Fungi - An amalgam of Toxins and Antibiotics: A Mini-Review.

Review Article

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ABSTRACT

Fungi are eukaryotes with many functions. Earlier, fungi were classified in the plant kingdom but were later classified as a separate kingdom due to their unique cell walls. Fungi are heterotrophs like animals and are more closely related to animals. The perception of fungi is inconspicuous due to their small sizes and their ability to grow symbiotically in plants, animals, other fungi, and parasites. Fungi are used for their nutrition, fermentation potential, and bactericidal potential. However, fungi are also toxic due to certain bioactive compounds known as mycotoxins. Candida and Aspergillus are invasive species that contribute to a high percentage of mycoses in oncological and haematological patients. The mortality rate due to invasive aspergillosis and candidiasis is high, at 4% and 2%, respectively. In the agriculture sector, a significant contributor to damage to crops globally is the invasion of filamentous fungi. Fungi invasion destroys over 125 million tons of wheat, rice, soybeans, potatoes, and maize annually. If prevented, 600 million people may be fed. Therefore, it is vital to consider the dual role of fungi, therapeutic, and pathogenic.

Keywords: *Filamentous fungi, β- lactam antibiotics, Mycotoxins, Gene transfer, Secondary metabolites.*

INTRODUCTION

Fungus, plural fungi, are eukaryotes and consist of yeasts, rusts, smuts, mildews, molds, and mushrooms. Earlier, fungi were classified in the plant kingdom. However, the organisms were then isolated as a separate kingdom due to their mode of nutritional intake, i.e., vegetative growth and lack of chlorophyll and unique structural and physical characteristics. Fungi are of significant environmental and medical importance. While some can live freely in the soil or water, others live symbiotically with plants and animals. The mode of nutrition for fungi is digestion of organic matter externally and absorption using their mycelia. The growth of fungi is evident by their tips of filaments known as hyphae. Fungi are friends and foes simultaneously. The mortality rate due to invasive aspergillosis and candidiasis is high, at 4% and 2%, respectively.[1]

On the one hand, the filamentous fungi *Aspergillus terreus* is pathogenic as it causes invasive aspergillosis by producing numerous mycotoxins. These mycotoxins are a significant cause of spoilage of food such as nuts and cereals in the subtropical and tropical regions. On the other hand, *A. tereus* also serves as a source of secondary metabolites and organic acids, and due to which it is used enormously by the pharmaceutical and biotechnological industries. Lovastatin is a polyketide derivative of *A. terreus*, which acts as a cholesterol-reducing agent. In the agriculture sector, a significant contributor to damage to crops globally is the invasion of filamentous fungi. Fungi invasion destroys over 125 million tons of wheat, rice, soybeans, potatoes, and maize annually.[2] If prevented, 600 million people may be fed.

Additionally, it has been successfully utilized for the treatment of coronary artery disease, one of the major causes of middle-aged deaths in the Western world.[3] *A. terreus* is also a source of gliotoxin that has the potential to be used as an immunosuppressive agent. Another fungus, *Claviceps purpurea*, produces ergot alkaloids, which are natural mycotoxins that contaminate the grains. Consuming food poisoned by ergot alkaloids leads to ergotism, which has caused deaths in the middle Ages in Europe, exceeding 40,000. Therapeutic and pathogenic properties of ergot alkaloids are known for centuries, and currently, these alkaloids are employed in the manufacture of synthetic drugs for the treatment of migraines.[4] *Ashbya gossypii* is one of the common fungi which cause pathogenesis in plants such as stigmatomycosis in citrus fruits and cotton. Ashbya gossypii has been recorded as one of the primary producers of riboflavin, commonly known as vitamin B2. Riboflavin is an essential vitamin that is not synthesized by humans; thus, it has to be provided by dietary supplements and food. Currently, *Ashbya gossypii* is utilized in the industry as a riboflavin producer.[5]

FILAMENTOUS FUNGI AS PRODUCERS OF SECONDARY METABOLITES.

Filamentous fungi possess extensive metabolism. Therefore, they serve as crucial producers of significant bioactive compounds. Secondary metabolites produced by fungi have contributed significantly to the food and crop industry.[2,6] Secondary metabolites do not impact intermediary metabolism, and these are not important for the survival of fungi.[7] Secondary metabolites are found to provide melanin, and they exhibit significant potency as anti-bacterial, antifungal, and insecticidal activity.[7-9] The diversity of secondary metabolites is very high, and genes for biosynthesis are organized in clusters that are controlled by chromatin remodelling and transcriptional regulation.[10] They have been organized into different classes of compounds, namely fatty acid derivatives, polyketides, non-ribosomal peptides, alkaloids, and terpenes.[7] In December 1971, Cyclosporine A was discovered in a soil sample and manifested with immunosuppressive activity in Norwegia.[11] Such ‘‘silent’’ clusters of the gene have been activated by the over expression of global regulators or cluster-encoded, epigenetic modifications as well as co-cultivation experiments.[9] Co-cultivation of *Aspergillus nidulans* triggers the synthesis of orsellinic acid inducing expression of transcriptional regulator AfoA of *Aspergillus nidulans* that further trigger the synthesis of asperfuranone, a polyketide.[12,13] These unique methodologies may lead to the identification and engineering of new secondary metabolites, which may prove to be beneficial for pharmaceutical and biotechnological industries.

HORIZONTAL GENE TRANSFER IN FUNGI.

Horizontal gene transfer (HGT) has been observed in prokaryotes and was not given importance in eukaryotes. However, recent evidence indicates the importance of HGT in unicellular organisms. In fungi, various mechanisms have been identified that facilitate HGT owing to the transfer of foreign genetic material into recipient cells to allow expression of functional protein via host genomes. HGT supports selective advantage to the hosts in order to prevent pseudogenization. HGT and lateral gene transfer (LGT) across different species is a well-known phenomenon for bacterial evolution. However, recently it has been discovered to play an essential role in fungal evolution as well.[14,15] Marcet-Houben et al. reviewed sixty fully sequenced prokaryotic-derived genomes utilizing strict phylogenomic criteria. The findings revealed that has revealed that 713 bacterial genes were transferred to the genetic material of fungi, indicating the importance of HGT in fungal evolution.[16] Genes transferred by bacteria to the fungal genome requires adaptation into the new eukaryotic host system. The expression of secondary biosynthesis genes in eukaryotes is regulated through various regulators. Such eukaryotic regulators are VeA and LaeA, both of which are components of a multi-subunit based protein complex, and it controls gene expression. The protein complex also includes genes that encode for β-lactams involved in the secondary metabolite synthesis of fungi.[17,18]

BETA-LACTAM ANTIBIOTICS.

Fungi have an essential role in the therapeutic approaches used in modern medicine. Many species contribute to antibiotics due to their metabolites. Currently, β-lactam antimicrobial drugs are widely used as anti-bacterial agents globally and are produced using small peptides of fungi.[19] Penicillin G is naturally occurring penicillin; however, synthetic penicillins have broader spectrums of biological activity. When compared to penicillins, Cephalosporin C has been reported to have a broader spectrum of anti-bacterial activity. Penicillium chrysogenum can biosynthesize both penicillins and cephalosporins. The corresponding genes responsible for the biosynthesis are a constituent of an early cluster of genes that includes pcbC and pcbAB as well as a late cluster of genes which comprises of cefEF and cefG genes.[20-22] Different genes of *Ac. chrysogenum* has been transferred to Penicillium chrysogenum via genetic engineering as an alternate biosynthetic producer of Cephalosporin C.[22] Two reactions in the biosynthesis of β-lactam antibiotics are catalyzed by isopenicillin: 1) N synthase and 2) non-ribosomal peptide synthetase, leading to the production of an intermediate compound, isopenicillin N, which is integral to the class of penicillins.

The antibiotic potential of Cephalosporin C has been improved via semisynthetic derivatives.[21] Pharmaceutical industries have reported the development of these cephalosporins as effective against methicillin-resistant Staphylococcus aureus (MRSA), the burden of which has increased in hospital-acquired infections. Recently, the cephalosporin ceftobiprole has been identified as the pioneer of broad-spectrum cephalosporin for its potential against MRSA.[23] Another cephalosporin derivative, ceftaroline, has also been marketed for use against resistant infections.[24,25] This indicates that the derivatives of cephalosporins are vital antibiotics for future applications in medicine.

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CONFLICT OF INTEREST

The Authors declared no conflicts of interest.

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