The Relationship Between Human Exposure to Drug-Resistant Fungi and Climate Change

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Abstract

With average global temperatures rising, the climate crisis continues to be exacerbated. Although climate change causes a plethora of environmental issues, it also directly affects human health on a global scale. Due to the steep increase of global temperatures, pathogens are able to adapt to new environments at faster rates as the warming accelerates. Moreover, as environmental temperatures rise, fungi adapt to higher temperatures, and this adjustment allows these pathogens to bypass the human body's natural heat defense and survive within the body's systems. Additionally, global warming is also responsible for creating heat stress, which has been linked to accelerated mutations in pathogenic fungi and accelerates adaptation. Ultimately, this literary review aims to analyze the correlation between global warming and the prevalence of drug-resistent fungi. The review analyzes the strength of this relationship by determining the impact of this rise in fungal pathogens due to climate change on patients and individuals world-wide and various mitigation strategies.

1 Introduction (climate change)

Climate change is the long-term shift in regional and global temperatures and weather. Particularly in recent decades, the trend of climate change has exponentially worsened, impacting countless aspects of daily life. This is detrimental to life around the globe, for climate change directly results in increasingly less-suitable and dangerous living conditions. However, a notable area of impact is the increased prevalence of drug-resistant fungi. In recent years, fungal diseases have emerged as a public health issue. This is evidenced by the global emergence of antifungal resistance, where the growing resistance of harmful fungi has a mortality rate similar to tuberculosis and HIV and surpassing breast cancer and malaria; unfortunately, the presence of pathogenic fungi has been increasing at alarming rates, posing serious threats to social-ecological systems (Fisher et al., 2018). Furthermore, separate species of pathogenic fungi have recently been observed to emerge and develop significant rates of resistance at similar times, which was previously largely unobserved (Lockhart et al., 2023). Due to a combination of the rising emergence of antifungal resistance and an increasing number of people in developed nations who are at risk, such as those with immunological deficiencies, hematological malignancies, solid organ transplant recipients, chronic obstructive pulmonary disease, or exposure to ongoing corticosteroid therapy, the incidence of deadly invasive fungal diseases is also rising (Arastehfar et al., 2020). Thus, with more than a billion people exposed globally, studies report an approximation of 3.8 million deaths per year attributable to fungal diseases including 2.5 million instances directly linked to fungal infections (Chen et al., 2025). Together, these trends underscore the growing global burden of fungal disease and highlights the need to understand the factors driving their emergence.

2 Resistance-Favoring Climate Conditions

In recent decades, global warming has significantly contributed to rising global temperatures and increased human exposure to pathogenic fungi in varying ways. First, as global temperatures rise, previously benign environmental fungi are developing more thermal tolerance and virulence. For instance, when examining, *C. auris*, recent environmental surveillance has successfully cultured isolates from tropical climate surrounding Andaman Islands, which strongly implicates a natural environmental presence; however, selective pressures exerted by climatic warming may trigger evolutionary adaptations in fungal pathogens and exacerbated by environmental exposure to antimicrobial agents and human fragmentation of natural habitat (Wiederhold, 2021). Second, besides the direct warming caused by climate change, experts forecast that as global temperatures continue to climb, severe weather occurrences will become both more common and more intense. The ecological ramifications of severe weather events, in turn, manifest as immediate and enduring modifications to fungal habitats because high-energy environmental disruptions breach soil and vegetation boundaries and aerosolize localized fungal spores, directly correlating with shifted exposure risks and infection rates as observed in coccidiodomycosis's fungal dispersal attributable to dust storms (Williams et al., 2024). Collectively, these climate-driven environmental changes create conditions that promote the emergence and spread of pathogenic fungi.

3 Adaptation and Resistance Development

When reviewing the impact of climatic factors on drug-resistant fungal pathogens, it is essential to note that environmental adaptation may increase persistence and treatment difficulty. Presently, current therapeutic interventions for invasive fungal pathogens are confined to only three to four major distinct antifungal classes comprising of azoles, nucleotide analog, echinocandins, and polyenes, and this narrow spectrum is continually compromised by the emergence of resistant subpopulations, limiting treatment options and escalating the clinical burden of refractory mycoses. At the molecular level, resistance arises through several genetic and epigenetic adaptions. Noting that azole antifungal agents are largely used to combat fungal pathogens, a primary mechanism of azole resistance involves specific amino acid subsituations with hot-spot regions of the drug target, identifiable in a strong correlation with homologous *ERG11* mutations and fluconazole resistance, or adaptations to allow the survival of a drug's effects, in distinct geographic clades of *Candida auris* (Lee et al., 2020). Epigenetic mechanisms can also be observable as DNA methylation involving the addition of methyl groups to specific nucleotide basis to modify the DNA sequence without changing the original genetic code; histone modification relying on dynamic post-translational modifications (PTMs) to alter chromatin compaction and regulation of gene expression; and chromatin remodeling requiring the reposition of nucleosomes and long-range 3D DNA looping to structurally transition to a repressive chromatin state (Chang et al., 2019). These resistance mechanisms are further intensified by climate-driven environmental stressors. Importantly, rising temperatures due to global warming directly contribute to heat stress that accelerates genetic mutations in fungal pathogens, like *Cryptococcus deneoformans*. Because of heightening transposon mobilization at elevated temperatures, there is a fivefold increase in activity at 37 degrees Celsius compared

to 30 degrees Celsius, promoting in vitro antifungal resistance, thermotolerance, virulence, and overall pathogenicity (Williams et al., 2024).

While mutations and epigenetic mechanisms are significant contributors, extracellular vesicles and their mechanism further allows for antifungal resistance. Extracellular vesicles (EVs) biogenesis within fungal biofilms has been heavily implicated in the protection of the biofilm from conventional antimycotic therapies. Data demonstrates that biofilm-derived EVs actively mediate drug tolerance, which may be attributable to sequestering antifungal agents that rearrange matrix composition or aiding in intercellular communication, ultimately neutralizing the efficacy of standard antifungal medications (Jiang et al., 2024).

Another key contributor to multidrug resistance is the activity of fungal efflux pumps Fungi use specialized efflux pumps to actively transport compounds that are structurally unrelated out of intracellular space, and these pumps protect vulnerable molecular targets through maintaining sub-therapeutic intracellular drug concentrations, resulting in phenotypic resistance and fungal survival ubiquitous across taxa (Engle & Kumar, 2024). Together, these mechanisms display how climate change not only promotes fungal survival but also strengthens resistance pathways, exacerbating pre-existing difficulties of treatment. Therefore, treatment difficulties and persistence may increase due to alterations or amplifications in mechanisms essential to antifungal resistance.

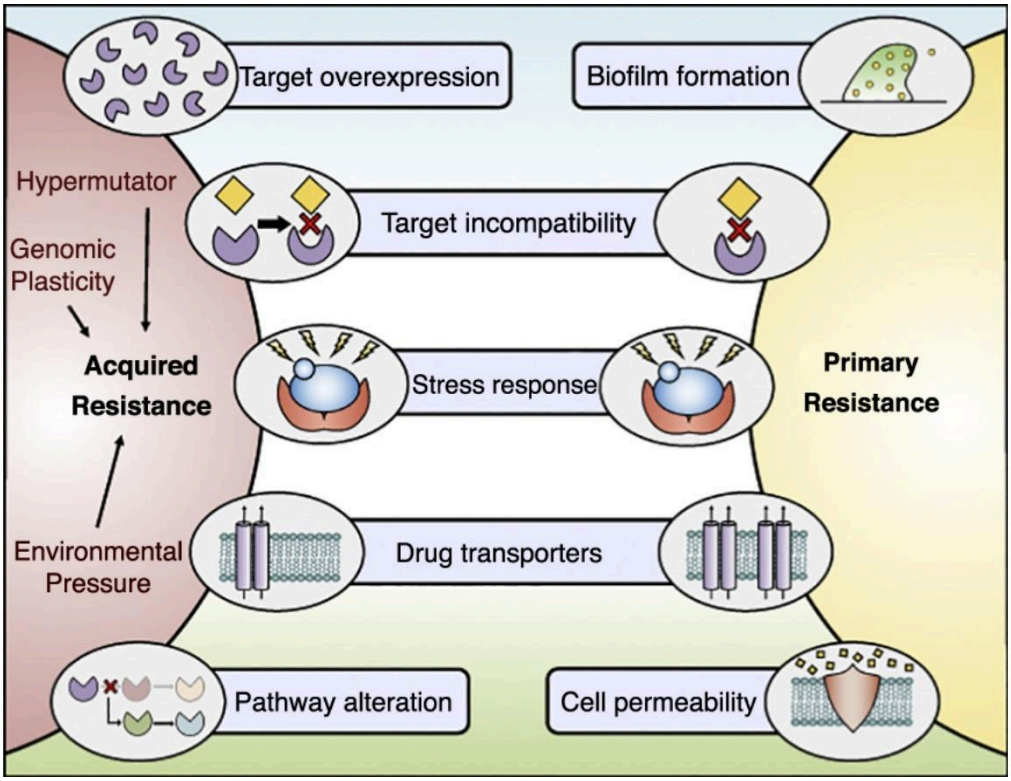

Figure 1. Pathogenic fungi have developed increasing antifungal resistance due to environmental stressors and cellular mechanisms. This diagram shows how climate change introduces worsening environmental pressures that allow fungal pathogens to develop resistance against traditional drugs and mitigation strategies due to their enhancement of cellular mechanisms. Adapted from "Antifungal drug resistance: evolution, mechanisms and impact" by Revie et al., 2018, *Current Opinion in Microbiology*, *45*, 70–76.

4 Environmental Reservoirs and Human Exposure

Beyond the evolution of antifungal resistance, climate change also influences where pathogenic fungi persist and how they are transmitted to human populations. Although environmental adaptation and antifungal resistance increase fungal survival, these changes become clinically significant only when resistant fungi encounter human populations. Examining where drug-resistant fungi persist and how they enter human populations provides valuable insight into the pathways connecting climate change to public health outcomes.

Studies have highlighted several emerging environmental reservoirs that are important pathways for both fungal persistence and dissemination. First, fungal pathogens can also survive on plastic and disperse with microplastics, a material abundantly present and easily dispersible across the planet, as seen in *Candida Auris*. Environmental persistence trials demonstrate that C. auris can survive as biofilm for over a month, demonstrating enhanced longevity on plastic surfaces relative to glass. This prolonged colonization of plastic vectors gives way to significant pathways for human exposure and pathogen dissemination across vast terrestrial and aquatic ecosystems during macro-environmental events like flooding. Furthermore, the stabilization or growth of populations on submerged plastics in seawater, in comparison to a linear decline in river water, highlights a distinct halotolerance that reflects either *C. auris*'s marine evolution origins or the protective capacity of plastic reservoirs against hypersaline stress (Akinbobola et al., 2023). Moreover, wastewater systems are another important environmental niche for the spread of fungi. Recent studies have identified *Candida auris* within municipal sewage and wastewater treatment infrastructures globally, which arose as a consequence of the fungal pathogen entering plumbing systems via shed skin and fecal matter from colonized individuals. This environmental persistence poses critical health threats, since wastewater runoff can introduce yeast into vast marine ecosystems, while the potential reuse of effluents for irregular risks widespread environmental disruption and unexpected transmission routes through air dust and recreational water establishments (Silva et al., 2024).

As these environmental reservoirs expand, opportunities for human exposure also increase. This emergence of pathogenic fungi and their resistance enhanced by environmental reservoirs has caused the body's respiratory system to be susceptible to infection, especially the lung pathway. Fungal sensitization is another consequence of the spread of fungal pathogens via

environmental factors where an allergic reaction occurs to molds and fungi and the immune system incorrectly creates specific antibodies. With a new high sensitivity, the repeated inhalation of the fungi can cause persistent sinus issues or severe asthma attacks. These fungal interactions are driven primarily by indoor and outdoor environmental exposures, exacerbating systemic inflammation and elevating mortality (Jaggi et al., 2024).

Once introduced into human populations, healthcare settings further amplify the transmission of drug-resistant fungi, like *C. auris*. Studies highlight several major compounding factors of transmission including direct contact with colonized patients or contaminated environments in as little as four hours, utilization of invasive medical devices, application of ventilation or other technologies in immunocompromised patients, which have all favored C. auris proliferation due to building resistance from increased exposure to antibiotic and antifungal mechanisms (Bhargava et al., 2025). Furthermore, healthcare environments present numerous reservoirs for microbial biofilms, including patient skin, mucous membranes, contaminated hands of healthcare personnel, and clinical water supplies; these reservoirs can be detrimental because fungal cross-contamination significantly increases healthcare costs and patient length of stay due to diagnostic and therapeutic interventions required (Garvey et al., 2025). Ultimately, environmental and healthcare reservoirs create interconnected pathways that worsen the growing public health burden of drug-resistant fungal pathogens.

5 Mitigation Strategies and Therapeutic Responses

Developing effective therapeutic and public health mitigation strategies has become increasingly important. This review has categorized these responses into drug-based mitigation and environmental mitigation. Beginning with drug-based strategies, studies prove that singular drugs can effectively alter resistance gene expression to favor the effectiveness of antifungal treatments. For instance, sub-inhibitory concentrations of rafoxanide significantly downregulated the expression of resistance across both bacterial and fungal isolates, which suppressed key target genes like *blaCTX-M-1*, *ERG11*, and *cyp51A* to restore susceptibility to antifungal treatments (Bendary et al., 2023). Furthermore, miramistin exhibited broad-spectrum antifungal efficacy against susceptible and drug-resistance fungal strains, proven by protecting *Galleria mellonella* larvae from lethal *C. albicans* and *Aspergillus fumigatus* infections at optimal dosages (Osmanov et al., 2019).

Beyond repurposing individual compounds combination drug therapy offers an extremely promising strategy because it is significantly faster and more cost-effective than developing entirely new pharmaceutical agents, as observable by 100% synergy in combining colistin with caspofungin (CAP) to promote fungicadal activity versus clinical strains of *Candida albicans* (Gharehbolagh et al., 2021). Furthermore, the increased effectiveness in combination drug therapy is also observable in a new compound named BLA with caspofungin. Researchers

systematically assessed the combination of caspofungin and BLA against World Health Organization (WHO) critical-priority fungal pathogens, comprising *C. albicans*, *C. neoformans*, and *C. gattii*, finding that fractional inhibitory concentration index (FICI) values dropped below 0.5; this enhanced the efficacy of echinocandins, first-line treatments for severe fungal infections, against *Cryptococcus neoformans* and achieved rapid fungicidal activity that eliminated refractory pathogens to maintain total mycological sterilization for at least 15 days post-treatment (Chen et al., 2025). Interestingly, naturally-found marine compounds can combine with current antifungal drugs to create a powerful synergistic effect. For example, a compound named ECTA created allowed fluconazole, a drug commonly used against pathogenic fungi, to be 35 times more effective against resistant strains (Abdelmohsen et al., 2016).

In addition to optimizing existing drug therapies, scientists have now highlighted metabolic pathways that could potentially serve as key targets for the creation and efficacy of novel antifungal medications. Specifically, the glyoxylate cycle is a specialized metabolic pathway that allows harmful fungi to conserve carbon and survive in host environments that are depleted with nutrients. A key enzyme in this pathway, isocitrate lyase (ICL) is essential for fungal survival, and although absent in humans, it serves as a promising novel target for developing new antifungal medications. Despite previous ICL inhibitors' toxicity rendering them impractical for medical use, newly discovered natural compounds, mohangamide A and mohangamide B, successfully block this fungal enzyme without damaging human cells (McCarthy et al., 2017). Another promising therapeutic strategy focuses on overcoming drug resistance by targeting fungal efflux pumps. Fungi can develop resistance to multiple, unrelated medications through multi-drug resistant (MDR) efflux pumps that actively transport antifungal drugs out of the cell, dramatically lowering the internal drug concentration and preventing the medication from hitting its target (Engle & Kumar, 2024). Moreover, products naturally found in marine environments offer another promising method to block fungal efflux pumps and allow antifungal drugs, like fluconazole, to regain efficacy (Abdelmohsen et al., 2016).

Then, effective environmental mitigation strategies along with infection-control remain essential for limiting fungal transmission. One of the key infection-control mitigation techniques in hospital environments to prevent risk of pathogenic fungal contamination is disinfection, primarily in items and equipment commonly found in hospitals. Medical devices are categorized by infection risk based on tissue contact: critical items that enter sterile tissues, semi-critical items that touch intact mucous membranes, and non-critical items that contact only intact skin. Due to their differences in risk severity, critical items require absolute sterility via heat, gas, or liquid sterilants; semi-critical devices necessitate at least high-level disinfection targeting resistant mycobacteria; and non-critical items require merely low-to intermediate-level disinfection paired with physical cleaning (Garvey et al., 2023). These commonly followed infection-control practices currently employed by hospitals have proven to be effective. Studies showed that

adherence to hand hygiene and 70% ethanol disinfection effectively reduces overall colonization rates, but approximately 15% of fungal species persist following treatment (Garvey et al., 2025). Additionally, climate surveillance plays a critical role in preventing future outbreaks as environmental conditions continue to favor fungal pathogenic proliferation. For instance, climate change alters critical soil characteristics, such as pH, mineral composition and organic content, and thereby shifting the ecological niche suitable for fungal survival (Williams et al., 2024). Therefore, since favorable soil environments have already started to expand significantly past their historical boundaries, monitoring favorable habitats and soil conditions can be key to minimizing the spread of harmful fungi populations. Together, current advances in antifungal therapeutics, infection-control measures, and environmental surveillance provide a multifaceted approach to mitigating the growing public health threat posed by climate-driven drug-resistant fungi.

6 Conclusion

Overall, this systematic review demonstrates a growing relationship between climate change and the emergence, adaptation, and spread of drug-resistant fungal pathogens. Evidence suggests that rising global temperatures are not only expanding the geographic distribution of fungi but are also facilitating adaptive mechanisms, such as increased thermotolerance and accelerated genetic mutation, that enhance fungal survival within the human host. These environmental pressures have enabled species such as *Candida auris* to overcome traditional thermal barriers, thereby increasing their capacity to colonize and infect human populations. Climate change and global warming has created an environment more favorable to the rise of drug resistant fungal pathogens.

Despite these findings, current evidence supports climate change as an indirect contributor to increased human exposure through environmental alteration and adaptive fungal responses, although direct causal pathways remain incompletely understood. Accordingly, more research must be conducted in several aspects: to ascertain the extent of climate factors in isolation from external influences and to improve the discovery of more effective combative measures, including drug-based mitigation and environmental prevention strategies.

In light of these findings, strengthening infection control practices, improving antifungal stewardship, and advancing surveillance systems are critical steps in mitigating the spread of these pathogens. As climate change continuously reshapes environmental conditions, coordinated efforts in research, surveillance, infection control, and antifungal drug development will be essential to limiting the impact of drug-resistant fungal pathogens on global health, particularly among vulnerable populations.

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