due to the infection of this fungus.	No; No description, preservation & molecular identification of fungus was done.	51	Male	Surgery and Caspof.	Cured	46
	A case report of first-time endocarditis in a non-immuno-compromised patient.	yes,	30	Male	Voricz and LamB	Cured	47
	A severe aplastic anemia by infection of this fungus who underwent allogeneic stem cell transplantation	No, no description, preservation & molecular identification of fungus was done	29	Male	Am B.	Cured	48
	A constrictive pericarditis of a lung transplant patient by infection .	No	59	Male	AmpB, voricz, etc	Died	59
T. viride	A n infection of blood of one patient who was infected from contaminated saline. This is the first case of *Trichoderma* infection in human.	No	26	Female	AmB	Cured	60
	A pulmonary mycetoma caused bythis fungus in a with chronic lung disease	No, no description, preservation & molecular identification of fungus was done	46	Male	Surgery	Not recorded	61
	A peritonitis caused by this fungus	No, no description, preservation & molecular identification	47	Male	No scope of treatment as patient died very soon.	Died	62

		of fungus was done					
	A peritonitis caused by this fungus	No, no description, preservation & molecular identification of fungus was done	NA	NA	NA	NA	63
	A haematoma infected by this fungus of liver transplant recipient.	No	44	Female	Surgery; AmB and Flucz.	Died	64
	A nonfatal pulmonary infection caused by *T. viride* in leukemia patient.	No	54	Female	Voricz. and caspof	Cured	65
T. koningii	A peritoneal fluid infection of a patient	NO	63	Female	Removal of Catheter	Cured	69
	A peritoneal fluid infection of a patient	No	41	Female	AmpB and Flucz., 5-FC	Died	70
T. harzianum	A peritonitis (peritoneal fluid) infection by this fungus	No	82	Male	5-FC and ketoz	Died	71
	A systemic *T. harzianum* infection in a renal transplant patient.	No	68	Male	No scope of antifungal treatment as fungus was identified after postmortem examination	Died	66
	An infection in a leukemic pediatric patient.	yes	9	Male	LamB	Died	67
T. pseudokoningii	A systemic infection of this fungus in a bone marrow transplant recipient	No	45	Female	LamB and flucz.	Died	71
	A peritonitis (peritoneal fluid) infected by *T. pseudokoningii*.	No description of fungus, no molecular identification but preserved in culture collection centre	33	Male	removal of catheter	Cured	72
T. citrinoviride	It has been isolated from blood cultures of a patient in aplasia associated with lymphoma.	NF	Nf	NF	NF	NF	21
	A nonfatal pneumonia caused by this fungus in an acute myeloid leukemia patient.	No description and molecular identification of fungus and preservation in any culture collection center	49	Female	AmB.	cured	73
T. reesii	A case of *Trichoderma* infection of a cerebrospinal fluid	No	61	Male	Antifungal	Survived	74

	shunt device in a non-immune-compromised patient.						
T. atroviride	A case of this fungal infection in liver transplant patient	Yes	49	Male	Flucz. and Voriz.	Died	75

Note: AmB, Itraz., Voriz,, Flucz., Kitonz, 5-FC and LamB are the short or abbreviated forms of Amphotericin B, Itranozole, Voriconazole, Kitanozole, 5 Flucytosine and Liposomal amphotericin B respectively.

ANALYSIS OF PATHOGENECITY OR VIRULENCE FACTORS AND MOLECULAR EVOLUTION

The evidences from case reports published since 1970 indicate that *Trichoderma* strains are potential opportunistic pathogens in immunocompromised patients. Truly speaking, pathogenecity or virulence associated factors in fungal pathogens are less understood and concurrently the investigation on pathogenicity or virulence factors of clinical *Trichoderma* strains is very few. Here some proposed factors or characteristics are raising which are supposed to be act as pathogenicity or virulence factors (Fig.2).

1. Kredice et al. (83) recorded the extracellular proteolytic enzymes of six clinical *T. longibrachiatum* isolates. They noted chymotrypsin-like, trypsin-like, and chymoelastase-like protease activities. So protease production ability is one of virulence factors or pathogenicity factors (Fig.2)

2.The opportunistic human infection nature of fungi relies on the ability to grow upto 37°C temperature 37 or 40^0C (84). It has been investigated that protease activity of *Trichoderma* isolates at 37°C is more than at other temperatures (85). Growth temperature 37^0C or 40^0C may represent another important virulence factor of opportunistic *Trichoderma* strains In addition potential virulence factors of *T. longibrachiatum* as an opportunistic pathogen are hemolytic ability, toxicity to mammalian cells and the resistance to pH values ranging from 2 to 9 (86). These workers worked on virulence factors of 12 clinical and 9 saprophytic *T. longibrachiatum* strains on some parameters like growth temperature, pH, C and N source, sensivity of antifungal drugs and their capacity to cause human infection. On the whole on the basis of experimental results they come to conclusion that there were no significant differences in the examined features between clinical or soil isolates. It is surprising to note that workers recorded no specific phylogenetic traits of the clinical isolates in comparison to environmental isolates, and the correlation between virulence and genomic structure was not observed (84,37). Furthermore, here a comparative analysis of clinical isolate and soil isolate (MTCC No 11582) of *T. longibrachitum* on cultural and microscopical characteristic parameters has been presented (Table 2). It indicates that there is no difference between clinical and environmental isolates on those parameters. The question is coming that whether all environmental isolates of *Trichoderma longibrachiatum,* if come to contact with us under immunocompromised state, have the ability to infect or not.

Table 2 A comparative analysis of clinical and environmental isolate of *Trichoderma longibrachiatum* on the basis of cultural and microscopical characteristics

Trichoderma longibrachiatum			
Clinical isolate		**Environmental Isolate (MTCC**11582)	
Cultural characteristics	**Microscopical characteristics**	**Cultural characteristics**	**Microscopical characteristics**
On PFA (Potato flakes Agar) medium, fungus can grow very good at upto 35^0C and the colonies are floccose having concentric yellow -white and green to green pale rings after 4 days of growth (56) or can grow at upto 42^0C temperature (55). In addition, colony texture initially smooth, glabrous, translucent, and awatery white but later became light green to olivaceous green and woolly with concentric rings. The color of reverse plate is lemon yellow (55)	The hyphae -hyaline, smooth, septate, and branched; conidiophores- long, branched with main branches. The main branches with few, short, often slightly curved side branches at right angles, each terminating in a phialide. Phialides (5 - 11 /2 - 3 µm) - bottle shaped, mostly solitary, inflated in the middle and bent at the apex, and slightly constricted at the base and. Terminal phialides - more elongate, not constricted at the base, and were upto 14 µm long. Phialoconidia (3.4 - 6.4 /2.4 - 3.0 µm)- smooth walled, green, ellipsoidal to cylindrical. Chlamydospore (5 to 10 µm in diameter)- occasional seen, thick walled. smooth, subglobose to ellipsoidal (55).	Colonies grow rapidly, covering full PDA plate in 4 days with concentric zones of white and yellow or green, color at first white, then turns paler green (Fig1A). Reverse plate usually greenish yellow (87).	Hyphae- hyaline, branched and smooth. Conidiophores -colorless, smooth, arising from substratum or from aerial hyphae, form irregular tufts, main brunches usually long and relatively straight, septa conspicuous and distant, Phialides -usually single or in verticils of 2-3, swollen near the beak and attenuated abruptly near the beak, apex usually bent at sharp angle. Conidia- smooth, ovoid to sharp cylindrical, dilute green in color, apex broadly rounded, 3.4-5.2 µm × 2.3-3.5 µm in size (Fig. 1D) (87.88).

3. The resistance to antifungal drug is another virulence factor and *T. longibraciatum* is also resistant to antifungal compounds such as fluconazole, itraconazole, and amphotericin B (56,89). However, most important thing is that *T. longibrachiatum* not only causes disease, at the same time, it secretes potential antifungal agents which are inhibitory to *Aspergillus* and *Candida* species (89,90). By producing and secreting of antifungal agents *Trichoderma* secures its own territory.

4. Iron acquisition or sequestration ability from host is one of important virulence factors. It is very essential in microbes for running their cellular processes. It has been recorded that amount of iron in animal cells has 20 and 100 times lower in comparison to plants (91,92), and the iron tightly binds to diverse types of molecules in intracellular (heme, iron-sulphur proteins, and ferritin, as well as in other proteins) as well as extracellular (transferrin and lactoferrin proteins) (93,94). Invasive microbial pathogens (e.g *Erwinia* sp, *Pseudomonas aeruginosa, Burkholderia, Rhizopus*, etc) apply strategy for iron acquisition from environment or host cells and one of the important mechanisms is the production and secretion of small iron-chelating protein called siderophore (95-99). In some cases like the plant pathogen *Erwinia chrysanthemi*, siderophores have been shown to serve as pathogenicity factors (100,101). In *Cryptococcus neoformans*, fungal pathogen of pneumonia and meningitis, it has been noted that that the iron-responsive transcription factor (Cir1) regulates genes employed in iron acquisition, and also controls important virulence characteristics (102). A correlation between the ability of iron acquisition and cross-kingdom pathogenicity has been noted in some cases. Similarly, many *Trichoderma* spp produce different siderophores for acquisition of iron from environment. *Trichoderma spp* produce coprogens (103). We observed that *T. longibrachiatum* can produce hydroxamate and carboxylate type of siderophore, although the strain was not clinical but it parasitizes larvae of insect *Leucinodes orbonalis* (11, 104). In our and other workers' study it was also recorded that other spp *T. harzianum, T. viride, and T. asperellum* by siderophore acquire iron (11,13,105,106) .

5. Biofilm formation is an important virulence factor for pathogenic fungi. Both yeasts and filamentous fungi can attach and anchor on host surface and abiotic surfaces, creating a compact organized communities that are resistant to host antimicrobial surveillances and antimicrobials agents and biofilm has effect on immunomodulation of host. Biofilm formation can protect fungal pathogens from many aspects of the innate immune system including killing by neutrophils and monocytes. Many clinically relevant fungi have been shown to form biofilms such as *Aspergillus* sp, *Candida* sp., *Cryptococcus neoformans, Rhizomucor sp, and Rhizopus* sp.(107-110). Biofilm formation of pathogenic fungi impairs the hosts innate immune responses, Biofilms of *Candida albicans* and *A. fumigatus* interfere the function of macrophages and neutrophils. Kernien et al. (111) summarized the innate immune responses impaired by biofilms of *Candida albicans* and *A. fumigatus*. Biofilm of *C. albicans* decreases fungal killing, modifies cytokine production of monocytes, inhibits migration of macrophages, decreases killing of fungus and hampers neutrophil extracellular trap (NET) release and ROS production, and phagocytosis(111) of neutrophils. Genetic or antibody-mediated damage of biofilm reduces virulence (112,113,109) (Fig.2). Biofilm formation capacity of *Trichoderma viride* on roots of plants has been reported (114,115). It also causes opportunistic human disease. Tascini et al.(47) were able to isolate *T. longibrachiatum* from catheter tip of a patient only when it was subjected to vortex and sonication but the plain washing failed to isolate the fungi as the biofilm was formed by it

on the sample surface. So, clinical isolates of *Trichoderma* may have capacity of biofilm formation and it may act as pathogenicity or virulence factor but for more evidence more experimental investigations are needed .

6. Immuno-modulation by fungal products as pathogenecity factor

Immunomodulation in host by pathogen is one of important pathogenicity factor. Fungal metabolites or components may modulate the immune system. Fungal molecules trigger immune down modulation; specially here to mention cyclosporin A (CsA) which is produced by *T. harzianun* fungi, is well recognized immunodown regulating drug (116- 1180. The main mechanism of immunomodulatory function of CsA includes inhibition of calcineurin (119), inhibition of NO production (120) and downregulation of the signaling pathway of the NFκb transcription factor through the inhibition of TLR4 expression (119). For its unique immunosuppressant action, CsA is potentially used in medical science for preventing acute rejection in organ transplantation (121,122). The impact of CsA from environmental fungi may be as one of pathogenecity factor in human. In addition, other fungal product's toxicity specially the toxicity of the gliovirin and gliotoxin (ETPs) may be important pathogenecity factor by diminishing expression of tumor necrosis factor resulting the inhibition of the AP1 and NFκb-factors transcription (123). Furthermore, gliotoxin, impairs some mechanisms of innate immunity like phagocytosis, activation of the NADPH oxidase complex that is for the generation of reactive nitrogen species (ROS), NFκB nuclear factor, etc(124). Gliotoxin in human monocyte cell lines, creates a cytokine imbalance by blocking IL-10 (interleukin -10) production (125). A group of *T. virens* strains known as Q strains produces gliotoxin, which is a virulence factor in *A. fumigatus* 1. Chitin and β-glucan polymers of fungus act as pathogen-associated molecular patterns (PAMPs) and are able to modulate the innate immune response of various cells like macrophages, monocytes, macrophages, neutrophils, and NK (126 – 128). Helvolic acid secreted by clinical strains of *Aspergillus fumigatus* blocks the respiratory oxidative burst which is necessary to the innate immune response in animals (129).The compromised immune system may favor the development of opportunistic pathogens (130) and even neoplastic diseases (131) (Fig.2).

Now we can look on the molecular evolution of fungus from saprophytic to human pathogens. The transfer of fungi from environmental organic niche to human cell leads them a tuff challenging condition, so fungi adopt several evolutionary processes to normalize their growth in new niche or host jump. The use of different "omics" like genomics, proteomics, transcriptomics, metabolomics etc to human pathogenic fungi indicated that different genetic machineries or processes are involved in acquisition of pathogenicity associated genes. In this case gene duplication to provide raw materials for new ORFs (open reading frame) has been highly accepted in CGA (comparative genomic analysis) studies for explaining evolution of virulence factor of pathogenic fungi (132). Gene duplication can facilities the fungi to fit in new niche by performing new functions. The CGA of *Saccharomyces* and *Candida* genome give us information that three cell wall associated gene families (proteins: ALS, IFF, PGA 30) are dominant and tandem duplicated in pathogenic strains and they have great role in host parasitic interaction (133). In *Candida glabrata*, Epa gene family produces proteins that act as host recognition and adhesion (132). In most fungi (e,g *Aspergillus fumigates*), the telomeric proximal zones have duplicated genes for pathogonenecity but in *C. albicans*, they are dispersed (134). According to Fedorova et al.134 the telomeric zones of *Aspergillus* function as "gene factories". Another speculation for new gene or pathogenicity gene appearance is due to horizontal gene transfer (HGT). Although it is prominent in bacteria and marginal in fungi, recently HGT cases are surfaced in good number in fungi. As for examples we can site that URA1 of the *S. cerevisiae*, has come from *Lactobacillus* sp through HGT. So *S. cerevisae* evolved to grow as anaerobic (135). Similarly a cluster of genes which are responsible for secondary metabolism in plant pathogenic fungus *Magnoporthe grisea*, has been transferred to *A. clavatus(*136). The most striking feature of gene transfer between the interkingdoms has been recently documented when a gene encoding a proline racemase and a gene involved in the metabolism of phenazine have been transferred from *Burkholderia* spp. to *C. parapsilosis* (137). So it may have a role in evolution of virulence in fungi including *Trichoderma.* Another case is the adaptive evolution of gene sequence involving positive selection that may have a role in evolution of pathogens. Several gene families showed positive selections like IFF-HYR1 in *Candida* sp (133). Recently, Moran et al. (132) summarized the genomic processes involved in the evolution of human fungal pathogens during discussion of comparative genomics and the evolution of pathogenecity in human pathogens. It includes four events: i. Gene duplication and expansion, ii) Telomeric expansion, iii. Gene loss and pseudogenization, and iv. Horizontal gene transfer. Workers mentioned that virulence and its associated factors have evolved by same mechanism in primary and opportunistic human pathogens. During adaptation in host, *C. albicans* exhibits several transcriptional programs, which become activated as soon as it faces host conditions including oxidative stresses, alkaline pH and morphogenetic signals138. These transcriptional programs might play a role in the evolution of *C. albicans* from an ancestral, environmental yeast to pathogenic(139). Although above findings are not related to *Trichoderma,* we may predict that same genomic machineries are operating in evolution of *Trichoderma* pathogenicity or virulence. In future CGA or Transcriptomics studies on both clinical strain and environmental strains of *Trichoderma* may solve this problem.

A PROPOSED LINAGE OF EVOLUTION OF OPPORTUNISTIC *TRICHODERMA* PATHOGEN

Saprophytic fungi have evolved to grow in organic matters, some of its factors which influence its growth in this environmental nice, invariably allow it to survive and flourish in human with immunocompromised state. Opportunistic pathogens grow on the substrates rich in organic matters, and have low virulence against living hosts. But, if suitable host species become immune-compromised, these pathogens can cause severe or fatal disease. The evolution of obligate and facultative pathogens has come from opportunistic infections of pathogen (140,18). So, it is presumed that opportunistic disease causing isolates or strains of *Trichoderma* could followed its evolution in the following linage: Saprophyte

(thrive on a wide range of organic substrates) → Mycoparasite or mycotrophy (parasite on another fungi) → symbiotic association with plants (endophyte) → Plant parasite (on some members of plants → animal parasite (on some animals) → opportunistic human parasite → obligate and facultative pathogens ?? (Fig.3). In support of this proposed line of evolution it has been noted that maximum members of *Trichoderma* are ubiquous and grow in soil or rhizospheric soil as saprophyte (141, 33,34, 30) and appear in other environments. They frequently come in contact with members of other fungi (same kingdom), involve in host parasitic interaction and gradually become mycopararasite (8-13).

In the course of evolution of *Trichoderma*, some genes are acquired by antagonistic *Trichoderma* and these genes are responsible for antagonistic mechanisms like mycoparasitism, antibiosis, competition, inactivation of enzymes secreted by pathogens, etc. In- depth analysis showed that these genes are involved for synthesis of enzymes (like chitinase, protease, glucanolytic enzymes), biosynthesis of poliketides, non-ribosomal peptides, terpenoids, pyrones, aegerolysin, etc (142). It was documented by the fact that parasitic spp. (*T. atroviride* or *T. virens*) of *Trichoderma* contain more genes (near about more 3000 genes) than non- or lesser antagonistic spp. of *Trichoderma* (*T. reesei*) (143).

Mycoparasitism, by which *Trichoderma* draws nutrients from another fungus, has been recognized as an ancestral trait of this genus (144,1). Next some members (e.g *T. viride*) of them after frequent associated with plants become symbiotic (endophyte) (145) and also adopted as plant pathogens as found from the reports of some workers (25-30). It means that it developed cross –kingdom host jump as proposed by van Baarlen et al. (18). At the same way we found that some spp of *Trichoderma* involved in host –parasitic interaction and acquired parasitism ability or genes (e.g., Tc toxin gene[146]) to invertebrate animal like insects as evidence from our works that *T. longibrachiatum* parasitizes to larvae of *Leucinodes orbonalis*(104) and *T. asperellum* on larvae of mosquitoes (147, 148) and some spp (*T. longibrachiatum*, *T. viride*, *T. harzianum*, *T. koningii*, *T. atroviride, T. pseudokoningii*, *T. reesei* and *T. citrinoviride*) have developed to be opportunistic pathogens to vertebrate specially in human. It means this genus again developed cross –kingdom host jump. Now question may come how different kingdom hosts may be infected by same pathogen or same pathogen how can invade the barrier of defense of different kingdom hosts. Here we can site some information: Comparative genomics of the eukaryote give us that the number of disease associated genes of human are 289 (identifiable), nearly 80 % of disease associated genes in human genome has a distinct orthologue in the insect *Drosophila melanogaster*, about 70 % has an orthologue in another invertebrate, the nematode *Caenorhabditis elegans* (149) and 60% of these human disease-associated genes have an ortholouge in the plant species *Arabidopsis thaliana* (150). These indicate that the molecular machinery needed for host defense has major fundamental similarity, and at the same time, the ability of pathogen to invade a specific defense mechanism in one host and same ability is successful partially or fully to overcome similar mechanisms of defense in other hosts. Most probably, the capacity of a microbe to cause disease in different kingdom hosts is depended on the homologies in innate defense machineries among hosts (18).

TREATMENT STRATEGIES

Antifungal drug susceptible of some species of *Trichoderma* with MIC (minimum inhibitory concentration) values as recorded by scientists are presented in the table 3. The 5-flucytosine and fluconazole are resistant to maximum spp of *Trichoderma* and major members of *Trichoderma* are found to be high to moderate sensitive to itraconazole, amphotericin B, ketoconazole and myconazole (52,53, 55) (Table 3). The MIC values of amphitericin B and itaconazole were 24 and 64 µg/ml against *T. longibrachiatum* (Table 3), so this sp is becoming resistant against these two antifungal drugs(39) .In the case of *Trichoderma* infection in a neutropenic patient with pulmonary cancer and HIV, the central venous catheter was removed and antifungal therapy includes empirical treatment with amphotericin B for seven days and then it was shifted to oral voriconazole (400 mg twice-daily on day 1, and then 200 mg twice-daily) for 2 months. This therapy was able the patient free of fungal infection (82). A 3- year- old patient was treated empirically on renal adjusted doses of fluconazole (3 mg. kg-1 every 24 h) along with antibacterial antibiotics and the caspofungin dose (67 mg kg-1 per day) was started. Intravenously voriconazole was applied instead of oral as its solubility in water is poor58. Festuccia et al.(53) administered voriconazole intravenously at a loading dose of 400 mg twice a day on the first day, followed by maintenance dose at 200 mg twice a day against *Trichoderma* infection. Mycafungin as presumptive antifungal therapy was applied against *T. longibrachiatum* until a neutrophil count reached to >500/µL. Later on L-AmB was administered at a dose of 1 mg.kg-1 for three days and patient was recovered 48. Amphitericin B and voriconazole were administered in a patient with constrictive pericarditis of a lung transplant patient who was infected by *T. longibrachiatum* after a pericardiectomy but the patient did not survived (59). Tasina et al.47 initially administered 200 mg bid oral voriconazole to the patient infected by *T. longibrachiatum*, after a loading dose of 400 mg bid for only the first day. After 3 days, the concentration of voriconazole in plasma was evaluated and it was below the sensitivity limit (0.01 mg/L). So voriconazole was administered by intravenously. Later on voriconazole was replaced by liposomal amphotericin B. An invasive pulmonary infection in a neutropenic patient and by treating with voriconazole combined with caspofungin, patient became disease free19 . In case of stomatitis infected by *T. longibrachiatum*, the mouth of patient was regularly washed by a syrup of amphotericin B (100 mg/ml) along with swallowing of oral itraconazole capsules (200 mg/day). Later on amphotericin B (50 mg/day) was applied intravenously on day 25. The patient was administered a total dose of 1160 mg of amphotericin B but the patient did not survived (56). Trabelsi et al.(57) applied voriconazole to a renal transplant recipient who was infected by *T. longibrachiatum* and patient was completely cured. Sequin et al.(51) administered amphotericin B and surgical removal to a patient, having brain abscess infected by *T. longibrachiatum* and the patient become recovered. Invasive sinusitis in a liver transplant patient due to *T. longibrachiatum* was also successfully treated with surgery and long antifungal therapy (53). A paediatric patient with aplastic anaemia recovered from a cutaneous lesion due to *T. longibrachiatum* with antifungal therapy (52). In case of disseminated *Trichoderma* infections the mortality of patients was near about 100% (32). Overall treatment strategy indicates that in cases of suspected or confirmed cases

of *Trichoderma* infection, amphotericin B alone or in combination with itraconazole or ketoconazole is advocated as perfect choice of treatment, but the duration of therapy must be individualized to each case on the basis of the type and intensity of the infection and predisposing conditions of patient (52). Surgical removal of infection is also another strategy whenever feasible (32).

Table 3 Antifungal sensivity study of some species of *Trichoderma* and MIC of antifungal drugs as reported by some workers

Trichoderma	MIC(µg/mL) of antifungal drugs							
	Amphotericin B	Fluconazole	Itraconazole	5-flucytosine	Voriconazole	Caspofungin	Ketokonazole	Reference
T. atroviride	1	64	8	64	8	0.5	NT	75
	0.016-8	64-256	0.5-32	NT	NT	NT	0.008-1	89 .
T. longibrachiatum	2	16	1	>256	NT	NT	NT	55
	24	NT	32	NT	NT	NT	NT	39
	1.16	80	0.3	>322	NT	NT	NT	53
	2	>64	2	>64	NT	NT	NT	52
	2.5	12.5	1.25	50	NT	NT	NT	51
T. citrinoviride(2 isolates)	0.064 and 2	>256	24	NT	NT	NT	0.25 and 0.5	89
T. koningii(2)	0.5 and 8	>256	2 and 4	NT	NT	NT	0.25	89
T. pseudokoningii	0.25	>256	8	NT	NT	NT	0.25	89
T. pseudokoningii	0.09	25	0.18	>100	NT	NT	NT	71
T. viride	0.78	NT	NT	100	NT	NT	1.56	62
T. viride	0.25	NT	8	NT	2	NT	NT	65
T. viride	3.1	25	1.6	50	NT	NT	0.8	64
T. harzianum	2	128	32	256	NT	NT	NT	67

Note : NT indicates not tested

ANALYSIS OF CASE REPORTS

From the literature survey as described above, since the first report of *Trichoderma* disease, we found that total 42 case studies have been recorded by different scientists. Out of 42 cases, 35 cases *Trichoderma* was identified upto species level and in seven case reports *Trichoderma* was identified upto genus only but in maximum cases methods of identification was based on phenotypical characters but not molecular method, and most probably, latter was unavailable in clinical sector. The spp were *T. longibrachiatum* (nineteen cases), *T viride* (six cases), *T. koningii* (Two cases*),T. pseudokoningii* (two cases), *T. harzianum* (three cases), *T, citrinoviride* (two case), *T. reesii* (one case) and *T. atroviride* (one case) . In only 11 of 36 cases molecular (PCR bases ITSs zone of r DNA) method was adopted to identify the fungus upto species level. Here it must be mentioned that the report of *Trichoderma koningii by* Ragnaud et al.(69) and similarly case reports of *T. viride* by Loeppky et al. (62), and also another case report of *T. viride* by Jacobs et al (64) as human opportunistic pathogen were questionable as their descriptions and preservations were not available for verification of their identity (141). Out of six cases where fungus was upto genus *Trichoderma*, two cases (case report presented by Venugopal et al.(76) and by Amato et al.(77) showed no details like patient's age, gender, treatment strategy. Out of remaining four cases, 3 were male and 1 was female; 3 were recovered after treatment and one expired. Out of 42 cases, nineteen cases were due to *T. longibrachiatum*. So, it reveals that *T. longibrachiatum* is most frequent and dangerous pathogen. Out of 42 cases, the numbers of male patients were 22 and female were 14 and gender of other(six cases) was not mentioned in their case study. It may infer that female are more prone to this fungal genus infection. The age ranges from 3 to 82 year. In four cases age of patient was not available. So 38 [42-6] cases age were mentioned.The minor age group upto 18 year old patient consists of eight cases. The number of patients above 60 year were 8. Age group 19 to 60 consists of 26 cases. Within range of 30 to 60 year age, the number of patients were 16. It indicated that age group 19-60 were more vulnerable to this fungal infection. It was interesting to note that all patients were immune-compromised or immune-suppressed except two cases where one case was endocarditis in a 30- year- old male patient due to the infection by *T. longibrachiatum* as presented by Tascini et al.(47) and another was infection of a cerebrospinal fluid shunt device by *T. reessii* in a non immunocompromised patient of 61-year old male presented by Piens et al.(74). In maximum cases antifungal drugs such as amphitericin B, itraconazole, fluconazole, voriconazole, 5-fluorocytosine and ketoconazole were administered. Amphitericin B administration by intravenously was first choice. Fungal important target sites are mainly two such as plasma membrane and cell wall. The antifungal used in maximum cases were plasma membrane (PM) target specific like Amphotericin B (polyene macrolide group) that is ergosterol specific, and itraconozole, fluconazole, ketokonazole and voriconazole (azole group) which are PM sterol biosynthesis inhibitors. But 5-flucytosine which is RNA specific target site. Cell wall target specific fungicides like caspofungin and mycafungin which are β 1, 3 glucan biosynthesis inhibitor were used in few cases but chitin biosynthesis inhibiting agents were not used as they were not available. Surgical removal of infection which was restricted to defined zone or organ was done also in few cases. Regarding outcome, it was revealed that out of 42 cases, 5 cases had no mention of outcome of patient. So out of 37 cases [42-5], 15 patients died but 32 patients were successfully cured after antifungal drug treatment. So near about 40% patient died. In case of *T. longibrachiatum*, out of 19 cases, 1 patients' outcome was not recorded. So out of 18[19-1], 6 patients died and 12 patients survived. So, death rate in case of *T. longibrachiatum* was 33.3%.

Conclusion

Trichoderma is now enlisted in list of genera containing emerging fungal pathogens, so, *Trichoderma* isolates are major threat for our health care. Till now no case report of this fungus in COVID19 patients has been reported but we can suspect that *Trichoderma* may line up in a queue behind mucormycosis which is already invading in COVID19 patients. In this work the proposed pathogenicity or virulence factors of clinical spp, molecular evolution and linage of evolution of *Trichoderma* from saprophyte /mycoparasite to human pathogen may create interest among young workers and provide some clues for further analysis. The whole-genome sequencing of clinical spp like *T. citrinoviride* and *T. longibrachiatum*, which have been completed, will direct CGA and CTA (comparative transcriptome analysis) among spp of *Trichoderma*, as a result evaluation of the microevolutionary steps occurring on a relatively recent timescale and revealing new genes and their products which are responsible for cross kingdom jump. From the case reports analysis, we can say that they are threatening us as they are difficult to diagnostic early and so, we are facing therapeutic challenges. Furthermore, they are resistant to most antifungal agents. Therefore, without rapid and proper diagnosis and treatment their clinical manifestations can be fatal, The proper and quick identification of clinical strains upto species level is crucial for proper therapy or treatment; however, it is only possible by reliable molecular methods such as PCR based the ITSs regions of rDNA, a fragment of the tef1 gene and other genomic markers. Moreover, by introducing next generation antifungal drug in medical science, we can solve the antifungal resistance traits of *Trichoderma*. So new fungal target specific drugs for antifungal therapy in medical science is very urgent. After all, awareness and a joint effort from researchers, physicians, clinicians and the drug manufacturing companies are necessary to fight against this emerging fungal opportunistic pathogen.

Declarations

COMPETING INTERESTS

Author has no financial and non financial conflict interests

CONTRIBUTORS

SKG is sole contributor of the conceptual idea, analysis, literature collection, interpretation as well as writing the Ms and figure creation.

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Figures

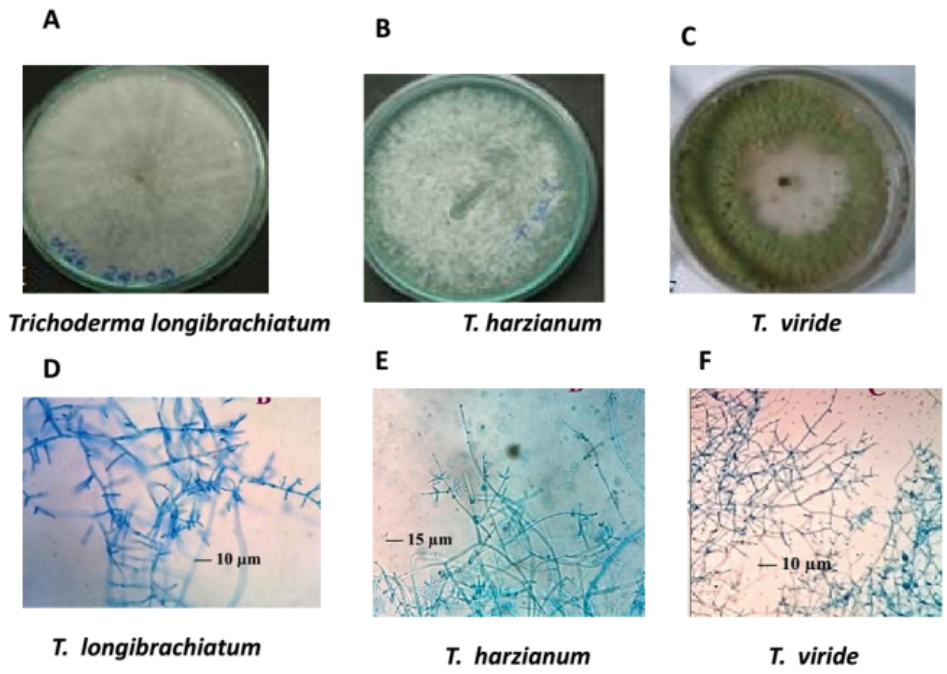

Figure 1

Cultural (A, B, C) and microscopical characteristics (D, E, F) of *T. longibrachiatum (A, D), T. harzianum* (B, E) and *T. viride* (C, E)

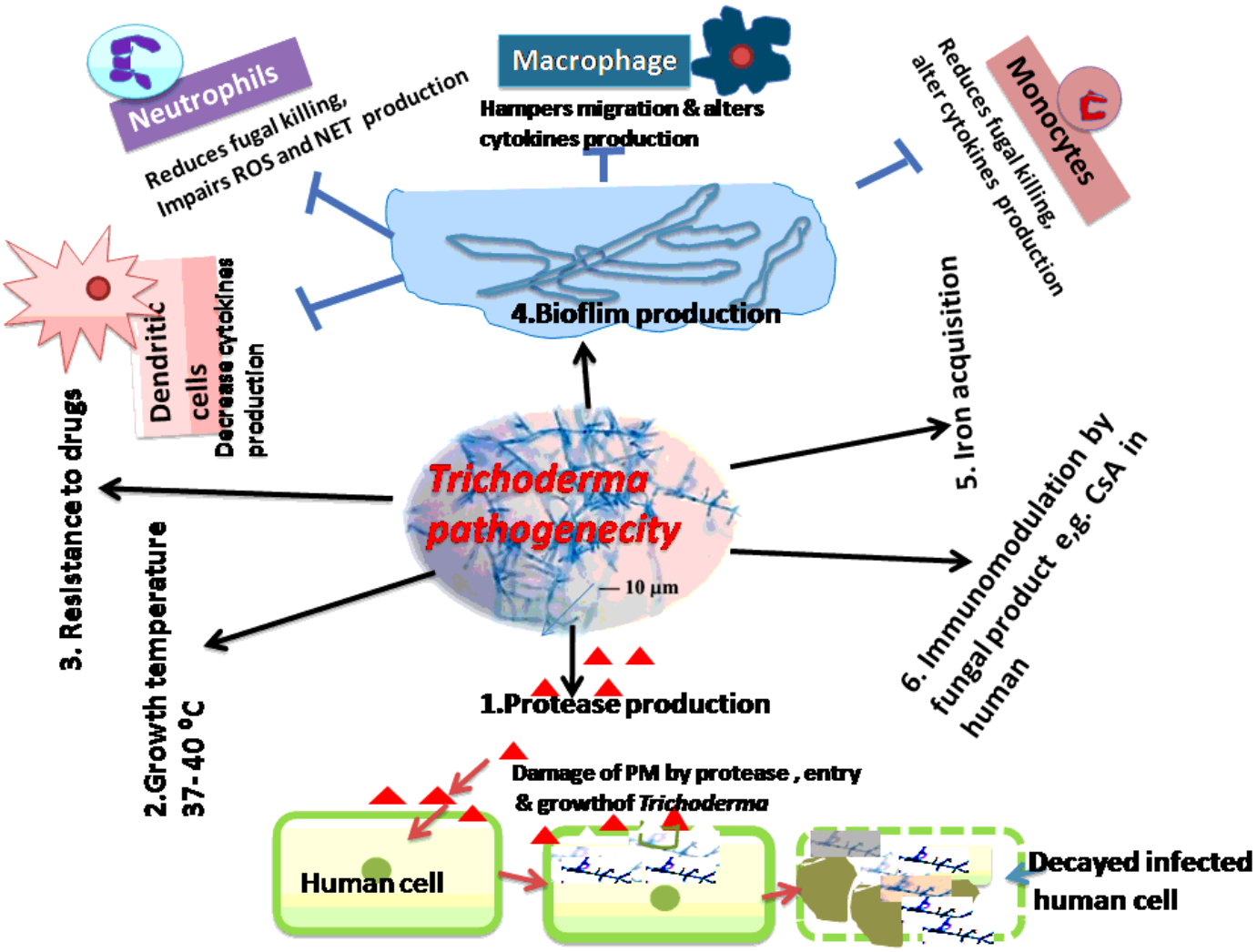

Figure 2

Diagrammatical presentation of pathogenicity or virulence factors (PM indicates plasma membrane)

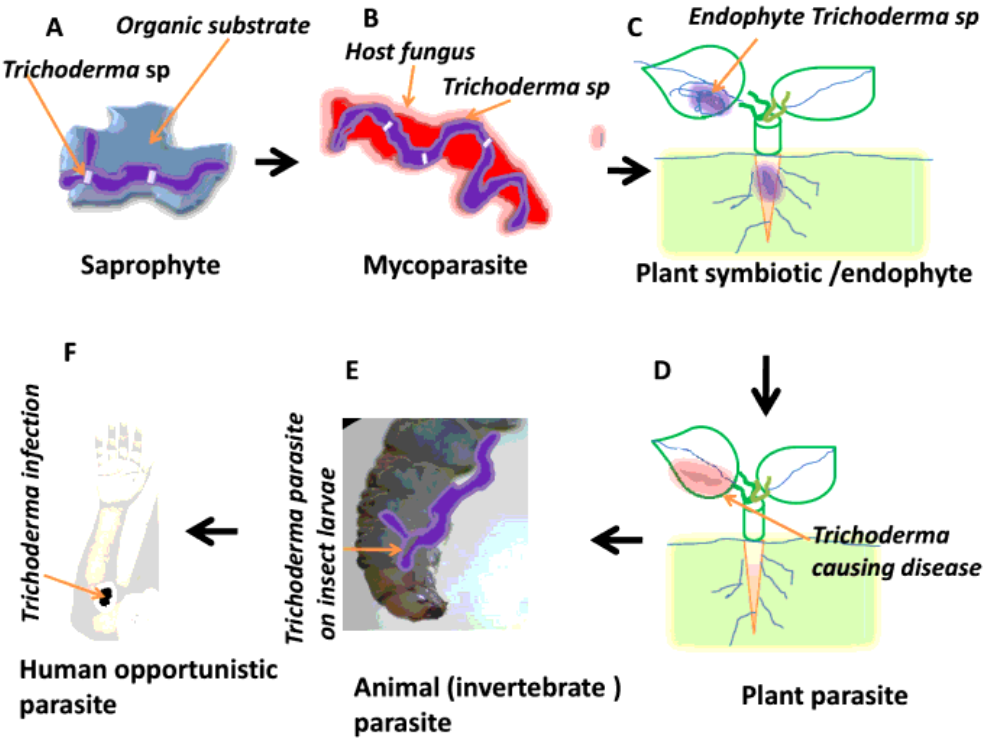

Figure 3

Pictorial representation of proposed linage of evolution of *Trichoderma* from saprophyte to parasite a, Saprophyte indicating hyphae of *Trichoderma* (Purple) grows on organic substrate, B Mycoparasitism indicates hyphae (purple) of *Trichoderma* coiled around host fungus (red) and parasitizes C, Plant symbiotic or endophyte shows endophytic *Trichoderma* (pink) in leaf and root cells. D, Plant parasite indicates disease symptom on leaf. E, Animal invertebrate parasite shows *Trichoderma* hyphae (pink) grows on larva of insect. F, Human opportunistic parasite showing lesion (black) on skin of human hand. All figures were drawn on the basis of information of references (18, 25-30,33,34. 141,144, 145,147,148,104,138)