Rising environmental temperatures and polluted surface waters: the prelude to the rise of mycoses in South Africa

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South Africa's rivers are frequently used by communities lacking proper sanitation infrastructure for domestic purposes; however, these surface waters may pose a health risk to immunocompromised individuals due to the presence of opportunistic pathogenic fungi in the polluted water. Although only a few studies have focused on the presence of clinically relevant fungal species in South African rivers, many known opportunistic pathogenic species were found to be predominant in these waters. Furthermore, strong evidence exists that increased numbers of clinically relevant species may be observed in future due to fungi acquiring thermotolerance in response to the global increase in temperature. Thermotolerance is a major factor contributing to pathogenesis in fungi, due to the generally low tolerance of most fungi toward mammalian body temperatures. It is therefore contended that combinatorial effects of water pollution and rising environmental temperatures could lead to an increase in the incidence of mycoses in South Africa. This is especially concerning since a relatively large population of immunocompromised individuals, represented mostly by HIV-infected people, resides in the country.

INTRODUCTION

Despite the global increase in the incidence of fungal infections, which affect 1 billion individuals and cause nearly 1.6 million deaths annually (Brown et al., 2012; Bongomin et al., 2017; Almeida et al., 2019), only a few fungal taxa have been identified as causative agents of mycoses (Robert and Casadevall, 2009; Almeida et al., 2019). This phenomenon was ascribed to the relatively low maximum thermal tolerances of most fungi, which are lower than mammalian body temperatures (Robert and Casadevall, 2009). Nevertheless, fungi that can grow at mammalian body temperatures cause infections that may vary from being superficial, to subcutaneous to systemic (Dupont et al., 2000; Garber, 2001; Bicanic and Harrison, 2014; Almeida et al., 2019). Incidents of such mycoses are scrupulously reported in developed countries; however, the opposite is true for developing countries, where the statistics on fungal infections are likely underestimated to a great degree. Furthermore, the largest populations of individuals suffering from HIV/AIDS reside in developing countries (Vearey, 2011; UNAIDS, 2017; Schwartz and Denning, 2019), which could potentially increase the incidence of fungal diseases in these regions, since such immunocompromised individuals are at greater risk of acquiring fungal infections (Dupont et al., 1994; Schwartz and Denning, 2019). This is especially relevant to South Africa, with its disproportionately large population of HIV-infected people (UNAIDS, 2021; Schwartz and Denning, 2019; Weimann and Oni, 2019).

There are various mycoses known to be associated with immunocompromised individuals (Guarner, 2017). Candidiasis, caused by ascomycetous yeasts belonging to the genus *Candida*, is the most common opportunistic fungal infection among HIV-infected patients (Garber, 2001; Moran et al. 2012; Guarner, 2017). Of the estimated 3.2 million fungal infections reported annually in South Africa, candidiasis represents nearly 2 million (Schwartz and Denning, 2019). Other important mycoses include invasive aspergillosis, cryptococcal meningitis, histoplasmosis, as well as *Pneumocystis*- and dermatophyte infections (Guarner, 2017). The causative agents of these infections are regularly isolated from natural and anthropogenic environments (Garber, 2001).

Although mycoses may be obtained from nature, hospital-acquired fungal infections are most common and represent the majority of candidiasis and other fungal disease cases reported in literature (Garber, 2001; Suleyman and Alangaden, 2016; Moazeni et al., 2018). These clinical cases often include fungal infections as a result of contaminated catheters, needles, and decreased immunity during organ transplants (Suleyman and Alangaden, 2016). Additionally, infections caused by members of the genus *Aspergillus* are acquired due to the exposure of airborne propagules associated with, among others, construction sites and ventilation systems of hospitals (Cortez et al., 2008; Benedict et al., 2017). Aspergillosis may also develop due to close interaction with certain contaminated foodstuffs and vegetation (Walsh and Dixon, 1989). Other habitats, such as decaying trees and pigeon guano, harbour notorious members of *Cryptococcus*, which can infect humans in proximity via inhalation (Restrepo et al., 2000; Garber, 2001). Additionally, representatives of pathogenic fungal species were recovered from polluted river systems (Luplertlop et al., 2016; Postma, 2016; Assress et al., 2019). Although pathogenic fungi are plentiful in nature, studies commonly focus on nosocomial mycoses (Jarvis, 1995; Guinea, 2014). The prevalence and interactions of opportunistic fungal pathogens within the natural environment, such as rivers, are rarely studied, despite indications

that fungal virulence results from adaptations that have evolved for protection against adverse conditions in nature (Steenbergen et al., 2001; Bosch et al., 2020). These conditions include rising environmental temperatures and other anomalies as a result of climate change, and have been linked with increases in the prevalence of fungal diseases in mammals, including humans (Garcia-Solache and Casadevall, 2010; Araújo et al., 2017). Research on the ecology of opportunistic fungi in environments conducive to their proliferation, such as river systems, is therefore expedient. Focus should be given to developing countries such as South Africa, with its large population of immunocompromised individuals (UNAIDS, 2021) and inadequate infrastructure accompanied by rapid urbanisation (Schwartz and Denning, 2019). With the ultimate goal of obtaining an indication of the potential effects of climate change and anthropogenic pollution on the ecology of opportunistic pathogenic fungi in South African rivers, the aim of this literature review was to survey existing knowledge on the occurrence of these fungi in the river systems of the region. Additionally, this review reflects on the potential effect of increased environmental temperatures, in combination with pollution, on the biology of opportunistic pathogenic fungi occurring in these rivers.

POLLUTED SURFACE WATERS

Rivers may become polluted as a result of various anthropogenic activities: agricultural practices, industrial processes, expanding urban communities with poor sanitation infrastructure, as well as faulty wastewater treatment operations (Vearey, 2011; Wang et al., 2012; Glińska-Lewczuk et al., 2016; Liyanage and Yamada, 2017; Cullis et al., 2019). These may largely contribute to the fungal load in water due to the nutrient-rich characteristics of most pollutants. For several decades, the quality of water, whether it be used for drinking, ablutions, or irrigation purposes, was evaluated by determining the microbiological load thereof (Havelaar et al., 1986). Bacterial indicators have been, and are being, extensively used to determine water quality, especially in relation to the level of faecal pollution (Havelaar et al., 1986; Haack et al., 2009). Only relatively recently were studies conducted linking fungal numbers to pollution levels in river systems (De Almeida, 2005; Brandão et al., 2010; Medeiros et al., 2012; Stone et al., 2013). Previously the only indicators of fungal contaminants used were taste, odour and the number of culturable moulds in the water (Doggett, 2000). While very few studies were aimed at investigating the link between fungal numbers and pollution, several authors have studied fungal diversity in a wide range of surface water sources – including tap water, rivers, lakes and estuaries (Kwasnieskwa, 1988; Hageskal et al., 2009; Pereira et al., 2009; Magwaza et al., 2017; Assress et al., 2019). Some of the fungi identified during these studies include known clinically relevant yeasts and filamentous fungi.

CLINICALLY RELEVANT FUNGI

Pathogenic and opportunistic pathogenic fungi are ubiquitous in the environment (Restrepo et al., 2000; Gostinčar et al., 2011; Babič et al., 2017). While the occurrence of some of these fungi has been studied extensively in atmospheric (Newbound et al., 2009) and terrestrial environments including animals, plants and soils (Restrepo et al., 2000; Gostinčar et al., 2011), relatively little knowledge exists on the ecology of clinically relevant fungi in aquatic environments, with only a few studies focusing on polluted water. Regardless of the lack of available information, some findings have allowed researchers to hypothesise that fungi, particularly yeasts, have the potential to be used as indicators of pollution in rivers and other water bodies (De Almeida, 2005; Brandão et al., 2010; Medeiros et al., 2012; Stone et al., 2013; Postma, 2016). However, it should also be made a priority to determine the pathogenic fungal taxa occurring in polluted rivers, since individuals utilizing these water sources are at risk of acquiring mycoses (Weimann and Oni, 2019).

Filamentous fungi

The most common water-borne filamentous fungi are members of the genera *Penicillium, Trichoderma, Acremonium, Cladosporium, Aspergillus, Fusarium* and *Mucor* (Babič et al., 2017). Representatives of the latter three genera are considered opportunistic, causing invasive fungal infections in immune-deficient individuals. Members of the remaining genera cause allergies, as well as subcutaneous and superficial infections, especially among those suffering from immunodeficiency. Despite the low health risk, compared to invasive infections, superficial infections remain concerning due to the associated negative impact on quality of life (Weimann and Oni, 2019).

To date, no substantial evidence exists on the presence of pathogenic filamentous fungi in the river systems of South Africa. This, however, does not negate the danger associated with the presence of these fungi in rivers, but rather encourages researchers to investigate neglected environments (Schwartz and Denning, 2019). Investigating such understudied environments is of particular importance considering current evidence of disease-causing filamentous fungi detected in different European water sources – especially tap water (Novak Babič et al., 2018). It is well known that surface waters are sources for drinking and tap water (UN Water, 2006; WHO, 2017). These water sources are treated before distribution, but the treatment processes are not feasible for rivers, lakes and other surface waters that are used as primary water sources by some communities (Colvin et al., 2016; Edokpayi et al., 2018). Recent studies, however, have revealed that fungi can survive conventional treatment processes and persist in tap water, as was observed in some hospitals (Arroyo et al., 2020; Caggiano et al., 2020). Nevertheless, the fungal composition of treated surface water could be significantly different from untreated surface water and therefore in this review only fungi present in rivers and other natural water sources were evaluated.

Globally, two major fungal groups were detected in the few river systems that were studied: Mucoromycota and Ascomycota (Arvanitidou et al., 2005; Pietryczuk et al., 2018; Machido et al., 2015). Mucoralean fungi were found to be the only representatives of the phylum Mucoromycota that occurred within rivers in Greece. These included members of *Mucor, Absidia* and *Rhizopus* (Arvanitidou et al., 2005). Species within these genera cause mucormycosis – an invasive fungal infection which can manifest in the lungs, cutaneous and subcutaneous dermis, nose cavities, brain, intestines and bloodstream (Spellberg and Maertens, 2019). Recently, cases of mucormycosis have increasingly been reported among patients suffering from Covid-19 (Garg et al., 2021; Werthman-Ehrenreich et al., 2021). Members of *Absidia* have also caused infections in individuals suffering from burn wounds (Christiaens et al., 2005). These infections are invasive, invading organs and the bloodstream, with detrimental health outcomes (Harrison and Brouwer, 2009).

It must be noted that although immunosuppressed individuals are especially susceptible to invasive fungal infections, rare cases of rhinocerebral mucormycosis, as well as other mycoses, have been observed in immunocompetent patients (Hussain et al., 1995; Leyngold et al., 2014). In contrast, non-invasive superficial fungal infections caused by a variety of different fungi are very common among patients with immune deficiencies (Huang et al., 2004), and noticeable superficial infections on epidermal regions are considered a presenting feature of individuals diagnosed with AIDS (Lohoué Petmy et al., 2004; Benedict et al., 2017).

Some fungi that are known to occur in rivers are capable of causing both invasive and superficial infections (Arvanitidou et al., 2005). These include members of the genera *Aspergillus* and *Penicillium* belonging to the orders Eurotiales; *Alternaria* and *Curvularia* of the order Pleosporales; as well as *Fusarium* and *Verticillium* belonging to Hypocreales. Representatives of the genera *Aspergillus* and *Penicillium* spp. were among the most frequently isolated filamentous fungi found during a survey of rivers in Greece. Although many beneficial strains representing *Penicillium* exist that are used in the food and pharmaceutical industries (Sousa et al., 2001; Elander, 2003), it is known that some members of this genus can cause keratitis, pneumonia, endocarditis, necrotising esophagitis, endophthalmitis, urinary tract infections and peritonises (Hu et al., 2013). *Aspergillus fumigatus* and *Aspergillus niger* that were found in Polish rivers (Pietryczuk et al., 2018) are both associated with aspergillosis, which is one of the leading causes of death among AIDS individuals (GAFFI, 2017). Recently, cases of Covid-19 associated pulmonary chronic aspergillosis have also been reported (Arastehfar et al., 2020).

Verticillium, another genus harbouring waterborne fungi (Schiavano et al., 2014; Novak Babič et al., 2018), is represented by species associated with peritonises, as well as subcutaneous infections. The latter ensues when a microorganism breaches the epidermal barrier and migrates into the innermost layer of skin where blood vessels and nerves are located (Kujath and Kujath, 2010). While it is known that some bacteria produce proteins that enable infiltration of blood vessels, little information is available for fungi presenting the same mechanisms (Lipke, 2018). Nonetheless, in the probable event that some pathogenic fungi harbour these proteins, the proximity between the microorganisms and blood vessels in subcutaneous tissue could lead to systemic infections where the infectious agents are disseminated to other parts of the body. The subcutaneous tissue is also found directly on top of the musculoskeletal tissue, an area that some representatives of *Fusarium* are known to infect (Koehler et al., 2016). Both *Fusarium* and *Verticillium* spp. have been associated with superficial and invasive infections (Kujath and Kujath, 2010; Koehler et al., 2016), while other members of the Hypocreales from rivers, such as species of *Acremonium* and *Cylindrocarpon,* are more commonly known to cause superficial infections, such as mycetoma (Welsh et al., 2007; Arvanitidou et al., 2005; Pietryczuk et al., 2018).

Of the pleosporalean fungi that were found in Greek rivers, members of *Curvularia* and *Pyrenochaeta* were rarely encountered, whereas representatives of *Alternaria* were frequently isolated (Arvanitidou et al., 2005). *Curvularia* and *Pyrenochaeta* harbour species associated with cutaneous infections and invasive fungemia. *Alternaria* species, however, are involved in other less invasive infections such as rhinosinusitis, onychomycosis and oculomycosis (Pastor and Guarro, 2008). Additionally, in a recent study done by Pietryczuk et al. (2018), *Alternaria alternata* was identified in 4 out of 5 rivers surveyed in Poland.

Onygenalean fungi, which represent members that cause tineas, were also detected in natural surface waters (Arvanitidou et al., 2005; Machido et al., 2015; Novak Babič et al. 2018). Two genera, *Emmonsia* and *Chrysosporium*, were frequently encountered in Greek rivers (Arvanitidou et al., 2005) and represent fungi typically associated with disseminated- or superficial infections, respectively (Kenyon et al., 2013; Mijiti et al., 2017). Other members of the Onygenales which were isolated from river systems in Europe and Africa were representatives of *Microsporum* and *Trichophyton* (Arvanitidou et al., 2005; Machido et al., 2015), genera that include keratolytic fungi and are frequently associated with tineas (Schwinn et al., 1995; Brito-Santos et al., 2017). For example, *Microsporum canis*, which has been isolated from surface waters, as well as *Trichophyton tonsurans* and *Trichophyton violaceum* that have been isolated from rivers (Machido et al., 2015; Pietryczuk et al., 2018; Novak Babič et al., 2018), are all known to cause tinea capitis (Sombatmaithai et al., 2015; Pasquetti et al., 2017; Morales et al., 2019).

Other ascomycetous filamentous fungi occurring in surface waters that have mostly been associated with cutaneous infections are members of the order Chaetothyriales (Novak Babič et al., 2018; Pietryczuk et al., 2018). A chaetothyrialean fungus, *Exophalia dermatitidis*, associated with both cutaneous infections, as well as with respiratory infections in cystic fibrosis patients, was isolated from Polish rivers (Pietryczuk et al., 2018). Also isolated from these rivers were microascalean fungi belonging to the genus *Scopulariopsis*. Representatives of this genus are known to be the causative agents for different mycoses, ranging from superficial, to pulmonary and systemic infections (Iwen et al., 2012; Sandoval-Denis et al., 2013). It is important to mention that Microascales also harbours emerging pathogens such as members of the genus *Scedosporium*, which are commonly associated with wastewater sources (Skiada et al., 2017). Considering that wastewater is a major component of the pollution in rivers, further investigation into the diversity of *Scedosporium* spp. and other opportunistic filamentous fungi in natural surface waters is imminent.

Yeasts

The majority of fungal infections are caused by yeasts (Miceli et al., 2011; Bongomin et al., 2017; Lamoth et al., 2018; Ocansey et al., 2019; Schwartz and Denning, 2019). These opportunistic unicellular fungi usually belong to genera such as *Candida* and *Rhodotorula*, which were among the prevalent yeasts occurring in polluted surface waters (Sláviková and Vadkertiová, 1997; De Almeida et al., 2005; Gadanho et al., 2006; Coelho et al., 2010; Medeiros et al., 2012; Pietryczuk et al., 2014; Monapathi et al., 2020). The invasive infections caused by these yeasts often have devastating effects on human organs, including the liver, heart, lungs, and brain. These infections, however, are rare among immunocompetent individuals and occur mostly among immunocompromised patients, such as those suffering from HIV/AIDS (Low and Rotstein, 2011).

Compared to filamentous fungi, more literature is available on the prevalence and presence of unicellular fungi in surface waters (Buzzini et al., 2017). This can be attributed to the non-spreading nature of yeast colonies on microbiological media, enabling researchers to more readily enumerate yeasts and link their numbers to environmental factors (Sláviková and Vadkertiová, 1997; De Almeida, 2005; Gadanho et al., 2006; Coelho et al., 2010; Medeiros et al., 2012; Stone et al., 2012; Van Wyk et al., 2012). Additionally, more yeast-related surveys could have been conducted in water sources than what were carried out for filamentous fungi, due to the disproportional disease burden associated with yeasts and the implicated higher health risk (Miceli et al., 2011; Bongomin et al., 2017; Lamoth et al., 2018; Ocansey et al., 2019; Schwartz and Denning, 2019).

A number of surveys on yeasts occurring in rivers was conducted across the globe (Table 1), yet there is still a paucity of published information available on yeasts associated with river systems in South Africa (Table 2). Limited data originating from only two provinces have been published thus far: Western Cape and North-Western Province (Stone et al., 2012; Van Wyk et al., 2013; Monapathi et al., 2017; Monapathi et al., 2020).

The most dominant of the opportunistic pathogenic yeasts identified in rivers of South Africa (Table 2), as well as other countries (Table 1), were found to be ascomycetous yeasts, especially members of the genus *Candida* (De Almeida, 2005; Coelho et al., 2010; Medeiros et al., 2012; Van Wyk et al., 2012; Monapathi et al., 2017). Whether the predominance of these clinically relevant ascomycetes is associated with certain environmental parameters is still unclear. Considering the positive correlation observed

Table 1. List of clinically relevant yeast and yeast-like fungi found in surface waters of countries other than South Africa

Yeast species (synonym)	Infections	Water source reference
Ascomycetes		
Aureobasidium pullulans	Fungemia, subcutaneous infections, disseminated infections [1,2,3]	Sláviková and Vadkertiová (1997)
Candida albicans	Candidal vulvovaginitis, candidemia, candidiasis	Buck and Bubucis (1978); Arvanitidou et al. (2005); Yamaguchi et al. (2007); Pietryczuk et al. (2018)
Candida blankii	Fungemia [4]	Medeiros et al. (2012)
Candida catenulata	Superficial- and invasive infections [5,6]	De Almeida (2005); Medeiros et al. (2012)
Candida glabrata	Candidiasis (urogenital tracts), candidemia [7,8,9]	Yamaguchi et al. (2007); Coelho et al. (2010); Medeiros et al. (2012)
Candida inconspicua	Candidemia [10]	Sláviková and Vadkertiová (1997)
Candida intermedia	Fungemia [11]	Sláviková and Vadkertiová (1997); De Almeida (2005)
Candida lambica	Fungemia, polyarthritis [12,13]	Sláviková and Vadkertiová (1997)
Candida palmioleophila	Endophthalmitis, fungemia [14,15]	Coelho et al. (2010); Medeiros et al. (2012)
Candida parapsilosis	Sepsis, wound and tissue infections (subcutaneous and cutaneous) [9]	Sláviková and Vadkertiová (1997); De Almeida (2005); Yamaguchi et al. (2007); Coelho et al. (2010); Medeiros et al. (2012)
Candida pararugosa	Fungemia [16]	Medeiros et al. (2012)
Candida rugosa	Candidemia (burn patients) [17]	Medeiros et al. (2012)
Candida tropicalis	Candidemia [9]	Sláviková and Vadkertiová (1997)
Candida zeylanoides	Fungemia, endocarditis [18,19]	Arvanitidou et al. (2005); Coelho et al. (2010)
Clavispora lusitaniae (Candida lusitaniae)	Intra-abdominal candidiasis [20]	De Almeida (2005); Coelho et al. (2010)
Debaryomyces hansenii (Candida famata)	Invasive fungemia, central nervous system infections, fungemia [21,22,23,24,25]	Sláviková and Vadkertiová (1997); De Almeida (2005); Gadanho et al. (2006); Coelho et al. (2010); Medeiros et al. (2012)
Geotrichum candidum	Disseminated infections, superficial infections [26,27]	Sláviková and Vadkertiová (1997)
Kluyveromyces marxianus (Candida kefyr)	Candidemia [28]	Coelho et al. (2010); Medeiros et al. (2012)
Metschnikowia pulcherrima (Candida pulcherrima)	Fungemia [29]	Sláviková and Vadkertiová (1997)
Meyerozyma guilliermondii (Candida guilliermondii, Pichia guilliermondii)	Onychomycosis (tinea), invasive infections (rare), Fungemia [30]	Sláviková and Vadkertiová (1997); De Almeida (2005); Coelho et al. (2010); Medeiros et al. (2012)
Meyerozyma caribbica (Candida fermentati)	Fungemia [31]	Coelho et al. (2010)
Pichia anomala (Candida pelliculosa, Hansenula anomala)	Fungemia (paediatric), urinary tract infection [32,33,34]	Sláviková and Vadkertiová (1997); Coelho et al. (2010)
Pichia kudriavzevii (Candida krusei, Issatchenkia orientalis)	Fungemia [35]	Sláviková and Vadkertiová (1997); Coelho et al. (2010); Medeiros et al. (2012)
Saccharomyces cerevisiae	Fungemia [36]	Sláviková and Vadkertiová (1997); Coelho et al. (2010)
Yarrowia lipolytica (Candida lipolytica)	Fungemia, superficial infections [37]	Coelho et al. (2010); Medeiros et al. (2012)
Basidiomycetes		
Cryptococcus albidus (Naganishia albida)	Cryptococcaemia, superficial infections [38,39]	Sláviková and Vadkertiová (1997); Pereira et l. (2009); Coelho et al. (2010); Medeiros et al. (2012)
Cryptococcus laurentii (Papiliotrema laurentii)	Superficial infections, lung abscesses, fungemia, endophthalmitis [39]	Sláviková and Vadkertiová (1997); Coelho et al. (2010); Medeiros et al. (2012)
Cryptococcus luteolus	Diffuse infiltration of lungs, tenosynovitis [40]	Medeiros et al. (2012)
Cryptococcus magnus	Vulvovaginitis, cryptococcosis in cats [41,42]	Medeiros et al. (2012)
Filobasidium uniguttulatum (Cryptococcus uniguttulatum)	Meningitis [43]	Coelho et al. (2010)
Rhodotorula glutinis	Fungemia, meningitis, onychomycosis (tinea) [44,45,46]	Sláviková and Vadkertiová (1997); Coelho et al. (2010); Medeiros et al. (2012)
Rhodotorula minuta	Endophthalmitis, onychomycosis (tinea), fungemia [47,48,49]	Sláviková and Vadkertiová (1997)
Rhodotorula mucilaginosa (Rhodotorula rubra)	Fungemia, meningitis, endocarditis, peritonises, endophthalmitis, onychomycosis (tinea) [45,50,51,52,53]	Sláviková and Vadkertiová (1997); De Almeida (2005); Gadanho et al. (2006); Coelho et al. (2010); Medeiros et al. (2012); Pietryczuk et al. (2018)
Sporobolomyces salmonicolor	Pseudomeningitis, dermatitis, endogenous endophthalmitis, fungemia [54,55,56,57]	Sláviková and Vadkertiová (1997)
Trichosporon cutaneum	Disseminated infections, endocarditis, superficial infections [58,59,60]	Sláviková and Vadkertiová (1997)
Trichosporon mucoides	Onychomycosis, fungemia [61,62]	Pietryczuk et al. (2018)

References to yeast epidemiology: [1]Kaczmarski et al. (1986); [2]Joshi et al. (2010); [3]Bolignano et al. (2003); [4]Nobrega De Almeida et al. (2018); [5]Radosavljevic et al. (1999); [6]Ha et al. (2018); [7]Leaw et al. (2007); [8]Jarvis et al. (1995); [9]Silva et al. (2012); [10]Guitard et al. (2013); [11]Ruan et al. (2010); [12]Trowbridge et al. (1999); [13]Vervaeke et al. (2008); [14]Datta et al. (2015); [15]Sugita et al. (1999); [16]El Helou and Palavecino (2017); [17]Pfaller et al. (2006); [18]Levenson et al. (1991); [19]Whitby et al. (1996); [20]Vergidis et al. (2016); [21]Carrega et al. (1997); [22]Prinsloo et al. (2008); [23]Beyda et al. (2013); [24]Wong et al. (1982); [25]Wagner et al. (2005); [26]Kassamali et al. (1987); [27]Sfakianakis et al. (2007); [28]Taj-Aldeen et al. (2014); [29]Bereczki et al. (2012); [30]GŘler et al. (2017); [31]Lockhart et al. (2009); [32]Baron et al. (1988); [33]Qadri et al. (1988); [34]Chakrabarti et al. (2001); [35]Scorzoni et al. (2013); [36]Muños et al., (2005); [37]Boyd et al. (2017); [38]Hoang and Burruss et al. (2007); [39]Kordossis et al. (1998); [40]Hunter-Ellul et al. (2014); [41]Ghajari et al. (2018); [42]Poth et al. (2010); [43]Pan et al. (2012); [44]Shinde et al. (2008); [45]Hsueh et al. (2003); [46]Wirth and Goldani (2012); [47]Goldani et al. (1995); [48]Pinna et al. (2001); [49]Zhou et al. (2014); [50]Lo Re et al. (2003); [51]Gyaurgieva et al. (1996); [52]Eisenberg et al. (1983); [53]Merkur et al. (2002); [54]Sharma et al. (2006); [55]Bross et al. (1986); [56]Bergman and Kauffman (1984); [57]Tang et al. (2015); [58]Gold et al. (1981); [59]Marier et al. (1978); [60]Madhavan et al. (1976); [61]Rizzitelli et al. (2016); [62]Colombo et al. (2011)

Table 2. List of clinically relevant yeast and yeast-like species found in surface waters of South Africa

Yeast species (synonym)	Infections	Water source reference
Ascomycetes		
Candida albicans	Candidal vulvovaginitis, candidemia, candidiasis	Stone et al. (2012); Monapathi et al. (2017); Monapathi et al. (2020)
Candida bracarensis	Candidemia [1]	Monapathi et al. (2017); Monapathi et al. (2020)
Candida catenulata	Superficial- and invasive infections [2, 3]	Van Wyk et al. (2012)
Candida glabrata	Candidiasis (urogenital tracts), candidemia [4, 5, 6]	Belford (2013); Postma (2016); Monapathi et al. (2017); Monapathi et al. (2020)
Candida globosa	Candidiasis [4, 5]	Van Wyk et al. (2012)
Candida haemulonii	Candidiasis [7]	Monapathi et al. (2020)
Candida parapsilosis	Sepsis, wound and tissue infections (subcutaneous and cutaneous) [6]	Monapathi et al. (2017); Monapathi et al. (2020)
Candida rugosa	Candidemia (burn patients) [9]	Van Wyk et al. (2012)
Candida sake	Endocarditis, peritonises, candidemia [10]	Van Wyk et al. (2012); Monapathi et al. (2020)
Candida tropicalis	Candidemia [6, 11]	Van Wyk et al. (2012); Belford (2013); Bezuidenhout (2013); Postma (2016); Monapathi et al. (2017); Monapathi et al. (2020)
Clavispora lusitaniae (*Candida lusitaniae*)	Intra-abdominal candidiasis [12]	Van Wyk et al. (2012); Bezuidenhout (2013); Postma (2016); Monapathi et al. (2017); Monapathi et al. (2020)
Cyberlindnera fabianii	Pneumonia, fungemia, endocarditis, prostatitis [13]	Monapathi et al. (2017); Monapathi et al. (2020)
Cyberlindnera jadinii (*Candida utilis*)	Candidemia [14, 27]	Belford (2013); Postma (2016); Monapathi et al. (2020)
Kluyveromyces marxianus (*Candida kefyr*)	Bloodstream infection [15]	Monapathi et al. (2020)
Meyerozyma guilliermondii (*Candida guilliermondii, Pichia guilliermondii*)	Fungemia [16]	Van Wyk et al. (2012); Bezuidenhout (2013); Monapathi et al. (2017); Monapathi et al. (2020)
Meyerozyma caribbica (*Candida fermentati*)	Fungemia [16]	Monapathi et al. (2020)
Pichia anomala (*Candida pelliculosa, Hansenula anomala*)	Candidemia [8]	Van Wyk et al. (2012)
Pichia kudriavzevii (*Candida krusei, Pichia guilliermondii*)	Fungemia [17, 18]	Belford (2013); Bezuidenhout (2013); Postma (2016); Monapathi et al. (2017); Monapathi et al. (2020)
Saccharomyces cerevisiae	Fungemia [19]	Belford (2013); Postma (2016) Monapathi et al. (2020)
Wickerhamomyces anomalus	Fungemia (neonates) [20]	Bezuidenhout (2013); Monapathi et al. (2017); Monapathi et al. (2020)
Yarrowia lipolytica (*Candida lipolytica*)	Fungemia, superficial infections [21]	Monapathi et al. (2020)
Basidiomycetes		
Cryptococcus laurentii (*Papiliotrema laurentii*)	Superficial infections, lung abscesses, fungemia, endophthalmitis [22]	Van Wyk et al. (2012)
Rhodotorula glutinis	Fungemia, meningitis, onychomycosis (tinea) [23, 24, 25]	Van Wyk et al. (2012); Bezuidenhout (2013)
Rhodotorula mucilaginosa (*Rhodotorula rubra*)	Fungemia, meningitis, endocarditis, peritonises, endophthalmitis, onychomycosis (tinea) [25]	Van Wyk et al. (2012); Bezuidenhout (2013)
Trichosporon ovoides	White Piedra (tinea) [26]	Postma (2016); Monapathi et al. (2020)

References to yeast epidemiology: [1]Warren et al. (2010); [2]Radosavljevic et al. (1999); [3]Ha et al. (2018); [4]Leaw et al. (2007); [5]Jarvis et al. (1995); [6]Silva et al. (2012); [7]Coles et al. (2020); [8]Jung et al. (2018); [9]Pfaller et al. (2006); [10]Juneja et al. (2011); [11]Zuza-alves et al. (2017); [12]Vergidis et al. (2016); [13]Park et al. (2019); [14]Scoppettuolo et al. (2014); [15]Seth-Smith et al. (2020); [16]GŘler et al. (2017); [17]Scorzoni et al. (2013); [18]Nagarathnamma et al. (2017); [19]Muñoz et al. (2005); [20]Yılmaz Semerci et al. (2017); [21]Boyd et al. (2017); [22]Molina-Leyva et al. (2013); [23]Shinde et al. (2008); [24]Hsueh et al. (2003); [25]Wirth and Goldani (2012); [26]Colombo et al. (2011); [27]Treguier et al. (2018)

between pollution indicators and yeast numbers, as well as the prevalence of ascomycetes in some studies, research on the link between yeasts and physicochemical parameters is imminent (Sláviková and Vadkertiová, 1997; Gadanho et al., 2006; Coelho et al., 2010; Medeiros et al., 2012; Stone et al., 2012; Van Wyk et al., 2012). Thus far, when researchers analysed the pollution levels of river water, results varied: some authors reported higher than normal concentrations of nitrogen and phosphate (Sláviková and Vadkertiová, 1997; Medeiros et al., 2012), others reported that yeast numbers correlate with temperature and pH (Gadanho et al., 2006; Van Wyk et al., 2012) or that yeast prevalence is related to faecal coliform numbers (Coelho et al., 2010; Stone et al., 2012).

The South African rivers that were investigated were considered to be diffusely polluted, contaminated with exceedingly high levels of dissolved solids, nitrates and phosphates (Van Wyk et al., 2012; Monapathi et al., 2017), as well as faecal matter (Stone et al., 2012). The latter is of considerable concern since members of clinically relevant species including *Pichia kudriavzevii* (syn. *Candida krusei*), *Candida tropicalis*, *Candia parapsilosis*, *Candida rugosa*, *Papiliotrema laurentii* (syn. *Cryptococcus laurentii*), *Cyberlindnera jadinii* (syn. *Candida utilis*), *Meyerozyma guilliermondii* (syn. *Candida guilliermondii*), *Rhodotorula glutinis* and *Rhodotorula mucilaginosa* (syn. *Rhodotorula rubra*) have previously been associated with sewage and sewage-polluted water (Cooke et al., 1960). In South Africa, many municipalities have neglected the maintenance of sewage treatment infrastructure, causing the release of raw and partially treated sewage into river systems (Herbig, 2019). The heavy load of excrement and other pollutants in sewage is well known to increase the quantity of organic carbon, including chemicals and other substrates that sustain growth of potentially harmful microorganisms (Liu et al., 2015). In tandem, anthropogenic waste depository from individuals residing near riverbanks extends the list of pollutants entering surface waters. Among the anthropogenic pollution entering river systems are chemicals such as antibiotics and even antifungals (Chitescu et al., 2015). While the above-mentioned aberrations with regard to physicochemical parameters are known to indicate pollution in river systems, no attempt was made thus far to correlate these parameters with the numbers of pathogenic yeast species in these polluted waters.

To enumerate and isolate clinically relevant fungi, including yeasts, from surface waters, an incubation temperature of 37˚C was employed by some authors, (Buck and Bubucis, 1978; De Almeida, 2005; Yamaguchi et al., 2007; Coelho et al., 2010). Others incubated their isolation plates at room temperature to determine overall yeast numbers in surface waters. Interestingly, Coelho et al. (2010) identified yeasts incubated at both room temperature and 37˚C, and found that the numbers of the predominant species cultivated at the latter temperature correlated with *E. coli* numbers and therefore with the level of faecal contamination. Yeast numbers occurring on isolation plates that were incubated at room temperature, however, showed no significant correlation with faecal coliform numbers.

The positive correlation between faecal coliform numbers and yeast counts obtained after incubation at 37°C, further suggests that these unicellular fungi are allochthonous – originating from other sources and subsequently introduced to the river water (Weimann and Oni, 2019; Arvanitidou et al., 2002). A potential source of these yeasts can be anthropogenic pollution (Dynowska, 1997; Coelho et al., 2010; Herbig and Meissner, 2019; Weimann and Oni, 2019). While the inhabitants of rural communities may be one of the sources of river pollution, they also tend to be at risk, especially individuals predisposed to infection because of immune deficiencies (Vearey, 2011).

It is disconcerting that some of the most clinically relevant species of *Candida* were isolated from South African rivers (Table 2): *C. albicans, C. tropicalis, C. glabrata* and *C. parapsilosis* (Miceli et al., 2011). The same representatives were isolated from surface waters in other countries such as Portugal, Greece, Poland and Brazil (Arvanitidou et al., 2005; De Almeida, 2005; Coelho et al., 2010; Medeiros et al., 2012, Pietryczuk et al., 2018). The occurrence of renowned clinically relevant yeasts in different geographical regions of the world emphasises the need for more ecological surveys for the presence of these unicellular fungi in ecosystems. To understand why these yeasts persist and grow within ecosystems, such surveys should be accompanied by analyses of anthropological activity including assessment of pollution indicators and measurement of physicochemical parameters. The latter includes parameters such as the nutrient levels, pH, as well as the temperature of surface waters.

RISING ENVIRONMENTAL TEMPERATURES

Life on Earth is sustained by the natural greenhouse gases found in the atmosphere; however, industrialisation and other anthropogenic activities involving fossil fuel combustion have impinged on the natural environment and largely contributed to climate change (IPCC, 2018; IPCC, 2021). Since the industrial revolution that started in 1760, the increased emissions of greenhouse- and other deleterious gases have contributed to a rise in global temperature. In addition, the exponential increase in the population caused agriculture to expand in order to meet the high food demand. Livestock farming, for instance, is now recognised as another contributor to global warming due to deforestation (land to farm) as well as an increase in released methane (Ilea, 2009). This has led to the total increase of an estimated 1°C in global temperatures and a further increase of up to 2°C has been hypothesised for future decades (IPCC, 2018; IPCC, 2021). In accordance with global predictions, South Africa has seen a 2°C increase since the industrial revolution (1760) and it is projected that a 0.12–0.5°C/decade rise will be observed in future (USAID, 2015).

This world-wide rise in temperatures has been collectively referred to as global warming (Lineman et al., 2015). Disastrous consequences of this anthropogenically influenced phenomenon include the loss of ice in Antarctica and Greenland, accompanied by a rise in sea levels (Hansen et al., 2016; IPCC, 2021). Thus far,

global warming has had detrimental effects on ecosystems and biomes across the globe. Increased temperatures were found to heighten the threat of species extinction within many habitats, such as montane forests and other terrestrial environments (Malcolm et al., 2006). Recent studies have shown that climate change also increases the temperature of freshwater aquatic environments (Morrison et al., 2002; Van Vliet et al., 2011; Chen et al., 2016; Nusslé et al., 2015; Pohle et al., 2019; Kedra, 2020; Liu et al., 2020). The rising river water temperatures in some of these studies were found to be congruent with the rise in air temperatures, suggesting a direct link between thermally altered waters and global warming (Van Vliet et al., 2011; Chen et al., 2016; Pohle et al., 2018; Kedra, 2020; Liu et al., 2020). As such, excess heat because of anthropogenic activities – also referred to as thermal pollution – may therefore be one of the main causes for increased water temperatures (Nordell et al., 2003; Verones et al., 2010; Liu et al., 2020).

The effects on the microorganisms present in thermally altered waters have not been fully described, despite their crucial roles in biogeochemical cycling and other processes essential for a fully functional and diverse ecosystem (Sigee, 2005). Fungi, in particular, are largely understudied in aquatic ecosystems, with little to no knowledge available on how thermal pollution in water affects these microbes (Grossart et al., 2019). However, potential links between the emergence of pathogenic fungi and rising ambient temperatures have been discussed by some mycologists (Garcia-Solache and Casadevall, 2010; Casadevall et al., 2020), and positive correlations have been observed between the presence of fungal pathogens in river systems and water pollution levels (De Almeida, 2005; Brandão et al., 2010; Medeiros et al., 2012; Stone et al., 2012; Postma, 2016). Thus, a holistic approach is needed to investigate the combinatorial effects of both water pollution and global warming on the emergence of fungal pathogens.

GLOBAL WARMING AND EMERGING MYCOSES

Fungi are well known infectious agents of various organisms, including plants and mammals as well as amphibians (Garber, 2001). *Batrachochytrium dendrobatidis* is a good example of a notorious causative agent of chytridiomycosis among many frog species. Since the emergence of this fungus, researchers have contended that the decline in frog species due to this pathogen is linked to the global rise in temperature (Longcore et al., 1999; Wake and Vredenburg, 2008; Fisher et al., 2009). Although the correlation analysis linking global warming to the decline of amphibian species has been queried by some (Rohr et al., 2008), many other researchers have emphasised the role of rising temperatures in species extinction (Pounds et al., 2006; Alford et al., 2007; D'Amen and Bombi, 2009). These studies employed statistical models to determine correlations between rising temperatures and declining species numbers (Pounds et al., 2006; Alford et al., 2007; Rohr et al., 2008; D'Amen and Bombi, 2009), but failed to consider other biological factors. Recently, however, researchers have begun to study the specific relationship between host and pathogen during climate changes (Cohen et al., 2017; Neely et al., 2020). The thermal mismatch theory was formulated, which states that as environmental conditions deviate from the optimal conditions required for host survival, susceptibility towards infectious agents will increase (Chen et al., 2011; Cohen et al., 2017). Although this theory is limited to cold-adapted hosts, it has provided opportunities to discover important traits of the associated pathogens. For example, it was found that microbial symbionts, specifically pathogens, have a broader thermal breadth than their hosts (Neely et al., 2020), due to the higher mass-specific metabolic rates of smaller organisms, thus allowing for a more rapid adaptation to environmental change (Cohen et al., 2017). Understanding these and similar microbial characteristics

provides opportunities to determine how environmental fungi may adapt to climate change and evolve to survive the conditions of a mammalian host. It must be noted, however, that little research has been conducted on intraspecies differences in thermal breadth, between pathogenic fungi recovered from natural environments and that of laboratory or clinical strains. Such studies may provide better insight into how environmental stressors like elevated temperatures could facilitate adaptation.

Garcia-Solache and Casadevall (2010) presented an important hypothesis averring that mammalian fungal infections will increase as a result of global warming. This hypothesis requires an understanding of how pathogens adapt to specifically overcome the restrictions associated with the mammalian body. In humans, fungal infections have mainly occurred in individuals with immune deficiencies, while relatively few cases were recorded among immunocompetent persons (Badiee and Zare, 2017). This is largely owing to the complex and effective immune systems unique to jawed vertebrates, which provide extensive protection against fungal pathogens (Shoham and Levitz, 2005). In addition, an equally effective preventative mechanism is the thermal restriction zone. Endothermic animals can regulate body temperature in response to infection during which basal temperatures increase in a process known as fever. Microorganisms such as unicellular- and filamentous fungi have a relatively low tolerance to high temperatures and therefore deteriorate during fever conditions (Robert and Casadevall, 2009). The high thermal susceptibility, in addition to the intolerance of the already high body temperature, effectively prevents fungal pathogens from frequently causing invasive infections. Thus, with the increase in ambient temperatures, and the potential ability of fungi to adapt to increased environmental temperatures, global warming threatens to expedite the emergence of mycoses by introducing more thermally tolerant fungi.

Two major restrictions prevent an exponential increase of mycoses cases in humans: a complex, highly adaptable immune system (Blanco and Garcia, 2008) and elevated body temperatures. The law of parsimony (Sober, 1981; McMeekin et al., 2008) would dictate that investigating the microorganism's ability to adapt to the thermal restrictions in mammals could provide a better indication of potential virulence than investigating its ability to evade host immunity. Therefore, this review will continue by discussing available fundamental knowledge on fungal thermotolerance.

THERMALLY TOLERANT FUNGI

For microorganisms to be considered thermotolerant, they should be able to withstand temperatures that exceed the population's optimal growth temperature (Robert et al., 2015). The upper thermal limit can range from 35°C to 62°C depending on the type of microorganism (Tansey and Brock, 1972; Maheshwari et al., 2000). Many bacterial species have been identified as thermally tolerant and some groups have also been recognised as thermophilic. Most fungi, however, have failed to attain this characteristic and remain susceptible to higher temperatures (Robert and Casadevall, 2009). Exceptions to this include some industrially important yeasts that tolerate high temperatures, which is essential for the success of some processes. Understanding the mechanisms of thermotolerance in these yeasts is crucial for industries to optimise bread and wine fermentation as well as biofuel production (Parapouli et al., 2020). These mechanisms have thus been scrupulously investigated due to their economic value. Conversely, studies investigating thermotolerant fungi associated with infection and disease are lacking.

Robert et al. (2015) investigated thermotolerance among a wide range of yeast species (CBS Culture Collection, Netherlands) and highlighted that many were able to grow at temperatures

above 35°C. Although these thermotolerant species represented a polyphyletic group of fungi, it was noted that thermotolerance was significantly more common among the ascomycetous yeasts than among the basidiomycetes. However, the maximum temperature of growth (T_{max}) for basidiomycetous yeast species has increased over the past decades. This suggests that basidiomycetes could be increasingly implicated in future novel fungal infections. Regardless, increasing T_{max} trends were observed for all yeasts investigated over the past few decades, potentially due to adaptation to the global change in temperature (Robert et al., 2015). Environmental stressors, such as temperature, are common agents in the evolution of microorganisms (Baquero, 2009) and it was contended that acquired thermotolerance among fungi could increase the incidence of infections (Araújo et al., 2017). In knowing the original environmental habitats of potentially pathogenic fungi and gaining a fundamental comprehension of their thermotolerant nature, researchers could in future determine the risk of these microorganisms becoming emerging pathogens (Araújo et al., 2017; Jackson et al., 2019). Well-known examples of such thermotolerant fungi that are contended to have emerged from the environment as pathogens are *Candida auris*, as well as the pathogenic cryptococci and aspergilli.

Candida auris

Candida auris is a multidrug-resistant pathogen, which is also known for its nosocomial transmission (Rhodes and Fisher, 2019). The simultaneous rise of infections caused by four genetically discrete clades of *C. auris*, in distinct geographical regions, has raised questions regarding the cause of the emergence of this pathogen (Kean et al., 2020). It was proposed that *C. auris* could be the model organism explaining emergence of novel mycoses as a result of global warming (Casadevall et al., 2020). *Candida auris* sp. nov. was first isolated from a hospitalised patient's ear (Satoh et al., 2009), an organ that represents cooler environments compared to the rest of the human body. It was therefore contended that the yeast could have gradually gained temperature tolerance while inhabiting the ear, possibly enabling invasive infection and subsequently causing many outbreaks of *C. auris*-related candidiasis (Casadevall et al., 2020; Jackson et al., 2019; Kean et al., 2020). Alarmingly, the frequency of these outbreaks and severity of *C. auris* infections has highlighted this yeast's epidemic potential (Meis and Chowdhary, 2019). Recently, cases of *C. auris* infections have increasingly been reported among patients suffering from Covid-19 (Rodriguez, et al., 2020; Almeida et al., 2021; Villanueva-Lozano et al., 2021).

With little knowledge available on the natural origin of *C. auris*, determining the cause of this yeast's emergence remains cumbersome. Studies have suggested that *C. auris* is of environmental origin and emerged as a pathogen only after being introduced to healthcare systems by patients carrying the yeast (Casadevall et al., 2020; Kean et al., 2020). Some hypothesise that, as observed for certain pathogenic cryptococcal species (Moschetti et al., 2017), *C. auris* may have initially inhabited birds (body temperature of 42°C) where it consequently attained its thermotolerance. The migration of these animals to areas where they are in close contact with humans could also explain the emergence of *C. auris* at distinct geographical regions (Moschetti et al., 2017; Kean et al., 2020). Another proposed habitat for this yeast is wetland systems (Casadevall et al., 2019) that are known to have anaerobic zones, in which *C. auris* would be able to exist. This species also tolerates elevated salt concentrations, which may explain why *C. auris* was recently isolated from a salt marsh (Arora et al., 2021). Except for one isolate, most of the environmental isolates were found to be antifungal-resistant and grew well at 37°C and 42°C. Subsequent phylogenetic analyses revealed the existence of single nucleotide

polymorphism differences between the environmental isolates and clinical isolates belonging to the same clade. The authors suggested that, once introduced into anthropogenic habitats, *C. auris* is capable of rapid adaptation to obtain both antifungal resistance and thermotolerance. They concurred, however, that more research is required to obtain a better understanding of the genetic diversity of this species in natural habitats. To date this species has not been detected in any other aquatic environment; however, frequent isolations of *Candida* spp. from aquatic environments (Table 1) as well as the recent findings of Arora et al. (2021) indicate that *C. auris* will potentially be found in more of these environments.

Cryptococcus spp.

Of the wide diversity of *Cryptococcus* spp. identified so far, infection is mainly caused by representatives of the *Cryptococcus gattii / Cryptococcus neoformans* species complex (Hagen et al., 2015; May et al., 2016). Their ability to withstand the mammalian core body temperature and to evade the immune response are key characteristics that facilitate systemic infections in humans and other mammals (Perfect, 2006) and it is known that cryptococcosis is one of the leading causes of mortality among immunocompromised individuals (UNAIDS, 2021). This infection is acquired after exposure to pathogenic cryptococci present in natural environments (May et al., 2016). Common natural habitats for these microorganisms are decaying plant material, such as trees, as well as the bodies and excreta of avian species (Ellis and Pfeiffer, 1990; Ellis and Pfeiffer, 1992; Lazera et al., 1996; Nielsen et al., 2007). The latter suggests that birds can serve as vectors for these cryptococci and subsequently distribute the pathogen to urban areas where interaction with humans might occur. These yeasts are introduced to the mammalian body through inhalation of aerosolised propagules (Perfect, 2006).

Recently, transcriptional regulation and signalling pathways were uncovered in pathogenic cryptococci that increase the virulence of these yeasts; many of these pathways are also up-regulated at higher temperatures (Juvvadi et al., 2014; Chatterjee and Tatu, 2017; Oliveira et al., 2020; Toplis et al., 2020; Bosch et al., 2021). Typical virulence factors observed in these yeasts include capsule enlargement and melanin production, which enable successful evasion of host immunity. Some of these virulence factors were also observed in non-pathogenic species (Petter et al., 2001; Watkins et al., 2017). For example, the basidiomycetous yeast, *Saitozyma podzolica* (syn. *Cryptococcus podzolicus*), produces virulence factors but is unable to cause disease in mammals due to its sensitivity towards higher temperatures (Petter et al., 2001). With the increased T_{max} observed among basidiomycetes (Robert et al., 2015), it is plausible that more non-pathogenic species of the basidiomycetous yeasts will cause fungal diseases in future in the event of acquired thermotolerance. Similar phenomena may also be observed for other fungal species; however, without establishing the level of thermotolerance of these potential pathogens, one cannot determine the risk of such a fungus becoming an emergent pathogen.

Aspergillus spp.

For most fungi, the thermal limit for survival is low and rarely breaches the basal temperatures of mammalian species (Robert and Casadevall, 2009). An exception, however, is the upper limit of some species of *Aspergillus*, a genus of filamentous fungi of which some representatives cause respiratory diseases among both immunocompromised and immunocompetent individuals (Kousha et al., 2011; Badiee and Zare, 2017). Members of this genus, such as *A. fumigatus*, can survive up to 70°C and actively grow at 37°C (Albrecht et al., 2010). The ability to grow at such high temperatures would suggest that this organism might be considered thermophilic; however, *A. fumigatus* and other species within this genus are capable of rapidly growing at mesophilic temperatures, allowing them to be predominant in natural environments (Paulussen et al., 2017). This characteristic distinguishes *Aspergillus* from thermophilic groups and delineates aspergilli as thermotolerant, with a broad thermal range. The ability to grow at mammalian body temperature enables the above-mentioned aspergilli, such as *A. fumigatus*, to infect humans even during fever conditions (Bhabhra and Askew, 2005). Aspergillosis is known for manifesting in the respiratory system, similar to what is seen for cryptococcosis. The spores of *Aspergillus* spp. are ubiquitous in nature, found in soil, air (both in natural environments and in buildings) as well as in natural water sources (O'Gorman and Fuller, 2008; Paulussen et al., 2017). Human contact with these fungi is therefore inevitable and poses a great risk to individuals predisposed to fungal infection because of defective immune systems. Additionally, antifungal resistance among *Aspergillus* spp. continues to complicate the treatment of aspergillosis. This resistance has also been observed in environmental isolates that have not yet been implicated in clinical situations (Hoda et al., 2019). Such intrinsic resistance towards antifungals adds further pathogenic potential to these aspergilli and poses a great threat to immunocompromised individuals who encounter these thermotolerant fungi in the environment.

MOLECULAR ASPECTS OF THERMOTOLERANCE

Temperature-related stress largely affects the physiology of an organism (Buckley and Huey, 2016). Alterations in a cell responding to elevated temperatures can be studied by investigating proteomic and genomic functionality under stressful conditions. In doing so, researchers identified stress response pathways that overlap among distinct fungal groups (Tereshina, 2005; Fuchs and Mylonakis, 2009; Leach et al., 2012; Juvvadi et al., 2014). The most common response pathway that is associated with thermotolerance is the heat shock response (HSR; Tereshina, 2005), which responds to sudden high increases in external temperature. It is a complex adaptation mechanism that focuses on downregulating housekeeping genes and upregulating cytoprotective genes in order to prevent or restore any damage due to the imposing heat shock (Verghese et al., 2012). The products and cofactors of these regulatory processes are proteins or chaperones known as heat shock proteins (HSPs). Their functions, in addition to gene regulation, include the denaturing, folding, refolding and transport of cytosolic proteins affected by the external stress (Tereshina, 2005). Additionally, HSPs assist in the transcriptional regulation of the cell wall integrity (CWI) and environmental stress response (ESR) pathways (Fuchs and Mylonakis, 2009; Verghese et al., 2012), both of which play a role in thermotolerance. The ESR involves many other signalling transductions responding to external changes in the microorganism's environment such as oxidative-, osmotic-, and pH stress (Verghese et al., 2012). The HSR, for instance, represents a subset within the ESR, since all of the genes involved in this pathway are included in the ESR regulon. The CWI pathway, on the other hand, harbours many other functions separate to environmental stress, despite having overlapping pathways with both the ESR and HSR (Dhar et al., 2013). Nevertheless, multiple regulatory proteins and genes in the CWI pathway have been identified and linked to thermotolerance. Within all these pathways and stress responses, a plethora of proteins and transcriptional factors all cooperate and cross-communicate to provide the microorganism with the proper machinery to adapt to thermal stress (Fuchs and Mylonakis, 2009; Verghese et al., 2013; Dhar et al., 2013).

Long-term thermotolerance and microevolution

Yeasts and other fungi adapt to environmental stress using several mechanisms which depend on the degree of stimulation as well as the duration thereof (Causton et al., 2001; Berry and Gasch, 2008; Dhar et al., 2013; Pereira et al., 2018). As for cells undergoing heat shock, the harsh stimulus is perceived, and various signals are sent to the rest of the cell to initiate repair as well as prevent further anticipated damage caused by the heat shock (Tereshina, 2005). During this process, housekeeping genes are paused while the cell rapidly responds to the external threat via HSR upregulation. However, during prolonged exposure to stressful conditions other signalling transductions occur simultaneously which aid in long-term adaptation, including regulatory factors of the CWI pathway and ESR (Causton et al., 2000; Berry and Gasch, 2008; Fuchs et al., 2009; Chen et al., 2012; Dunayevich et al., 2018; Sanz et al., 2018). Although most studies focused on industrially important yeasts, some researchers have investigated the molecular signalling constituents of thermotolerance in clinically relevant fungi (Argüelles, 1997; Juvvadi et al., 2003; Chang et al., 2004; Nichols et al., 2007; Chen et al., 2012; Chen et al., 2013; Chow et al., 2017; Yang et al., 2017; Brandão et al., 2018; Jung et al., 2018; So et al., 2018; Bloom et al., 2019). While the regulatory mechanisms of thermotolerance may vary among fungi, the underlying response pathways are similar (Alonso-Monge et al., 2009; Brown et al., 2020).

Generally, signalling pathways are induced by stimuli received through proteins located on the surface of a cell (Levin, 2005). These proteins or sensors can differ among species and rarely have singular roles. In fungi, precursors that form part of the CWI pathway mostly initiate signalling linked to thermotolerance (Verna et al., 1997; Zu et al., 2001; Verghese et al., 2012; Huang et al., 2018). The messages that these precursors receive are sent to other proteins that are part of various pathways, including the mitogen-activated protein kinase (MAPK)-, RAS-cAMP- and calcineurin signalling pathways (Fuchs et al., 2009; Parts et al., 2011; Verghese et al., 2012; Juvvadi et al., 2014). These pathways are also involved in many other cellular processes and are therefore not exclusively responsible for thermal stress adaptation (Causton et al., 2001; Berry and Gasch, 2008; Fuchs et al., 2009; Chen et al., 2012; Dunayevich et al., 2018; Sanz et al., 2018). Particular genes and proteins that form part of these pathways were linked to thermotolerance. However, the genome and transcriptome of yeasts were investigated only at severe heat shock conditions which might not provide an adequate representation of adaptation to gradual temperature increase (Fuchs et al., 2009; Parts et al., 2011; Verghese et al., 2012; Juvvadi et al., 2014). To gain a better perspective of fungi adapting to prolonged temperature increases, the genetic changes that occur over generations should be investigated.

Huang et al. (2018) carried out experimental evolution on a laboratory strain of *S. cerevisiae* by initiating adaptation through a stepwise increase in temperature, after which the genome was sequenced to investigate acquired thermotolerance. Considering that global temperatures increase gradually (IPCC, 2018), the approach of Huang and co-workers might provide an adequate representation of microevolution in fungi occurring in natural environments with temperature increases. The goal of their study was to experimentally evolve a yeast to obtain a high temperature growth phenotype (Htg⁺), as well as determining major contributing factors by investigating the mutations that occurred during the experimental evolution (Huang et al., 2018). The authors found mutations such as single nucleotide variants (SNVs), insertions and deletions (INDELs) and segmental duplications/deletions that could be associated with the Htg⁺ phenotype. Many of these mutations were nonsynonymous which altered the amino acid sequence of some proteins. Moreover, the mutations were multiple and sometimes parallel, increasing

the significance of the mutation and thus the probability of association with the Htg⁺ phenotype. As a result of their study, genetic mutations were identified that can contribute to long-term fungal thermotolerance. In addition, a combination of non-essential gene mutations was examined and it was determined that a genetically modified thermotolerant strain can be attained (Huang et al., 2018). Although this might seem like a breakthrough for industrial purposes (Amore and Faraco, 2012), it becomes increasingly concerning when considering the implications that global warming might have on fungal microevolution and consequently the emergence of novel fungal pathogens.

The dirty river, the fungus and the heat

So far, studies aimed at investigating microevolutionary changes in clinically relevant fungi have mainly focused on virulence and physiological reactions within the host (Magditch et al., 2012; Wartenberg et al., 2014; Ene et al., 2018). However, the combined contribution of pollution and global warming on fungal evolution has not been studied. Apart from the regulatory pathways or physiological reactions to environmental changes, little is known regarding fungal adaptation on a genetic level (Causton et al., 2001; Dhar et al., 2013). Moreover, studies often fail to consider the microevolutionary effects that result from interactions with other biotic and abiotic factors, e.g., other organisms, including plant life, and environmental conditions. The latter, for example, might include anthropogenic pollutants and climate change. Studies investigating pollution-associated microevolution are lacking despite the valuable insight that can be gained from understanding the effects of pollution on fungal growth. This is especially concerning since the pollutants may include antifungals released into the rivers (Chitescu et al., 2015). Thus, during the process of acquiring thermotolerance with the aid of global warming, fungi in polluted aquatic environments could potentially gain resistance towards antifungals, due to the presence of these compounds in surface waters. Future emerging pathogens could therefore be resistant to treatment before even causing infections. Pollution, such as organic pollution, also promotes the growth of fungi by serving as a rich source of nutrients (Wen et al., 2017), which might allow some species to outcompete more fastidious microorganisms and consequently disturb the natural mycobiome (Ortiz-Vera et al., 2018). Certain pollutants may also initiate virulence phenotypes in fungi, e.g., as seen for persistent organic pollutants (POPs) such as pentachlorophenol (Martins et al., 2018). Increasing anthropogenic activities resulting in polluted river water could therefore potentially cause a rise in fungal numbers, particularly pathogenic species. Considering the wide range of factors that may impact on fungi in natural environments, it is prudent to employ not only genomics but also more traditional techniques, such as biochemical, ecological, genetic, morphological, and ontological approaches (Naranjo-Ortiz and Gabaldón, 2019), to delineate the complex synergetic effect of climate change and increased pollution levels on fungal biology.

CONCLUSIONS

With the ever-increasing urbanisation to accommodate the equally growing population, increased environmental temperatures and pollution of rivers will have detrimental outcomes on human health (Fig. 1). South Africa is a developing country experiencing rapid urbanisation in informal communities with municipalities struggling to keep up and failing to implement proper sanitation infrastructure, causing communities to be dependent on natural water sources for their livelihoods (Colvin et al., 2016). Although little research has been conducted for South Africa, there is growing evidence that a wide diversity of fungi, including opportunistic species that can tolerate the
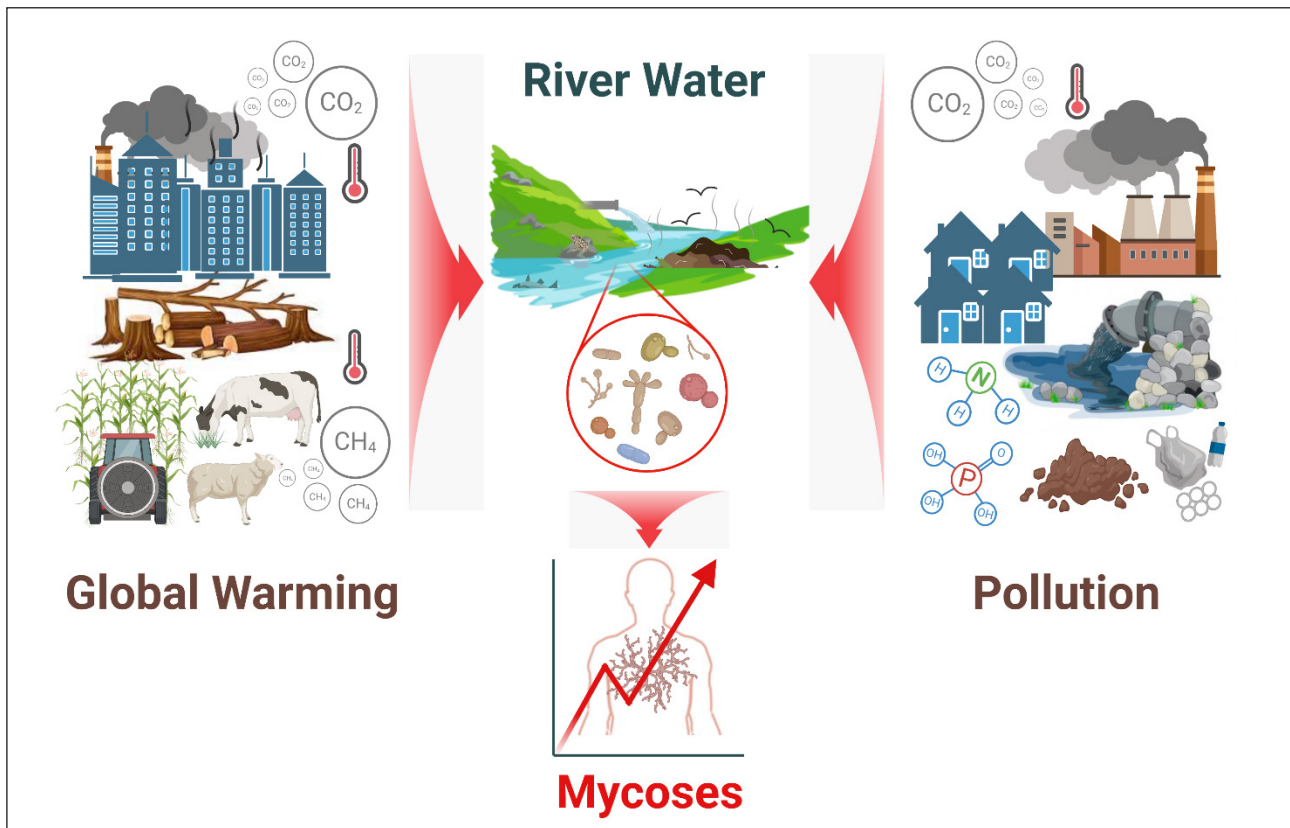
Figure 1. The illustration above signifies the contributing factors that may have an impact on humans susceptible to mycoses. Many individuals are dependent on river water due to rapidly growing urban areas with poor sanitation infrastructure. As pollution enhances the proliferation of fungi in the water and induces adaptation to chemicals such as antifungals, global warming simultaneously promotes long-term thermotolerance which aids in fungal pathogenesis. Together the increased temperatures and polluted water may lead to an increase of mycoses cases among immunocompromised people. This figure was created using BioRender.com.

mammalian body temperature, occur in South African rivers. The extent of the risk posed by waterborne fungi to community health therefore needs to be determined, especially in view of the fact that opportunistic yeasts, such as *Candida* spp., that infect individuals suffering from HIV/AIDS appear to be common in polluted rivers. Furthermore, rising river water temperatures will most probably induce increased thermotolerance amongst waterborne fungi. Worryingly, the fungal metabolism can adapt to these increases and current evidence indicates that more fungi will become thermotolerant as global temperatures rise. This, together with the fact that sewage-polluted rivers contain elevated concentrations of fungi, points to an imminent increase in the incidence of mycoses in the not-so-distant future. Important to note is that non-clinical isolates implicated in mycoses might represent antifungal-resistant fungi due to the various chemicals derived from agricultural-, industrial- and anthropogenic waste that end up in surface waters. However, few studies have been conducted to elucidate the resistance acquired from antifungal exposure in water sources. Nonetheless, the combinatorial effects of pollution (organic or inorganic) and global warming could be drivers in fungal microevolution and potentially lead to a rise in emergent pathogenic fungi, for which there is a limited range of anti-fungal drugs available. Efforts to better record the occurrence and delineate the ecology and antifungal resistance of clinically relevant fungi in South African river systems should therefore be a priority.

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