Review

Fungal impacts on Earth's ecosystems

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Over the past billion years, the fungal kingdom has diversified to more than two million species, with over 95% still undescribed. Beyond the well-known macroscopic mushrooms and microscopic yeast, fungi are heterotrophs that feed on almost any organic carbon, recycling nutrients through the decay of dead plants and animals and sequestering carbon into Earth's ecosystems. Human-directed applications of fungi extend from leavened bread, alcoholic beverages and biofuels to pharmaceuticals, including antibiotics and psychoactive compounds. Conversely, fungal infections pose risks to ecosystems ranging from crops to wildlife to humans; these risks are driven, in part, by human and animal movement, and might be accelerating with climate change. Genomic surveys are expanding our knowledge of the true biodiversity of the fungal kingdom, and genome-editing tools make it possible to imagine harnessing these organisms to fuel the bioeconomy. Here, we examine the fungal threats facing civilization and investigate opportunities to use fungi to combat these threats.

The global One Health approach seeks to better understand and improve the interconnectedness of people, animals, plants and their environment. Such insight will engender a more sustainable future for life on Earth. Fungi are essential to this quest, because they affect Earth's ecosystems in a myriad of beneficial and detrimental ways. The fungal kingdom is more than one billion years old and comprises millions of species[1–3] of remarkable morphological diversity, ranging from macroscopic mushrooms to microscopic unicellular yeasts. These eukaryotic organisms exhibit tremendous genomic and phenotypic plasticity, and this adaptive evolutionary potential has led to their centrality in Earth's ecosystems.

Fungi secrete a spectacular array of bioactive chemical compounds and enzymes; these have crucial roles in the biosphere, from digesting organic matter and recycling nutrients from dead plant and animal tissues, to mediating intimate and mutually beneficial associations with the roots of almost all land plants[4]. Fungi are a key source of food and fermented products, including many beverages and industrial feedstocks, as well as dozens of important enzymes and drugs. Conversely, some fungal species are pathogenic to plants or animals. These pathogenic species not only jeopardize food security worldwide by infecting and contaminating crops of agricultural and economic importance, but also cause devastating disease in hibernating bats and in ectothermic

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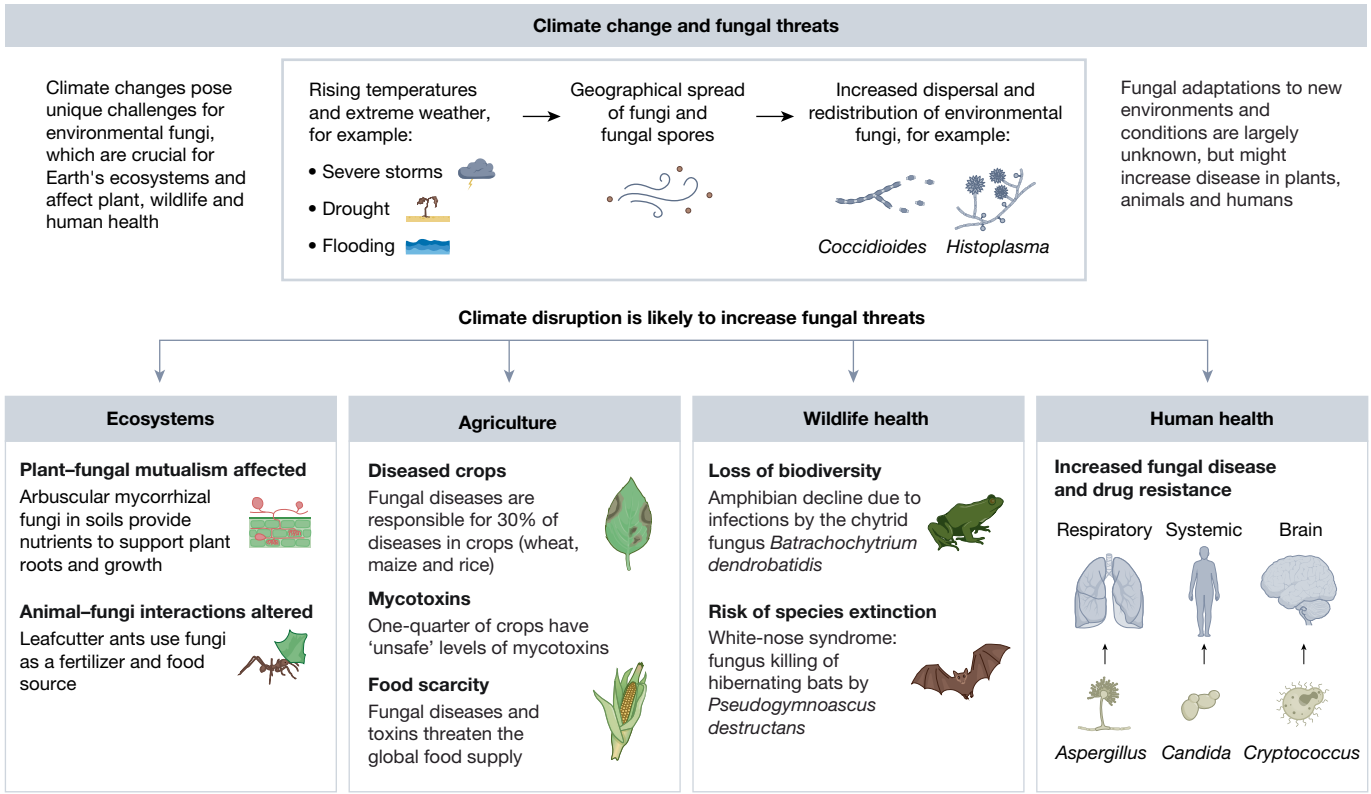

Fig. 1 | Climate change will disrupt fungal interactions in Earth's ecosystems and is likely to increase fungal diseases in plants, wildlife and humans. Environmental fungi have crucial roles as decomposers (restoring nutrients), as mycorrhizal root symbionts (supporting plant growth) and in insect–fungus mutualisms. Perturbing the balance of these interactions will affect Earth's ecosystems. Rising global temperatures and severe weather events (hurricanes, floods, wildfires and droughts) will increase the dispersal of fungal spores in the air and alter crop and soil health. The recent increased geographical spread of fungal diseases in wildlife, notably in amphibian and bat populations, is driving species loss. The spread to new environments and hosts, alongside selection by broad-spectrum and environmentally durable fungicides, imposes selection on fungi to adapt to survive and is likely to be fuelling the emergence of new human fungal diseases, some of which are resistant to antifungals.

animals, such as snakes, salamanders and frogs. Immune-competent and endothermic mammals are mostly resistant to severe fungal disease, probably owing to a combination of host adaptive immunity and high body temperature[5]. However, invasive fungal diseases are common in humans with impaired immunity, and are often recalcitrant to treatment, with a substantial burden of morbidity and mortality[6].

Although we are just beginning to appreciate the extent of fungal interactions on a global scale, anthropogenic environmental changes are likely to have a major impact on the fungal kingdom and its interactions with the biosphere (Fig. 1). Rising temperatures, changing concentrations of atmospheric gases and extreme weather events such as floods, hurricanes and drought have the potential to alter ecological relationships that underpin ecosystems worldwide[7], as well as the geographical distribution of both beneficial and pathogenic fungi[8–12]. A vast number of fungal species grow optimally at ambient temperatures[13], but as Earth warms, these fungi must migrate, adapt or perish[14]. Some fungi may evolve thermotolerance and, subsequently, the ability to cause new diseases or infect new hosts[15]. Increasing temperature and humidity, alongside flooding and water damage from extreme events, can promote the indoor growth of fungi known as moulds[16]. These fungi can exacerbate asthma, with fatal consequences in severe cases[17,18]; can lead to life-threatening infections in patients with cancer and in people who have undergone transplants[19]; and can affect mental health[20].

Hundreds of fungal species afflict humanity and infect its staple crops[21]. The huge impact of fungi on global food security necessitates the development of sophisticated and diverse means of crop protection[22]. At present, fungicides remain our front-line weapon in this fight. There are, however, relatively few classes of fungicides available for crop protection, and this paucity is mirrored in the clinical sphere, with only three major classes of antifungal drugs licensed for invasive human disease[23]. The widespread use of some of these classes in treating fungal diseases of both plants and people has triggered an emerging pandemic of antifungal-resistant human fungal infections[23]. The need for new antifungals is imperative, but their discovery is challenging and protracted owing to the conserved cellular mechanisms of eukaryotic fungi and their hosts.

Despite the importance of fungi to Earth's ecosystems, the enormous richness and genetic diversity of the fungal kingdom remain largely unexplored. Indeed, estimates suggest that more than 95% of fungal species remain undescribed[1]. Given the unmatched capacity of fungi to produce diverse secondary metabolites, ranging from antimicrobial drugs to hallucinogenic compounds, it is likely that many compounds that could be useful in biotechnology, agriculture and medicine have yet to be discovered[24]. Fungi promise to deliver new capabilities, such as plastic-degrading enzymes[25]; new materials, such as biocomposites for architectural construction[26]; and melanin for energy capture and protection against radiation[27]. It is crucial that we better understand all aspects of this diverse kingdom, given the human perils and ecosystem problems imposed by fungi, counterbalanced by their enormous biotechnological potential.

Fungi in the environment

Fungi occur in nearly every habitat on earth, including the air, marine environments, exposed rock surfaces, soils and every tissue of land plants. Deep sea thermal vents contain fungi and so do rocky

peaks—even reactor rooms in the damaged Chernobyl nuclear power plant exhibit the growth of heavily melanized fungi[28]. The flagellated swimming spores retained by some fungal phyla are a strong indicator of their aquatic origin. As fungi left aquatic habitats, they underwent extensive diversification in terrestrial ecosystems, paralleling diversification in land plants[29]. Fungi that are currently found in marine habitats are poorly studied but comprise mainly secondary invaders that have close phylogenetic relationships with terrestrial fungi[30]. These secondary invaders may have acquired traits on land that facilitate their ability to cause diseases in marine hosts. Particularly notorious is the sea fan coral disease in the Caribbean caused by *Aspergillus sydowii*, which may be triggered by warming seas and the input of terrestrial spores from Saharan dust storms[31]. *Cryptococcus gattii* infections of dolphins, porpoises and seals[32], *Coccidioides immitis* infections of southern sea otters[33] and *Paracoccidioides ceti* infections of dolphins[34] are also closely related to terrestrial human-associated pathogens.

Fungi also form important associations with insects, with both beneficial and harmful outcomes. Some fungi are crucial nutritional symbionts for termites[35] and attine ants[36], whereas others chemically manipulate behaviours to produce 'zombie hosts' and achieve the completion of their own life cycles[37]. Insect–fungal symbioses can result in extraordinarily damaging environmental consequences. For example, millions of hectares of trees have been killed by Eurasian spruce bark beetles (Curculionidae: Scolytinae) with assistance from their fungal symbionts[38]. These beetle-associated fungi alter the volatile composition of spruce bark, thereby producing compounds that attract swarms of beetles, leading to mass attacks[39] and forest losses across landscape scales, with untold ecosystem-level impacts. Fungi that have evolved ancient, benign and geographically endemic associations with hosts have the potential to cause global panzootics when human-mediated transport brings them into contact with naive hosts. Amphibians from Asia, for example, are colonized asymptomatically by aquatic chytrid fungi from the genus *Batrachochytrium*. Likewise, European bats are frequently colonized by *Pseudogymnoascus destructans*, and Manchurian ash trees (*Fraxinus mandshurica*) are hosts to *Hymenoscyphus fraxineus*. The geographical spread of all three pathogens has turned them into leading infectious disease threats to biodiversity: chytridiomycosis caused by *Batrachochytrium dendrobatidis* is a proximate cause of global amphibian declines and extinctions[40]; white-nose syndrome (WNS) caused by *P. destructans* has led to localized ecological extinctions of some populations of little brown bats (*Myotis lucifugus*), alongside the steep decline of other North American bat species[41]; and dieback will devastate up to 85% of European ash trees (*Fraxinus excelsior*)[42]. In these cases, global trade has led to the erosion of ancient endemic host–pathogen associations through cross-continental introductions into naive host assemblages. For example, genomic epidemiology has shown that *B. dendrobatidis* has emerged out of Asia at least four times during the twentieth century[43]. This was followed in 2010 by the emergence of *Batrachochytrium salamandrivorans* out of Asia into fire salamanders (*Salamandra salamandra*) of the Netherlands[44]. A single genotype of *P. destructans* sparked the epizootic wave of WNS emergence across bats of North America in the winter of 2006–2007, after an introduction from Eurasia into a single cave in New York[45]. Finally, *H. fraxineus* was introduced twice from East Asia into Europe[46]. The severity and scale of the declines in these host species underscore the ability of fungi to override density-dependent epidemiological processes when certain lethal combinations are fulfilled; namely, high-virulence pathogens with resilient environmental transmission stages, broad host ranges and high transmissibility in transported goods, including traded wildlife, horticultural products, wood, plant cultivars and seeds[47]. The destruction of biodiversity by these wildlife diseases has broad consequences in the One Health context: the decline of neotropical frogs has been associated with an increased incidence of malaria[48]; the decline of North American bats is valued at losses worth billions of dollars in agricultural and ecosystem services[49]; and ash dieback imposes enormous management and financial costs on stricken economies[50].

Other fungi, long ago adapted to wildlife, may threaten human health if humans migrate into their endemic regions. The best-studied examples are *Coccidioides* species, native to the New World, which evolved to a novel type of symbiosis—endozoan—that is the animal counterpart to a plant endophyte[51]. Migrating humans reached hot, dry areas of North America no earlier than 20,000 BCE, and first encountered *Coccidioides*. Today, sprawling urban areas of California, Arizona and Texas lie in proximity to the desert rodent hosts, and coccidioidomycosis has become a major human health concern[52], with a predicted expanding endemic range under climate-change models[53].

Control of environmental and wildlife fungal diseases

One method of treatment for wildlife disease that warrants further investigation is vaccination, applied either on a continental scale to mitigate global disease, or on a more limited scale to protect an endangered species or locally threatened population, thus affording additional time for natural resistance to evolve. For example, an orally ingested and topically applied vaccine to protect bats against *P. destructans* has been developed, which increased the survival of little brown bats after experimental challenge with *P. destructans* under laboratory conditions[54]. Field trials are now under way in at-risk bat populations.

The development of robust experimental models to elucidate mechanisms of infection and propagation can fortify strategies to mitigate WNS. The authors of a recent study generated a little-brown-bat keratinocyte cell line and hibernation model[55]. They showed that *P. destructans* infects bat skin cells by distinct mechanisms that depend on host body temperature, which fluctuate during hibernation[55]. Defining the invasive strategies of *P. destructans* identifies mechanisms to target for mitigation strategies. Similarly, temperature regulation has recently been examined as a strategy to mitigate chytridiomycosis, by deploying thermal refuges that are well tolerated by frogs but which reduce *B. dendrobatidis* infection[56].

There is a growing appreciation that fungi are host to other microorganisms, including bacteria and viruses. Most mycoviruses have small RNA genomes, reside in the cell's cytoplasm and range in effect from promoting hypovirulence to hypervirulence. Modest success has been achieved using mycoviruses to control chestnut blight disease in some locations in Europe[57], and a spray is under development that uses a mycovirus to convert the broad-host-range plant pathogen *Sclerotinia sclerotiorum* into a harmless endophyte[58]. Two of the most devastating wildlife pathogens, *P. destructans* and *B. dendrobatidis*, are known to harbour mycoviruses, associated with fungal hypervirulence[59,60]. Modulating mycoviruses to reduce fungal pathogenesis in environmental and wildlife populations holds promise as a biological control agent but needs further investigation.

Fungi in forestry and agriculture

Fungi form key mutualistic symbioses with agricultural crops as well as with forest ecosystems. For example, mycorrhizal fungi colonize the roots of more than 90% of land plants, and provide their hosts with nutrients and water in exchange for plant carbon and lipids[61]. Mycorrhizal fungi contribute greatly to plant growth and health, endowing resilience in the face of climate change, pest and pathogen attacks and nutrient limitations[62]. Indeed, planting seedlings with climate-matched mycorrhizal fungi increases the tolerance of trees to climate stress[63]. Moreover, endophytic fungi can enhance plant health and adaptation to both biotic and abiotic stresses by influencing plant physiology, resistance towards pathogens and microbiome composition[64–67]. Globally, plants are estimated to sink the equivalent of one-third of the current annual CO_2 emissions from fossil fuels[68] into their mycorrhizal fungi annually. This mycorrhizal sink represents a major asset, but one that

is under threat from deforestation and disruption of the symbiosis as atmospheric nitrogen deposition increases[69].

Despite being integral to human-made agroecosystems, fungi are also arguably the most important biotic threat to crop production[47,70,71]. The United Nations Food and Agricultural Organization lists more than 100 crops of global dietary importance. These plants fall into essential calorie crops, such as the 'big five' (wheat, maize, potatoes, rice and soybeans), and commodity or 'cash' crops, such as coffee, cocoa and bananas[72]. All are afflicted by fungal diseases. Although crop losses are variable, the disease burden, even after deploying disease mitigation practices, is estimated to be between 10% and 23% of total harvests[22]. Furthermore, post-harvest fungal rots account for a further 20% loss in the USA and up to 50% in some developing countries[73].

Although some fungal foes have been with us since the dawn of agriculture, human activities have fostered the emergence of new adversaries. Wheat, for example, provides an ideal playground for a frenzy of fungal feeding and breeding, because it is grown in densely planted monocultures, guarded by one or two inbred disease-resistance genes, and over a greater land area than any other cereal[22]. Wheat suffers constant attacks by various fungi, such as the wheat stem rust fungus *Puccinia graminis* and the blotch fungus *Zymoseptoria tritici* in temperate zones. A strain of *P. graminis*, first detected in Uganda in 1998, has caused devastating epidemics in Africa and the Middle East[74]. *Z. tritici* shows all the hallmarks of high evolutionary potential, including recombination as part of sexual reproduction, as well as high strain variability and mutation rates[75]. A third new major global threat of wheat is wheat blast, a disease caused by the fungus *Magnaporthe oryzae* pathotype *triticum*, which originated in Brazil in 1985 but has since spread through the wheat trade to Africa and Bangladesh[76].

Mycotoxins, which are fungal-produced compounds that are highly toxic to humans and livestock, also contribute substantially to crop losses in the field and by post-harvest contamination. An estimated 25% of all crops have 'unsafe' levels of mycotoxins for human consumption and 60–80% of all crops have detectable levels of mycotoxins[77]. Several hundred types of mycotoxins have been identified, including the aflatoxins produced by *Aspergillus* species, which affect crops including cereals, oilseeds, spices and nuts[78]. Although soil-borne *Fusarium* species produce a range of toxins, of particular concern is the growing incidence of Fusarium head blight (FHB) in wheat. An analysis of FHB mycotoxin data in European wheat revealed persistent single- and multi-mycotoxin contamination of the grain and a changing temporal geographical distribution of FHB[79]. When grain that exceeds the maximum allowable levels of FHB mycotoxin for human consumption is downgraded to animal feed, chronic effects in animals, including suppression of the immune system, have been reported[80]. Overall, a broad understanding of the acute and chronic impacts of mycotoxins on human and livestock health is lacking, as is data on the effects of a changing climate on mycotoxin production.

Control of plant fungal diseases

During the co-evolutionary arms race with plant hosts, pathogens have evolved sophisticated strategies to combat or evade plant immunity. Fungal pathogens secrete a cocktail of enzymes, effector proteins and phytotoxins to invade and suppress plant immune responses[81]. In turn, plants can recognize these effector proteins, leading to effector-triggered immunity to arrest the infection. Small RNAs (sRNAs) are also secreted by fungal pathogens[82,83]. They travel into plant cells and hijack key components of host RNA interference pathways, to silence plant immunity-related genes[82]. Conversely, plants can transport sRNAs into pathogens to induce the silencing of virulence-related genes[84]. This cross-kingdom conflict has led to a heavy reliance on inbred plant disease-resistance genes to provide pathogen protection. However, the highly variable and fast-reproducing fungi quickly outmanoeuvre their comparatively invariable plant hosts, tipping the co-evolutionary balance in favour of the pathogens. This imbalance has been produced by shifts in agriculture from small-scale and diverse practices to large-scale intensive monocultures of genetically uniform crops, thus increasing reliance on one or a very small number of plant disease-resistance genes, and by the use of single-target site fungicides[22]. This growing threat is compounded by the global movement of fungal pathogens in the face of climate change[85], and by their adaptability to changing stresses[22].

Fungicides are currently mainstays of disease control in agricultural settings[22]. There are six main classes of agricultural fungicides: morpholines, azoles, benzimidazoles, strobilurins, succinate dehydrogenase inhibitors (SDHIs) and anilinopyrimidines. Of concern, however, is the domination of single-target fungicides in the marketplace, with the azoles, strobilurins and SDHIs accounting for 60% of this monopoly[86]. Accordingly, fungicide resistance has emerged against these three classes in all major crop pathogens[23].

Several strategies could be used to improve crop disease resilience, such as: (1) the discovery of new broad-spectrum, environmentally benign fungicides—ideally, these fungicides would target several fungal processes and also activate plant defence mechanisms[87]; (2) better use of combinatorial mixtures of fungicides proven to reduce the rate of resistance emergence in theoretical and laboratory-based assays as well as in field trials[88]; (3) designing new fungicides by harnessing knowledge of fungal effectors and their mechanisms of delivery[89]; (4) manipulation of the arms race between plants and pathogens to favour the host, by developing RNA-based eco-friendly fungicides that target pathogen genes for plant protection[90–92]; (5) field evaluation of novel polygenic disease resistance cassettes[93]; and (6) exploring the potential of synthetic plant immune receptors[94] for use in the fight against fungi.

Fungi and human health

Globally, fungi are estimated to cause more than one billion superficial infections every year, including athlete's foot (tinea pedis), nail infections (onychomycosis), hair infections (tinea capitis), vaginal yeast infections (vulvovaginal candidiasis) and oral infections (oropharyngeal candidiasis)[95]. Although these fungal diseases may not be life-threatening in immune-competent individuals, they are often intransigent or require several rounds of treatment, which can drive antifungal resistance. Invasive fungal infections, which typically occur in immune-compromised individuals, are fewer, but lead to an estimated 2.5 million attributable deaths each year[6]. This high, yet neglected, burden of disease caused by fungi has recently been recognized by the World Health Organization Fungal Priority Pathogen List in an effort to focus and drive disease interventions[96]. Systemic fungal infections are caused by fungal species from several genera, including *Aspergillus*, *Candida*, *Cryptococcus, Pneumocystis*, *Coccidioides*, *Histoplasma*, *Emergomyces* and from the order Mucorales. Chronic conditions that underlie an increased susceptibility to fungal infection include HIV and AIDS, organ transplants, diabetes, cancer and diseases that are treated with steroids, as well as acute co-infections with influenza and COVID-19[97,98].

Rapid and specific identification of infection-causing fungi remains a clinical priority. Current diagnostic practices rely on correlating direct examination and culture with histopathological and cytological findings to confirm the infecting species. Commercially available nucleic acid amplification tests and lateral flow assays have improved fungal diagnostic testing. Moreover, mass spectrometry is now routinely used for the identification of yeasts from clinical samples, and increasingly for filamentous fungi. These approaches are limited by incomplete genomic resources for comprehensive species diagnostics, such as for rarely observed or geographically restricted pathogens, which can impede clinical responses. At the leading edge, whole-genome sequencing of fungal isolates has been used to investigate outbreaks of pathogens such as *Candida auris*. There is a clear need for investment in wider fungal genomic resources, which have lagged behind those for other microorganisms.

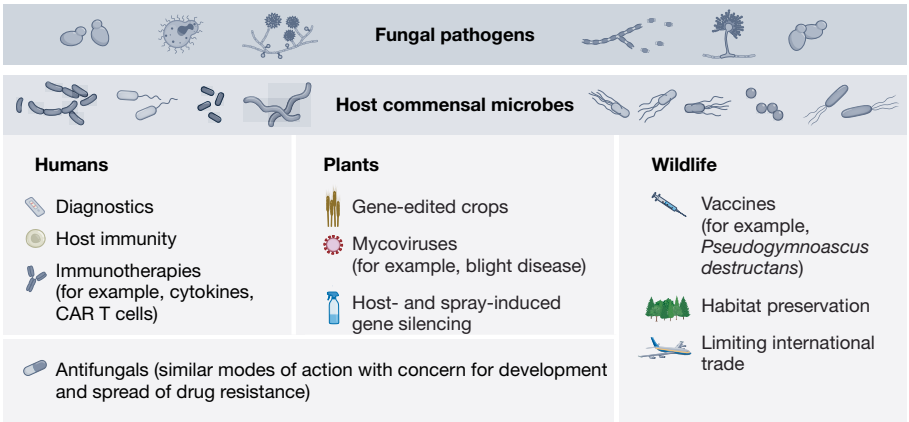

Fig. 2 | Control strategies to combat fungal infections. This figure highlights the interconnectedness of humans, plants and wildlife, illustrating how fungal pathogens affect all three domains of life and how control strategies often overlap across these systems. This interconnectedness is crucial, because advances in one domain, such as diagnostics or treatment methods in humans, can influence strategies in others, such as agriculture or wildlife management. In healthy humans, colonization resistance keeps commensal fungi and invading pathogens from causing active infections. When fungi cause disease, rapid and specific diagnostics and treatments (including immunotherapies and antifungal agents) represent a clinical priority. However, some classes of drug used in clinical settings are also used in agriculture, increasing the risk of environmental fungi becoming drug resistant. To mitigate fungal crop diseases, current efforts are focused on developing gene-edited crops, mycoviruses to target fungi or double-stranded RNAs to silence necessary pathogen genes on plant tissues. Fewer options exist for protecting wildlife; these include developing vaccines for specific pathogens, and mitigating disease drivers—for example, by curtailing environmental disturbance, providing artificial refuges to support wildlife population resilience and limiting the international trade of wildlife to prevent the introduction of non-native pathogens into native host populations. The figure underscores that efforts to combat fungal pathogens must be viewed holistically, recognizing that shared environments and similar approaches contribute to both challenges and solutions across these domains.

The human mycobiome

Human microbiome research has recently turned to the fungal component of the microbiome (the mycobiome), unveiling connections to various diseases and novel roles in maintaining or disrupting a balanced immune response across the human life course, from infancy to old age. Many recent advances in human mycobiome research have focused on the gastrointestinal tract (most often assessed from faecal samples), in which the fungal community makes up an estimated 2% of the total microbial biomass, dominated by *Saccharomyces* and *Candida* species[99]. Intestinal fungi have important roles in shaping bacterial community composition, regulating immune pathways and contributing both to health and disease[100–104]. Although *Candida albicans* is present asymptomatically in 20% of women and might have beneficial roles, it is also a common etiological agent in vulvovaginal candidiasis and vaginal infection[105]. The human skin mycobiome is dominated by *Malassezia* species, which have adapted to skin niches by using host lipids as nutrients, and then secreting antimicrobial products that deter bacterial pathogens[106]. The greatest diversity of skin-associated fungal species is on the feet, with altered fungal communities observed in toenail infections and athlete's foot[107].

Commensal fungi that colonize humans induce type 17 immunity. This form of immunity, which centres around pro-inflammatory T helper 17 (T_H17) cells and the production of the cytokines IL-22 and IL-17, is pivotal for activating protective antifungal responses on epithelial barrier surfaces[97]. About 20% of circulating memory T_H17 cells in humans recognize *C. albicans* antigens and are likely to be induced by commensal *C. albicans*[100]. Conversely, *C. albicans*-induced cross-reactive T helper 1 (T_H1) cells may complicate conditions such as inflammatory bowel disease[101,102] and allergic airway disease[103]. Skin-resident T_H17 memory T cells prevent the overgrowth of *Malassezia pachydermatis*, but promote inflammation when the skin integrity is compromised[108]. Lung and oral epithelial cells regulate the T_H17 pathway in resident immune cells to control the growth of *Blastomyces dermatitidis*[109] and *C. albicans*[110], respectively. Members of the human mycobiome also regulate humoral immunity. Gut fungi shape IgG and IgA antibody repertoires, including secretory IgA antibodies that target *C. albicans* hyphae. Although this promotes fungal commensalism when gut bacteria are absent[111,112] and, in turn, protects against *C. albicans* systemic infection[113], in a mixed microbial community, the hyphal form shows increased fitness, and production of the hyphal-specific toxin candidalysin promotes gut colonization[114].

Control of human fungal diseases

In contrast to antibiotics that target a wide variety of prokaryotic-specific pathways in bacteria, the chemical diversity and molecular targets of antifungal drugs have been quite limited. Indeed, only three distinct chemical classes have dominated the antifungal drug arsenal for the treatment of systemic human fungal disease for many decades: the azoles, polyenes and echinocandins. Moreover, this limited arsenal is plagued with issues of host toxicity, a narrow spectrum of action and antifungal drug resistance. Additionally, the multi-system deployment of antifungals has effects across hosts. For example, azole resistance in clinical isolates of *Aspergillus fumigatus* has been associated with molecular signatures consistent with environmental fungicide use[115]. Despite calls for innovation in antifungal drug discovery, little progress was made for many years. Recently, there have been promising new compounds and formulations approved for human use or in clinical trials[116,117]. Most encouraging are four new chemical classes of antifungals. However, for two of these (Fosmanogepix and Olorofim), agricultural fungicides with similar modes of action are nearing or have been approved for use. Their agricultural use will probably result in the rapid selection of environmental fungal strains that are resistant to such chemistries, and this will subsequently limit lifespan in the efficacious treatment of human infections[118]. Protecting the utility of the few classes of antifungal drugs in clinical settings heralds a call to 'ring-fence' drugs exclusively for agricultural or clinical practice.

The study of patients with genetically defined inborn errors of immunity and susceptibility to fungal infections has helped to elucidate the fine-tuning of fungal interactions with the human host and has paved the way to test immunotherapies for fungal infections. These include administration of pro-inflammatory cytokines, directed antibodies or cell-based therapies such as chimeric antigen receptor T (CAR T)

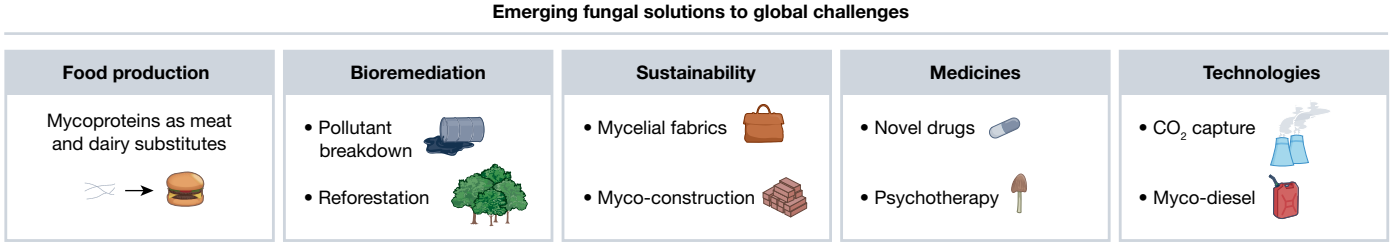

Fig. 3 | The fungal kingdom offers many known and emerging solutions to global challenges facing humanity. Mycorrhizal fungi associated with root structures store a substantial amount of global carbon underground, offering the potential to harness fungi as a carbon sink. These fungi could also have an important role in supporting reforestation efforts and aiding in bioremediation. The rapid and low-cost growth of fungi makes them ideal as protein substitutes for meat and dairy as we face agricultural losses and seek to reduce our dependence on food products with high carbon footprints. In addition to their possible use as a myco-fuel, fungi are proving to be an incredible natural resource for sustainable fabrics, textiles and building materials. Finally, although fungal diseases pose a threat to human health, fungi also have a tremendous capacity to be used for new antimicrobial medicines and therapeutics. Clearly, we are only beginning to capitalize on the myriad ways that fungi can be harnessed in technologies, medicines, food and sustainable products.

cells[97,119]. Although vaccines have considerably reduced mortality for many deadly infectious diseases, the pace of fungal vaccine development has been slower. Experimental vaccines against medically important fungi have shown promise, but only one vaccine against coccidioidomycosis and two against candidiasis have been tested in humans, and none have been commercialized[120]. Several immune-based therapies show much promise in pre-clinical models[121], but the development of future immunotherapies will need to overcome the daunting challenges of demonstrating efficacy across a wide range of host immunodeficiencies; evaluate the risk of immunotoxicity; address concerns about unwanted immune responses to commensal fungi; and face the underfinanced antifungal market space. Control strategies for combating fungal infections across humans, wildlife and plants are highlighted in Fig. 2.

Antifungal drug resistance and emerging infections

Recent years have seen the global emergence of fungal pathogens with high levels of antimicrobial resistance[122]. Azole resistance in *A. fumigatus* was unheard of in the 1990s; now 95% of isolates in southern Vietnam are resistant[123], almost certainly because of heavy use of azole fungicides. *C. auris*, first detected 15 years ago[124] on three continents, is frequently resistant to several classes of antifungal drug, and infections are associated with mortality rates of 30–60% (ref. 124). Since the initial detection of *C. auris*, environmental isolates have been identified[125], but it is still unclear whether these represent ancestral reservoirs of the yeast. Although direct proof is lacking, one hypothesis is that the dual use of azoles on crops and in the clinic has accelerated the rise of highly azole-resistant *C. auris*[126], in which multiple mutations contribute to resistance in most isolates[127,128]. It has also been proposed that synergies amongst drivers, such as global warming and chemical pressures, have contributed to the recent emergence of *C. auris*, with healthcare settings having a major role in ongoing transmissions and outbreaks[128–130]. Antifungal treatments purchased over the counter and administered on a long-term basis, such as terbinafine, have probably influenced the emergence of drug-resistant strains of the highly transmissible skin-lesion-forming fungus *Trichophyton indotineae*[131]. The most recent emerging fungus of concern to human health, *Sporothrix brasiliensis*, originated with zoonotic transmission from feral cats to tens of thousands of people in Brazil and neighbouring countries, with spread documented in the UK from imported cats[132,133]. The detection of *C. auris* both in feral dogs[134] and in a companion dog[135] speaks to the risk of spillover into other vertebrates, leading to zoonotic reservoirs or amplifiers of such emerging drug-resistant fungal pathogens[134]. Recognizing that the continuing emergence of invasive fungal pathogens poses a threat to public health, a national surveillance program in China screens and sequences isolates that cause human infections. This program recently identified two independent cases of infection with *Rhodosporidiobolus fluvialis*, which was previously considered to be an environmental fungus[136]. Growth at mammalian body temperature induces mutagenesis and yeast-to-pseudohyphal transition of *R. fluvialis*, which, in turn, elicits the development of antimicrobial resistance and virulence[136].

Fungi in the food industry

Fungi are used extensively to produce food products, including beverages (for example, beer, wine and sake), dairy items (for example, cheese), baked goods (for example, bread), cultivated mushrooms, protein-rich foods (for example, Quorn, tempeh and oncom), and food additives (for example, colourants, flavourings, organic acids and vitamins)[137,138]. The attributes that make fungi useful for food production include robust metabolic and fermentation capabilities, as well as the ability to grow on waste substrates under a range of conditions. Citric acid produced by *Aspergillus niger*[139] is one of the most valuable organic acids from fermentation and is an important additive to foods, such as carbonated beverages. Other, more recent innovations include the production of haem-containing proteins for use in meat substitutes, such as the Impossible burger, in which the protein-production capabilities of the yeast *Pichia pastoris* enables large-scale synthesis of leghaemoglobin, a red, haem-containing protein from soybeans[140]. As a food additive, this protein serves as a colourant as well as a key flavour component to provide a meat-like taste to a plant-protein-based product.

Outlook

It is clear that the fungal kingdom has a profound role in the One Health approach to appreciate the interconnectivity of humans, plants and other organisms with the shared environment. Past successes in harnessing the tremendous potential of fungi, as in the food industry, foreshadow the wealth of beneficial opportunities that are left to reap from this kingdom. Beneficial fungi that colonize global landscapes and wildlife populations have the potential to control disease in their host environments, and represent vast and largely untapped opportunities for human health. For example, fungi have tremendous potential as biocontrol agents to control other plant pests. Some fungi form remarkable traps to attack parasitic nematode worms that cause economically important diseases in crops[141], and fungal pathogens of insects can be used as biocontrol agents or as sources for new insecticidal compounds. Furthermore, both beneficial and antagonistic animal symbiotic fungi represent valuable sources of products with diverse uses, including drugs and industrial products. This is illustrated by the immunosuppressive drug cyclosporin, which is originally derived from the fungus *Tolypocladium inflatum* and evolved as part of its life cycle with the dung beetle[142]. Extending the long history of harnessing fungal secondary

metabolites for human health, which began with the discovery of penicillin[143], there has been a recent resurgence in efforts to assess the clinical efficacy and therapeutic benefits of psilocybin-containing 'magic mushrooms', with promising applications in the treatment of post-traumatic stress disorder, depression, addiction and chronic pain[144].

Fungal contributions to climate solutions extend beyond boosting plant performance and carbon sequestration towards reducing and remediating pollutants. For example, fungi have a key role in biofuel production by converting plant cellulose to ethanol. Although the current consensus is that electricity is a better option for powering vehicles than are biofuels, owing to the energy investment needed to grow temperate crops and to distil ethanol from batch fermentations[145], the need remains for aviation biofuels[146]. Fungi could also be used to counter ecosystem pollutants, such as harmful blooms of toxigenic algae triggered by agricultural run-off, 'forever chemicals' such as perfluoroalkyl and polyfluoroalkyl substances that threaten drinking water, and high-molecular-mass poly-aromatic hydrocarbons[147] that contaminate landfills and form plastics[25]. Beyond bioremediation and detoxification, fungi can be harnessed to produce both mycelium and fungus-derived compounds with diverse applications. For example, the past decade has seen the development of pure mycelium materials, such as myco-leathers, as well as the production of composite materials in which mycelium—mostly from mushroom-forming fungi—is used to bind together lignocellulosic substrates for use in construction and packing[148]. Moreover, fungi are hypothermic and might find a use in local cooling[149]. The myriad current and potential benefits afforded by fungi are highlighted in Fig. 3.

Humans and fungi have an intricate relationship that reverberates across the planet. Understanding the full implications of this relationship for the biosphere will require a deep exploration of the fungal kingdom, involving multidisciplinary approaches that include basic science, epidemiology and molecular taxonomy. Given the ongoing impacts of global warming, which will bring about rapid changes in fungal-host ecology, this effort is of great importance.

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Competing interests D.W.D. and family hold founder shares in F2G, a University of Manchester spin-out antifungal discovery company, and share options in TFF Pharma. D.W.D. acts or has recently acted as a consultant to Pulmatrix, Pulmocide, Biosergen, TFF Pharmaceuticals, Pfizer, Omega, Novacyt, Rostra Therapeutics, MucPharm, Mundipharma, Lifemine and Cipla; chairs a Data Review Committee for Pulmocide; and acts as a Phase 1 Medical Monitor for Biosergen. In the past three years, D.W.D. has been paid for talks on behalf of BioRad, Basilea and Pfizer. J.E.S. is a paid consultant for Zymergen, Sincarne and Michroma. L.E.C. is a co-founder of and shareholder in Bright Angel Therapeutics, a platform company for the development of novel antifungal therapeutics, and a Science Advisor for Kapoose Creek, a company that harnesses the therapeutic potential of fungi.

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