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Management of Mycotoxin Production and Fungicide Resistance by Targeting Stress Response System in Fungal Pathogens

Authors : Jong H. Kim, Kathleen L. Chan, Luisa W. Cheng

Abstract : Control of fungal pathogens, such as foodborne mycotoxin producers, is problematic as effective antimycotic agents are often very limited. Mycotoxin contamination significantly interferes with the safe production of foods or crops worldwide. Moreover, expansion of fungal resistance to commercial drugs or fungicides is a global human health concern. Therefore, there is a persistent need to enhance the efficacy of commercial antimycotic agents or to develop new intervention strategies. Disruption of the cellular antioxidant system should be an effective method for pathogen control. Such disruption can be achieved with safe, redox-active compounds. Natural phenolic derivatives are potent redox cyclers that inhibit fungal growth through destabilization of the cellular antioxidant system. The goal of this study is to identify novel, redox-active compounds that disrupt the fungal antioxidant system. The identified compounds could also function as sensitizing agents to conventional antimycotics (i.e., chemosensitization) to improve antifungal efficacy. Various benzo derivatives were tested against fungal pathogens. Gene deletion mutants of the yeast Saccharomyces cerevisiae were used as model systems for identifying molecular targets of benzo analogs. The efficacy of identified compounds as potent antifungal agents or as chemosensitizing agents to commercial drugs or fungicides was examined with methods outlined by the Clinical Laboratory Standards Institute or the European Committee on Antimicrobial Susceptibility Testing. Selected benzo derivatives possessed potent antifungal or antimycotoxigenic activity. Molecular analyses by using S. cerevisiae mutants indicated antifungal activity of benzo derivatives was through disruption of cellular antioxidant or cell wall integrity system. Certain benzo analogs screened overcame tolerance of Aspergillus signaling mutants, namely mitogen-activated protein kinase mutants, to fludioxonil fungicide. Synergistic antifungal chemosensitization greatly lowered minimum inhibitory or fungicidal concentrations of test compounds, including inhibitors of mitochondrial respiration. Of note, salicylaldehyde is a potent antimycotic volatile that has some practical application as a fumigant. Altogether, benzo derivatives targeting cellular antioxidant system of fungi (along with cell wall integrity system) effectively suppress fungal growth. Candidate compounds possess the antifungal, antimycotoxigenic or chemosensitizing capacity to augment the efficacy of commercial antifungals. Therefore, chemogenetic approaches can lead to the development of novel antifungal intervention strategies, which enhance the efficacy of established microbe intervention practices and overcome drug/fungicide resistance. Chemosensitization further reduces costs and alleviates negative side effects associated with current antifungal treatments.

Keywords : antifungals, antioxidant system, benzo derivatives, chemosensitization
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