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feature

Can agricultural fungicides accelerate the discovery of human antifungal drugs?

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Twelve drugs from four chemical classes are currently available for treatment of systemic fungal infections in humans. By contrast, more than 100 structurally distinct compounds from over 30 chemical classes have been developed as agricultural fungicides, and these fungicides target many modes of action not represented among human antifungal drugs. In this article we introduce the diverse aspects of agricultural fungicides and compare them with human antifungal drugs. We propose that the information gained from the development of agricultural fungicides can be applied to the discovery of new mechanisms of action and new antifungal agents for the management of human fungal infections.

Introduction

Fungi have co-existed with animals, plants and other organisms for a billion years. Whereas some are mutualistic and highly beneficial, others jeopardize food security, alter ecosystems and have forced extinction of animal species and agricultural crops [1]. Although human and animal diseases caused by mycotoxins (toxic natural products produced by fungi) have had wide-ranging effects on human history, human fungal infections generally receive less attention than bacterial and viral diseases [2]. Human fungal infections range from superficial nail and skin infections caused by dermatophytes to invasive, systemic fungal infections mainly caused by four genera: *Candida*, *Aspergillus*, *Cryptococcus* and *Pneumocystis* [2]. Although the incidence of systemic fungal infections is considerably lower than that of superficial infections, mortality rates from invasive fungal infections are very high, often exceeding 50%, despite the use of antifungal drugs [2,3]. Although early diagnosis of disease and identification of the fungal pathogen are probably the biggest challenges for the treatment of invasive fungal infections, the efficacy of currently used drugs is limited by issues with administration route, narrow treatment window, activity spectrum, bioavailability, toxicity, drug resistance and high cost [2,4].

Currently, 12 drugs from four antifungal drug classes are approved for the treatment of systemic fungal infections in the USA [5,6]. These include four drugs of the azole class (fluconazole, itraconazole, voriconazole and posaconazole), four different formulations of polyene amphotericin B (amphotericin B deoxycholate, amphotericin B lipid complex, amphotericin B colloidal dispersion and liposomal amphotericin B), three drugs from the echinocandin class (caspofungin, micafungin and anidulafungin) and one pyrimidine (5-fluorocytosine). These antifungal drugs differ in spectrum of activity, toxicity, modes of action and pharmacokinetics, and these characteristics guide selection of the most suitable drug for patients with invasive fungal infections [5].

Currently available drugs, however, do not meet the demand for the management of fungal infections in patients with increased susceptibility, such as patients with cancer, AIDS, HIV, diabetes, organ transplant, or surgery, among others [4,7]. New antifungal drugs are urgently needed [3], but finding mammalian-selective biochemical targets in eukaryotic pathogens is more challenging than in prokaryotes or viruses [2,3,6]. Additionally, because of the comparatively small market size, only a few smaller companies are working to develop new antifungal drugs, but discovery of successful new antifungal drugs has proven challenging, caused in part by toxicity and emergence of drug resistance [2].

How can the discovery of new antifungal agents to meet this pressing need be accelerated? One approach is to 'repurpose' pharmaceuticals already developed for other human

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TABLE 1

Major agricultural fungicides and their modes of action [10,11]

Chemical group/FRAC classification	Examples of commonly used agents	Mode of action
Triazoles/demethylation inhibitors (DMI)	Difenoconazole Epoxiconazole Fenbuconazole Myclobutanil Prothioconazole Tebuconazole	Inhibition of C-14α demethylase in ergosterol biosynthetic pathway
Strobilurins/quinone outside inhibitors (QoI)	Azoxystrobin Fluoxastrobin Kresoxim-methyl Picoxystrobin Pyraclostrobin Trifloxystrobin	Binding to quinol oxidation (Qo) site of cytochrome b, a part of cytochrome bc_1 complex, blocking electron transfer between cytochrome b and cytochrome c_1
Pyrazole carboxamides/succinate dehydrogenase inhibitors (SDHI)	Benzovindiflupyr Bixafen Fluxapyroxad Isopyrazam Penflufen Penthiopyrad Sedaxane	Inhibition of succinate dehydrogenase (respiratory Complex II), disrupting TCA cycle
Morpholines/amines	Aldimorph Dodemorph Fenpropimorph Tridemorph	Inhibition of Δ^{14} reductase and Δ^{8}-Δ^{7} isomerase in ergosterol biosynthetic pathway
Benzimidazoles/methyl benzimidazole carbamates (MBC)	Benomyl Carbendazim Fuberidazole Thiabendazole Thiophanate-methyl	Inhibition of microtubule (β-tubulin) assembly in mitosis
Anilinopyrimidines (AP)[a]	Cyprodinil Mepanipyrim Pyrimethanil	Inhibition of cystathionine lyase or synthase in methionine biosynthetic pathway
Phenylpyrroles (PP)[a]	Fenpiclonil Fludioxonil Pyrrolnitrin	Interference with osmotic signal transduction pathway leading to abnormal accumulation of glycerol

[a] Names of chemical group and Fungicide Resistance Action Committee (FRAC) classification are same.

uses [3]. We propose an additional approach: utilize agricultural fungicides to accelerate the identification of new modes of action and compounds that control human fungal infections. Considering the evolutionary similarity among fungi that cross host kingdoms to infect plants and humans [8], fungal pathogens infecting humans are likely to be susceptible to fungicides designed for agricultural uses. A similar approach has been explored for invention of antiprotozoan drugs [9].

Diversity and versatility of agricultural fungicides

The mechanisms of action of current antifungal drugs available for the treatment of clinically invasive fungal infections are mainly associated with ergosterol biosynthesis or plasma membrane ergosterol disruption [2,6]. Triazoles inhibit C-14α demethylase in the ergosterol biosynthetic pathway, blocking synthesis of ergosterol, a key component of fungal cell membrane, whereas polyenes bind to ergosterol in the cell membrane and form ionic transmembrane channels, leading to an increase in membrane permeability and a leakage of cellular contents [2,6]. In addition, terbinafine, an allylamine antifungal drug used for the treatment of superficial skin infections, inhibits squalene epoxidase in the ergosterol biosynthetic pathway, preventing production of ergosterol [2,6]. Meanwhile, echinocandins interfere with β-1,3-glucan synthesis via inhibition of β-1,3-glucan synthase, causing cell wall permeability and eventually lysis of the cell, whereas 5-fluorocytosine inhibits protein synthesis and DNA synthesis by incorporating into fungal RNA and inhibiting thymidylate synthetase, respectively [2,6].

By contrast to antifungal drugs targeting human diseases, agricultural fungicides are much more diverse in their biochemical modes of action and chemical structures. The different chemical groups of agricultural fungicides include triazoles, strobilurins, pyrazole carboxamides, morpholines, benzimidazoles, anilinopyrimidines, phenylpyrroles and numerous others [10,11]. These fungicides have been grouped based on their modes of action by the Fungicide Resistance Action Committee (FRAC; http://www.frac.info/), and the classification shows that agricultural fungicides target specific sites or multi-sites of more than ten different biochemical processes. Some important agricultural fungicides are summarized in Table 1. Strobilurins, pyrazole carboxamides, anilinopyrimidines and phenylpyrroles are among those that have not been commercially developed as human antifungals [7,12]. With their diversity of chemistry and numerous modes of action, agricultural fungicides should be attractive

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