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EMERGING FUNGAL PATHOGENS - A MAJOR THREAT TO HUMAN LIFE

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ABSTRACT: Statistical figures represent that fungal infections are the major cause of thousands of deaths each year. Despite the availability of treatment options invasive and systemic fungal infections have alarmingly higher mortality rates. This current review tabulates such fungal organisms that are pathogenic and fatal to human. This article provides a compilation of all Mycoses in human and also reports about the risk group of each fungus based on which, the level of risk caused by fungi can be determined. Infections caused by Dimorphic fungal pathogens (Blastomyces, Coccidioides, Marneffei) and Dematiaceous hyphomycetes (Cladophialophora, Rhinocladiella) belong to major fatal causing risk group 3 resulting in higher death rates of individuals. It also reports about various types of possible classification of mycoses *i.e.* based on reaction of human to fungi, host susceptibility, pathogen type, body location and risk group. The article highlights the estimated incidence of fungal diseases due to these pathogens, but these statistical figures are usually underestimated so there is a great need for advancement in understanding of fungus, their resistance along with immunity reports. In order to meet all these disease combating requirements, many high quality research initiatives with proper sources of funding and encouragement have to be provided. Article also reviews the major antifungal drugs available along with their brief pharmacokinetic profile. It also briefs some take home remedies in order to prevent and treat major fungal infection along with the alternative and novel modelling techniques developed recently for drug designing to target various development stages of fungal organism.

INTRODUCTION: The fungal kingdom incorporates a colossal difference of taxa with varied ecological niches, life-cycle strategies and morphologies. However, very little is known about the true biodiversity of this Kingdom. An estimation of about 1.5 million species belongs to this kingdom, of which only about 5% were formally classified [1].

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Formerly 600 species are known to cause disease, but 99 per cent of these diseases can be attributed to 30 different kinds of fungi [2]. Of these 600 species of fungi which can infect humans to cause a variety of diseases, over 90% of all fungus-related deaths are due to species belonging to only mainly the following genera: [3] Candida, Cryptococcus, Aspergillus, Pneumocystis and Histoplasma.

Fungal infections are the leading cause of death in both developed and developing countries. Fungal diseases affect a large proportion of the population ranging and severity of mind superficial infections to life threatening invasive diseases [5]. Each year fungi are responsible for around 1.5 million deaths and cost $12 billion to treat worldwide [4]. This is

due to the use of immune-suppressive treatment long term use of antibiotics and longer survival of immune-compromised individuals [6].

Fungal infections can cause serious illnesses, several of which may be fatal if left untreated. These include aspergillosis, coccidioidomycosis, candidosis, cryptococcosis, mycetomas, histoplasmosis, mucormycosis, and paracoccidio-idomycosis [7]. The dermatophytic and keratinophilic fungi mainly attack eyes, nails, hair, and especially skin and result in local infections such as ringworm and athlete's foot. Fungal spores are also a cause of allergies, and fungi from different taxonomic groups can provoke allergic reactions [8].

METHODS: The literature search was done for this systematic review by searching the electronic data base namely Myco Bank, Index fungorum, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE in Process and Other non-Indexed Citations, PubMed, the Guidelines The international Network (GIN), Excerpta medica database (EMBASE), international association for plant taxonomy (International Code of Nomenclature for algae, fungi, and plants - Melbourne Code), guideline. gov, ISI Web of Science, Google, Scopus, Ebsco, Index Copernicus, Science Direct, African Index Medicus (AIM), Thomson Reuters (ESCI), Chemical Abstracts Service (CAS), Scientific World Index (SCIWIN), Google Scholar, Index Medicus, various sites for ongoing trials namely clinical trial registry (www.clinicaltrials.gov), Indian Clinical Trials Registry and the World Health Organization (WHO) and abstracts of conferences namely Proceedings of international conference on fungal genetics, European conference on fungal genetics, Neurospora, Stratergies of the Fungal Infection Trust etc., References of papers were meticulously checked, and search strategies included the following Medical Subject Heading (MeSH) terms: Fungi, Fungal pathogens, Dermatophytoses, Mycosis, Fungal infection, Systemic infection, Superficial infection. All references were compiled into a database and managed with Endnote Library version X7 (End-Note, Philadelphia, PA, USA).

Fungal Infection - A Major Trait: In the early 50s fungal infections were not even known to human till antibiotic resistance occurred. These days fungal infections have become tough than the bacterial infections and there is also an alarming increase in the infections of opportunistic invasive fungal infections in immune-compromised individuals.

These fungal infections in humans can be classified into (a) allergic reactions to fungal proteins, (b) toxic reactions to toxins present in certain fungi and (c) infections (mycoses). Healthy individuals are susceptible to a host of superficial, cutaneous, subcutaneous and in certain instances, systemic infections [9]. Systemic infections are again categorized based on the health status of the individual affected as primary infection (affecting immune-competent individual) and opportunistic infections (immune-compromised individual).

Immuno-competent individual can be affected by fungi by inhalation of fungal spores, which can cause a localized pneumonia as the primary manifestation of infection and later turn into invasive fungemia spreading to all the other parts of the body. Many fungal infections are caused by opportunistic pathogens that may be endogenous (Candida infections) or acquired from the environment (Cryptococcus, Aspergillus infections) [10]. Immune compromise can be because of ailments such as AIDS, azotemia, diabetes mellitus, neoplastic disease, lymphoma, leukemia, other hematologic cancers, burns and therapy with corticosteroids, antibiotics, immune-suppressants, or anti-metabolites. Patients who spend more than several days in an ICU can become immune-compromised because of undergoing blood and marrow transplantation (BMT), solid-organ transplantation, and major surgery (especially gastrointestinal surgery) [11-14].

Table 1 presents different clinically relevant fungal pathogens which cause major and fatal fungal infections in human along with mainly risk group (2 and 3 mainly) that they are associated with.

Cutaneous Mycoses (dermatophytoses) are usually caused by antropophilic fungi (reside on human skin) such as Trichophyton, Epidermophyton, Microsporum and their transmission is mainly through infected skin scales. Their main source of nutrition is keratin so mainly infect skin, hair and nails [34]. Here the exception is that Microsporum

does not infect nails and Epidermophyton does not infect hair, they do not invade underlying non-keratinized tissues [35]. For example: Tinea pedis (athlete's foot) caused due to *Trichophyton rubrum, Trichophyton mentagrophytes* and *Epidermophyton floccosum* mainly affecting the feet with an estimated cases of around 1 billon [32]. *Tinea capititis* (scale ring worm) caused due to Trichophyton and Microsporum affecting the hair shafts with an estimation of 200 million cases [33].

TABLE 1: CHARACTERISTICS OF MAIN FUNGAL INFECTIONS WORLDWIDE

Infection type	Pathogen type	Frequent genus	Risk group	Body location	Organ	Estimated incidence*
Oral	Oppurtunistic	*C. tropicalis, C. glabrata, C. pseudotropicalis, C. guillierimondii, C. krusei, C. lusitaniae, C. parapsilosis,* and *C. stellatoidea*	RG-2	Mucosal	Mouth	~13.3 million [15]
Oesophagal	Oppurtunistic	*Candida* species (*C. albicans*)	RG-2	Mucosal	Oesophagus (gullet)	~3 million [16]
Vaginal	Oppurtunistic	*Candida* species	RG-2	Mucosal	Vagina	80 million [17]
Candidaemia	Oppurtunistic	*Candida species* (*glabrata, krusei, parapsilopsis, auris, tropicalis* etc.,)	RG-2	Systemic	blood	~400,000 cases [18]
Candida peritonitis	Oppurtunistic	*Candida albicans, C. tropicalis, C. glabrata* and *C. parapsilosis*	RG-2	Systemic	Stomach	60,000 - 100,000 cases [19]
Invasive aspergillosis	Oppurtunistic	*Aspergillus* (*fumigates*)	RG-2	Systemic	Lungs	10 million [20]
Cryptococcal meningitis	Oppurtunistic	*Cryptococcus neoformans* and *Cryptococcus gattii*	RG-2	Systemic	Brain	~1 million [21]
Pneumocystis pneumonia	Oppurtunistic	*Pneumocystis jirovecii*	RG-2	Systemic	Lungs	~14.8 million [22]
Mucormycosis	Oppurtunistic	Subcutaneous-*Rhizopus, Mucor, Rhizomucor, Lichtheimia, Basidiobolus ranarum, Conidiobolus coronatus* Saksenaea etc. Systemic-Rhizopus, Mucor, *Rhizomucor, Lichtheimia* etc.	RG-2	Subcutaneous Systemic	skin,, Sinus, brain,, lungs	13 per 100,000 [23]
Allergic bronchopulmonary aspergillosis	Oppurtunistic	*Aspergillus (fumigates*)	RG-2	Systemic	Lungs	4.8 million people [24]
Severe Asthma with Fungal Sensitisation	Oppurtunistic	*A. fumigatus* and *C. albicans,* with *A. alternata, Trichopyton* spp., *Cladosporium herbarum*, Penicillium chrysogenum* and *Botrytis cinerea*	RG-2 *RG-3	Systemic	Lungs	~6.5 million [25]
Allergic fungal sinusitis	Oppurtunistic	*Aspergillus* (*fumigate*)	RG-2	Mucosal	Sinus	~12 million [26]
Chronic pulmonary aspergillosis	Oppurtunistic	*Aspergillus (fumigates, niger)*	RG-2	Systemic	Lungs	1.2 million cases [27]
Coccidioido-mycosis	Primary	*Coccidioides immitis, C posadasii*	RG-3	Systemic	Lungs	25,000 cases [28]
Histoplasmosis	Primary	*Histoplasma capsulatum*	RG-3	Systemic	Lungs	50 million people [29]
Fungal eye infections	Oppurtunistic	*Candida, Fusarium, Aspergillus*	RG-2	Mucosal	Eye-cornea	1-6 million [30]
Onychomycosis (tinea unguium)	Primary	*Trichophyton rubrum, Candida albicans, Scopulariopsis brevicaulis*	RG-2	Superficial	Nails	~1 billion people [31]
Tinea pedis	Primary	*Trichophyton rubrum, Trichophyton mentagrophytes,* and *Epidermophyton floccosum, Scytalidium dimidiatum, Scytalidium hyalinum*	RG-2	Cutaneous	Feet	~1 billion people [32]
Tinea capitis	Primary	*Trichophyton* and *Microsporum.*	RG-2	Cutaneous; superficial	Hair	200 million cases [33]

*adapted from "The Fungal Research Trust. How common are fungal diseases? Fungal Research Trust 20th Anniversary meeting. London June 18th 2011. updated April 25th 2014"

Subcutaneous mycoses usually occur at dermal, sub tissue and bones usually chromo-blastomycosis, mycetoma and sporotrichosis. These are usually acquired through traumatic lacerations or puncture wounds [36]. Chromo-blastomycosis is generally caused by *Fonsecaea pedrosoi, Fonsecaea compacta, Cladosporium carionii, Phialophora verrucosa* and mycetoma is caused by

Pseudallescheria boydii, *Nocardia brasiliensis* [37]. Sporotrichosis caused by *Sporothrix schenckii* is an usual fungal infection characterized by Granauloma ulcer at a puncture skin usually a thorn prick and may produce secondary lesions along draining lymphatics [38].

Mucosal infections are usually caused by *Candida* spp. and have become opportunistic infections. Oral, oesophagal, vaginal have become most common *Candida* infections in immune-compromised patients. For example: Thrush is a mucosal fungal infection usually caused by *Candida* spp.(mainly) in the oral parts, oesophagus accounting for at least 3-13 million cases [15-16] and vaginal thrush reported from nearly 80 million cases [17]. Other mucosal infections resulting from both *Candida and Aspergillus species* are also seen. For *e.g.*: Allergic fungal sinusitis is a mucosal fungal infection caused due to *Aspergillus fumigates* affecting the sinus cavities estimated to have around 12 million cases reported [26]. Fungal eye infections caused due to *Candida, Fusarium* and *Aspergillus* mainly infect the cornea of eye reported to have around 1-6 million cases [30].

Systemic fungal infections are those which can affect any part of the body in the deep underlying tissue. These were initially considered to be primary infections mainly such as coccidioidomycosis and histoplasmosis.

Coccidioidomycosis is generally caused by *Coccidioides immitis, C posadasii* and affects the lungs with an estimation of upto 25,000 cases [28] and Histoplasmosis is caused by *Histoplasma capsulatum* affecting the lungs of around 50 million people [29]. Apart from primary infections these turned into opportunistic infections resulting into chronic, invasive and life- threatening fungal infections. Cryptococcus meningitis caused by *Cryptococcus neofarmans* and *Cryptococcus gattii* disseminates to brain resulting in fatal meningitis in the immune-compromised individuals accounting for upto 1 million cases [21].

Apart from all the above classification fungal pathogens are also classified based on the risk group. Risk groups are a way of categorizing the level of risk associated with a particular biological agent [39]. Risk groups range from lower *i.e.* Risk Group 1 (RG1) to Risk Group 4 (RG4) which includes those of highest risk. These are usually given by the European Economic Community (DIRECTIVE 93/88/EEC, Oct. 1993), NIH Guidelines on Recombinant DNA (April 2002), Canadian Laboratory Bio safety Guidelines (2nd ed. 1996), CDC/NIH Bio safety in Microbiological and Biomedical Laboratories (4th Edition 1999) accounting almost the same information with minor variations [40]. Based on these guidelines risk groups are categorized as:

Risk Group 1 means microorganisms that are unlikely to causes disease in humans, animals, plants or fungi.

Risk Group 2 means microorganisms that -

- May cause disease in humans, animals, plants or fungi but are unlikely to be a serious hazard to laboratory personnel, the community, animals or the environment and;
- Have effective treatment and preventative measures with respect to any infections that they may cause; and
- Present a limited risk of the spread of infection.

Risk Group 3 means microorganisms that are pathogens -

- That usually cause serious human, animal, or plant disease and may pose a serious hazard to laboratory personnel; and
- That could present a risk if spread in the community or the environment; and
- In respect of which effective preventative measures or treatments are usually available.

Risk Group 4 means microorganisms that are pathogens -

- Usually cause life-threatening human or animal disease and pose a serious hazard to laboratory personnel; and
- That is readily transmissible from:
    - An individual human to another human or to an animal; or
    - An individual animal to another animal or to a human; and
- In respect of which effective treatment and preventive measures are not usually available.

Table 1 presents different clinically relevant fungal pathogens which cause major and fatal fungal infections in human mainly based on the risk group (2 and 3 mainly) that they are associated with.

Treatment Options Available:

Antifungal Drugs: Antifungal drugs are utilized to treat fungal infection. From the small nail fungus to vaginal disease and to yeast along with other fungal infections, there it is an antifungal drug accessible to the condition in the form of tablets, capsule, fluid, syrups, cream and gels. Using anti fungal drugs also has its adverse effects if not taken correctly. There is every probability of the condition to reoccur and recurrent illnesses are common [41]. The best part is to know about the different antifungal drugs, their adverse effects as well as their severity. Here's a record of common antifungal drugs as well as what to anticipate from them.

Terbinafine: This can be the frequently used drug for antifungal infections due to dermatophytes [42].

Itraconazole: These are utilized for infection from molds or yeasts. It is drawn in simple doses that's, you take one pill a week monthly for months. Itraconazole is most successful in 45 to 70% of individuals utilizing it [43]. It signified that a normal nail was obtained from 53 to 80% of users. Drug interactions are common, particularly with antibiotics and asthma medicines [44].

Clotrimazole: It had been among the first azoles to be developed. It is utilized for treating *Candida albicans* as well as the dermatophytes [45]. It is also available in a wide range of combinations with antibiotics and corticosteroids. This drug was among the first successful antifungals for superficial dermatophyte infections as well as yeast diseases [46]. Adverse effects might include local discomfort or burning when first applied.

Fluconazole: This can be given once a week for many weeks. Dose adjustment is required in patients with renal function impairment [47]. It causes adverse effects like abdomen pain, sickness, constipation, diarrhea, lack of appetite, frustration, dizziness and sleepiness [48].

Ciclopirox: It is a topical antifungal drug and is utilized in the treatment of superficial antifungals. It is effective against dermatophytes both systematically and topically [49]. For the threatening fungal infections this drug is commonly suggested. Adverse effects are like itching, sting, irritation, including abdomen pain, sickness, diarrhea, constipation, lack of appetite and seldom hepatotoxicity [50].

The treatment options available and various anti fungal drug profiles are tabulated in **Table 2**.

Combination Therapy: Over the past fifteen years, there was a major rise in the number of readily available antifungal agents [112]. The newer agents are assessed to a lesser extent in children compared with adults. Amphotericin B is a wide spectrum antifungal agent and its products can be found as parenteral agents [90]. The lipid based agents which are most easily readily available for clinical use are Amphotericin B lipid complex and Liposomal Amphotericin B [113, 114]. A 3rd lipid based merchandise amphotericin B colloidal dispersion is correlated with more temperature and chills compared with traditional amphotericin [115]. The primary purpose for voriconazole is in the therapy of invasive aspergillosis, where it is become the favoured therapy of invasive pulmonary aspergillus in older kids and adults [116].

Currently in clinical practice, this agent has been used as salvage therapy in scenarios wherein first line antifungal agents have failed or are contra indicated due to toxicity. These agents are glucan synthesis inhibitors that specifically inhibit β-D-Gulcan synthesis, thus endangering the strength of the fungal cell wall [75]. It is always used coupled with Amphotericin B in the therapy of candida or Cryptococcus infection, notably requiring the nerve system [117]. Many experts advise combination treatment for many problems including nerve system fungal infections, illness with imperfect reaction to initial treatment, particularly where optimal dosage is compromised by toxicity [118]. Empirical treatment of serious illness presumed to be due to microorganisms which are known to have unique fungal susceptibility profiles and initial treatment of selected cases of invasive pulmonary Aspergillosis especially for diseases in moments from the major mediastinal blood vessels [119]. Medication overhears happened due to distress between the lipid established adductors and

conventional Amphotericin B. The dose of conventional Amphotericin B shouldn't exceed 51mg/kg/day Oral: Parentral; 6mg/kg neonatal; 3mg/kg/day for candidiasis; 6mg/kg/day to 12mg/kg/day for invasive fungal infection; 6mg/kg/day for suppressive therapy in HIV infected children with cryptococcal meningitis [120]. So combination therapy of Amphotericin B for candida infection and cryptococcal infection is always advised in order to reduce the dose.

TABLE 2: ANTI FUNGAL DRUGS PROFILES

Drug	Year of Introduction	MOA	Spectrum	Resistant species	Dose	Route of admin
Clotrimazole	1969	Inhibit specifically the demethylation of 24-methylene-dihydrolanosterol	Isolates of dermatophytes, pathogenic yeasts, and filamentous and dimorphic fungi, as well as some gram-positive bacteria.	*Candida* spp.	60-100 mg/kg	Topical [45, 51-54]
Econazole	1969	Disrupting cell membrane systems- 14-α demethylase inhibition	Dermatophytoses, Superficial mycoses, Cutaneous candidiasis, Actinomycetes, moulds	*Candida* spp.	50mg once daily for 15 days	Topical [51, 55-56]
Miconazole	1969	Alters the cellular permeability, and thus the exogenous respiration	Dermatophytes, yeasts, dimorphic fungi, *Aspergilli* and the mycetoma-causing agents	*Candida* spp.	100-200 mg	Topical [51, 57-59]
Oxiconazole	1979	Destabilize the fungal cyctochrome P450 51 enzyme (also known as Lanosterol 14-alpha demethylase)	Dermatophytes, yeasts, some gram-positive bacteria	*Candida* spp. *M. furfur*	100-200 mg	Topical [51, 60-64]
Ketoconazole	1981	Inhibit the biosynthesis of ergostero	Wide range of yeasts, dermatophytes and aspergilli	No data available	200-400 mg	Oral; Topical [65-67]
Fluconazole	1988	Inhibition of cytochrome P-450-dependent 14α-sterol demethylase	Yeasts, dimorphic fungi	*Candida* and *Aspergillus* spp.	100-400mg	Oral [43, 68-71]
Itraconazole	1988	Inhibition of cytochrome P-450-dependent 14α-sterol demethylase	Dermatophytes, yeasts, Moulds, some gram-positive bacteria	*Candida* spp.	100-400mg	Oral [43, 68, 72, 73]
Voriconazole	2002	Inhibiting the cytochrome P-450-dependent 14a-demethylase	Dermatophytes, yeasts, Moulds, some gram-positive bacteria	*Candida* and *A spergillus* spp.	200-400 mg	Oral [70, 74, 75]
Posaconazole	2005	Inhibiting the lanosterol-14alpha-demethylase	Dermatophytes, yeasts, Moulds, dimorphic fungi	Not present	600-800mg	Oral [70, 76, 77]
Caspofungin B	2001	Blocks the synthesis of β(1,3)-D-glucan of the fungal cell wall	Yeasts, Moulds	*Candida* spp.	35-70 mg	IV [78-80]
Micafungin B	2002	Potent inhibitor of 1,3-β-D-glucan synthase	Yeasts, Moulds	*Candida* spp.	50-150mg	IV [70, 81, 82]
Anidulafungin	2006	Acts on beta-1,3-D-glucan synthase inhibiting the formation of beta-1,3-D-glucan	Yeasts, Moulds	Not much reported	100-200mg	IV [83-86]
Amphotericin B	1958	Acts by binding to the	Yeasts, Moulds,	*Candida*	0.6-1.0	IV; Oral also [87-90]

		sterol component of a cell membrane, leading to alterations in cell permeability and cell death	dimorphic fungi, some gram-positive bacteria	species; *Pseudallescheria boydii*; *Malassezia furfur;* some species of *Trichosporon* and *Fusarium*	mg/kg/day	
Nystatin	1950	Impairs cell membrane function by binding to sterols in the membrane of susceptible organisms	Yeasts, Moulds, dimorphic fungi, some gram-positive bacteria	*Trychophytoncandida* spp, *S. cerevasiae, mucoplasma* spp	375 mg	Topical; Oral; [91-95]
Natamycin	1955	Binds to ergosterol in the plasma membrane, preventing ergosterol-dependent fusion of vacuoles, as well as membrane fusion and fission	Yeasts, Moulds, trichomonas, filamentous fungi	Almost not seen	300-400mg	Topical; [96-101]
Griseofulvin	1959	Inhibits fungal mitosis by disrupting the mitotic spindle through interaction with polymerized microtubules	Dermatophytes, *Microsporum, Epidermophyton*, and *Trichophyton* sp, deep mycoses, *candida* spp.	Some *dermatophyte* spp.(*in vitro*)	500 mg	Oral [87, 102-105]
Flucytosine	1971	The rapid conversion of 5-FC into 5-FU within susceptible fungal cells.	Yeasts, dematiaceous fungi, few molds	*Candida* spp. and *Torulopsis glabrata*	100 mg/kg/day	Oral [87, 106, 107]
Terbinafine	1991	Inhibits fungal ergosterol biosynthesis at the point of squalene epoxidation	Dermatophytes and dimorphic and filamentous fungi, yeasts.	*Trichophyton, Candida*	250 mg	Oral [42, 108-111]

Alternative or Home Remedies: Candida is yeast like fungus which has the function of helping to digest food. Normally the stomach has lots of beneficial bacteria that maintain candida in check, but overgrowth may take place if an individual eats a big quantity of sugar or incredibly unhealthy foods, takes pills for birth control, drinks alcohol or requires antibiotics [121]. Research workers happen to be on the trial of natural choices to be able to offer people with candida overgrowth with a few choices to antifungal drugs. Research has revealed several alternative medicines. Just how can an individual know if they have candida overgrowth? Some of the outward symptoms and signs include trouble concentrating, sugar cravings, chronic tiredness, depression, sleepiness, stomach gas, blockage, allergies, replicating yeast or bladder infection, complications, itchy eyes or ears and joint pain [122]. Among the top proven treatments for candida is turmeric [123]. Turmeric is often utilized in asain dishes and curry powder and it gives this brilliant yellow colour. Curcumin can be the active ingredient in turmeric that supplies its many health advantages. One research the study for turmeric discovered that turmeric is successful against fourteen strains of candida [124]. Curcumin comes in products and turmeric and may also be used on food.

Probiotics, the healthy bacteria found in yogurt, have been found to combat candida [125]. Physiology is study regarding the normal functions of living microorganisms and their parts. Probiotic treatment can be successful in treating fungal colonization of the intestine tract [126]. More particularly, *Lactobacillus acidophilus* heals fungal infections as well as the accompanying stomach inflammation [127]. *Acidophilus* supplements are accessible and are best taken before eating anything, before meals. Unsweetened yoghurt is also a great source of probiotics. Coconut oil was proven in a latest animal study to reduce the quantity of candida in the gut by more than 90% [128]. The researches stressed that antifungal drugs may be utilized to

decrease and control candida and prevent it from spreading to the blood stream, but repeated utilization of antifungal drugs might lead to drug resistant forms of fungal diseases.

Many natural and topical homeopathic remedies and pathogenic fungus treatments made up of natural elements are proven to be effective against nail fungus [128]. They are incredibly established nail fungus remedy that kills fungus and brings back yellow discolored nails to their original natural color. They offer their own carrier that ensures equal distribution of its formulation on the affected nail components especially the nail bed [129].

Alternative Modelling: *Candida albican* is the most typical pathogenic fungi that cause oral, skin, nail and sex organ diseases. Exposure to a pathogenic fungus isn't life threatening generally. It might prove fatal to immune compromised people with AIDS or cancer [130]. Current number of nail fungal drugs used for fungal infection treatment contain triazoles and polyenes [131]. The growth of resistance to such drugs by some fungal species has caused a comprehensive limit on the variety of those nail fungal endemics. Four cationic terepthalamide biureas substances are found with strong antifungal action outstanding microbial selectivity and low host toxicity [132]. These compounds comprise of little molecules that self assemble into fibers bind fungal membrane and erupt cells of the wide variety of pathogenic fungus species.

Their discovery increases the medication options for addressing drug resisting fungal species. These materials possess a Z like construction with the terepthalamide seated in the middle urea groups discovered on both of its sides and cationic charges at both of its ends. Distinct scrape *i.e.* ethyl butyl hexyl and benzyl amines were put into between the urea group and the cationic charge in substance preparation. The substances aggregate to type fibers with lengths which range from a few hundred nanometers to many micrometers when dissolved in water. Some of the fibers were of high rigidity.

All of the cationic substances proved successful in suppressing fungus pathogen, disregard of fungal awareness growing from 120 to 150 colony forming units per millilitre. The antifungal action potency of the substances is attributable to the development of fibers with exceptionally small diameters which range from 5 to 10 nanometers assisting fungal membrane rupture. The little diameter of the fibers allows the substances to quickly penetrate the multilayer fungal membrane of a pathogenic fungus, having low negative charges. By rupturing the fungal membrane and disrupting the bio-film the substances are able to eliminate a scientifically isolated drug resistant pathogenic fungus stopping its drug resistance development. The substances have been tested to be fairly safe to be used in fungal infection treatment and prevention.

In the field of molecular modelling, docking is a method which forecasts the desired orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the desired orientation in turn may be used to predict the strength of association or binding affinity between two molecules. Therefore docking plays an important role in the rational design of drugs [133]. Virtual screening was performed through molecular docking studies against potential antifungal targets, and it was found that Wortmannin (Wtmn), a potent phosphoinositide 3-kinase (PI3K) inhibitor obtained from *P. radicum* was predicted to impede the actions of these targets (1. mevalonate-5-diphosphate decarboxylase (1FI4), responsible for sterol/isoprenoid biosynthesis; 2. exocyst complex component SEC3 (3A58) where Rho- and phosphoinositide-dependent localization is present and 3. Kre2p/Mnt1p a Golgi alpha1, 2-mannosyltransferase (1S4N) involved in the biosynthesis of yeast cell wall glycoproteins) more efficiently than known antifungal compounds such as voriconazole and nikkomycin [134].

CONCLUSION: Statistics represent that fungal infections are the major cause of thousands of deaths. As far as the death toll is considered figures suggest that *Candida* species affecting skin and mucous membrane resulting to 50 % death rate, *Cryptococcus* affecting brain leading to 70 % death rate, *Aspergillus* affecting lungs resulting in 50-90% death toll, *Histoplasma capsulatum* affecting lungs causing 30 % and *Pneumocystis* results in 15-20 % death rates [2]. Despite the treatment options available Invasive fungal infections have alarmingly higher mortality rates. Other infections

caused by dimorphic fungal pathogens (*blastomyces, coccidioides, marneffei*) and dematiaceous hyphomycetes (*Cladophialophora, Rhinocladiella)* belong to major fatal causing risk group 3 resulting in higher damage to lives of individuals. These statistical figures are usually underestimated due to the inadequate epidemiological data, misdiagnosis because of unreliable diagnostics and a lack of global reporting in areas of the world with high endemic disease problems [4]. So there is a great need for advancement in understanding of fungus and their resistance along immunity reports. During the recent times one bigger provision by welcome trust, a strategic award for medical mycology and fungal immunology (WTSA) in favour of the University of Aberdeen worth £5 million to promote research and methods to cut the annual death toll of 1.5 million people affected due to fungal infections [135]. The Fungal Infection Trust has donated a total of £3.75 million to research and education on fungal diseases, mainly in the UK [136]. In order to meet all these disease combating requirements many such high quality research initiatives with proper sources of funding and encouragement have to be provided.

Despite the various treatment options available there is still a greater incline in the death toll due to fungal infections. This is mainly because of the fungal resistance developed due to misuse of drug doses. So there is also a greater need for awareness about their therapy (including pharmacokinetic, pharmakodynamic, pharmacological and toxicological data) for better management of these infections. Therapeutic drug monitoring is another option to limit the long term toxicities arised because of prolonged drug usage by individuals. In order to limit the number of doses, novel moieties are being developed using various molecular development technologies. These technologies help in designing a better, safer, targeted drug which also limits the expenses spent during the development and clinical trials of a new drug. These technologies are always helpful in disposing drugs with higher toxicity and help in creating a safer drug for future perspective.

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