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Review

Is the emergence of fungal resistance to medical triazoles related to their use in the agroecosystems? A mini review

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ABSTRACT

Triazole fungicides are used broadly for the control of infectious diseases of both humans and plants. The surge in resistance to triazoles among pathogenic populations is an emergent issue both in agriculture and medicine. The non-rational use of fungicides with site-specific modes of action, such as the triazoles, may increase the risk of antifungal resistance development. In the medical field, the surge of resistant fungal isolates has been related to the intensive and recurrent therapeutic use of a limited number of triazoles for the treatment and prophylaxis of many mycoses. Similarities in the mode of action of triazole fungicides used in these two fields may lead to cross-resistance, thus expanding the spectrum of resistance to multiple fungicides and contributing to the perpetuation of resistant strains in the environment. The emergence of fungicide-resistant isolates of human pathogens has been related to the exposure to fungicides used in agroecosystems. Examples include species of cosmopolitan occurrence, such as *Fusarium* and *Aspergillus*, which cause diseases in both plants and humans. This review summarizes the information about the most important triazole fungicides that are largely used in human clinical therapy and agriculture. We aim to discuss the issues related to fungicide resistance and the recommended strategies for preventing the emergence of triazole-resistant fungal populations capable of spreading across environments.

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Introduction

Fungicides are a key component in human therapy and the control of plant diseases caused by fungi that threaten human health and crop production.[1–5] Among the several types of fungicides, the azole group (triazole and imidazole derivatives) was first introduced in the 1970s.[3] Since then, azoles, especially the triazoles, have been widely used for the control of fungal diseases of several plants and human mycoses.[6–8] As opposed to other systemic fungicides, the specific site of action of triazoles is an inherent advantage that has led to improved control efficacy of the target fungus.[9,10] However, experience has shown that these compounds are prone to resistance in the pathogenic population, especially without the following of recommended practices that are aimed at prolonging the effectiveness of these fungicides.[9,11,12]

In this context, the efficacy of triazole fungicides can be affected due to cross-resistance or when an isolate develops resistance to all fungicides in a chemical group.[13,14] Some authors have also suggested that cross- and multidrug-resistance may be driving forces in the development of resistance in fungi that are at the interfaces of agroecosystem, domestic, and hospital environments.[15,16] For instance, emerging fungi in clinical environments include saprophytic or plant pathogenic fungi that have previously exposed to triazole fungicides and end up spreading into the environment and infecting humans.[6,17–19]

In this mini review, we summarize key aspects of the triazoles for therapeutic use and discuss the possible link between triazole-resistant clinical isolates and the widespread use of triazole fungicides for the control of fungal diseases, which would have a major impact in agriculture.

Basic aspects and therapeutic use of triazoles

The azole fungicides are of synthetic origin and are characterized by the presence of an aromatic five-membered heterocycle. These include triazoles (two carbon atoms and three nitrogen atoms), imidazoles (three carbon atoms and two nitrogen atoms), and thiazoles (three carbon atoms, one nitrogen atom and one sulfur atom).[20] The characteristics of the azole rings, which are distinguished by the number of nitrogen and sulfur atoms, change the physical and chemical properties, toxicity, and therapeutic efficacies of these compounds.[21] Therefore, the addition of different substitutes to the pristine 1,2,4-triazole molecule influences its fungicide or fungistatic effect.

Triazoles affect the biosynthesis of ergosterol, a fundamental component of the fungal cell plasma membrane.[22] The main target of antifungal azole drugs is lanosterol 14-α demethylase (Erg11 protein), a cytochrome P450 enzyme that is involved in the conversion of lanosterol to 4,4-dimethylcholesta-8(9),14,24-trien-3β-ol. The azole agents link to this enzyme using the aromatic five-membered heterocycle and thereby inhibit the cytochrome P450 catalytic activity.[9,23] The absence of ergosterol and the increase of intermediate compounds alter fungal membrane integrity as well as cell morphology, which inhibits fungal growth.[24,25]

Triazoles are among the most common systemic fungicides used in the control of plant diseases. Triazoles are absorbed and translocated in the plant, where they act preventively (before infection) or curatively (in the presence of symptoms) by affecting germ tube and appressoria formation or haustoria development and/or mycelial growth.[26,27] By widening the window of protection beyond protectant fungicides, which act only preventatively and are not translocated, the advantages of triazoles represent a breakthrough in increasing the productivity of various crops affected by fungal diseases.[2] Around a third of all fungicides used for the protection of crop yields include triazoles, among which more than 99% are inhibitors of demethylation (DMI).[28] However, triazole fungicides are also known to present long-term stability, allowing them to remain active in certain ecological niches, such as soil and water, for several months.[2,29]

The number of antifungals available in the medical field for the treatment of systemic infections is relatively limited compared to those used for controlling diseases in plants, which is mainly due to problems related to erratic efficacy, drug toxicity, and intrinsic resistance.[30] These compounds are usually effective in both topical and prophylactic treatments of invasive fungal infections.[31] However, new triazoles that are less toxic to humans and with more specific targets have been investigated.[32–34] The first generation of triazoles for human therapy included itraconazole and fluconazole. The second generation is represented by voriconazole and posaconazole, which proved to be less toxic, safer, and with a broader spectrum of activity, including activity against fungi that were resistant to the previous generation.[35,36] Presently, isavuconazole, ravuconazole, and albaconazole are being investigated in phase III clinical trials as extended-spectrum triazoles with fungicidal activity against a wide number of clinically important fungi.

Development and monitoring of triazole resistance

The development of resistance to triazoles as a result of selective pressure by the continued use of regular or sub-regular dosages of fungicide is typically quantitative and expressed by a gradual change in the frequency of resistant isolates.[10] The main mechanisms involved have been reviewed and relate to the overexpression of the *CYP51* gene due to mutations (insertions or duplications) in the promoter region and an increase in molecular efflux by ABC transporters caused by the overexpression of genes coding for membrane transport.[9,37,38] Recently, a study that examined *A. fumigatus* isolates from a range of clinical environments suggested point mutations of *CYP51* and TR_{34}/L98H genomic regions in isolates obtained from patients with long term use of triazole-based therapy for the treatment of chronic aspergillosis.[16]

A key element in the sustainable use of fungicides is to monitor the sensitivity of the pathogen population to a certain compound.[39–41] There are a number of direct and indirect methods recommended for specific fungi that are aimed at estimating the EC_{50} (effective concentration at which 50% of fungal growth is inhibited) and MIC (minimum inhibitory concentration) values.[10,42–45]

In the medical field, the surveillance and prevention of resistance to antifungal agents have been subject to many