ABSTRACT
Infections caused by bacteria and fungi resistant to antimicrobials are one of the main public health problems in the world. These microorganisms are associated with high rates of morbidity and mortality and also with high hospital costs. Their emergence and spread are closely related to the excessive and inappropriate use of antimicrobials in medical and veterinary practices and in animal production. For the treatment of Candida spp. there are few classes of antifungals available for treatment, the classes being: azole derivatives,
polyenes and echinocandins. The class of azoles includes imidazole derivatives (ketoconazole, miconazole, clotrimazole), triazole derivatives (fluconazole, itraconazole and voriconazole) and posaconazole. These drugs can be used for topical us as well as in the treatment and prophylaxis of invasive infections. The wide use of these drugs has led to a strong selection of strains resistant to them, which is increasingly growing. The need to produce new antimicrobial drugs requires different strategies, among which we highlight the importance of bioprospecting for secondary metabolites of environmental bacteria and fungi with potential antimicrobial activity.

Keywords: Fungi, Candida, treatment.

RESUMO
As infecções causadas por bactérias e fungos resistentes aos antimicrobianos constituem um dos principais problemas de saúde pública no mundo. Esses microrganismos estão associados a altas taxas de morbimortalidade e também a altos custos hospitalares. Seu surgimento e disseminação estão intimamente relacionados ao uso excessivo e inadequado de antimicrobianos nas práticas médicas e veterinárias e na produção animal. Para o tratamento de Candida spp. existem poucas classes de antifúngicos disponíveis para tratamento, sendo as classes: derivados azólicos, polienos e equinocandinas. A classe dos azóis inclui derivados imidazólicos (cetoconazol, miconazol, clotrimazol), derivados triazólicos (fluconazol, itraconazol e voriconazol) e posaconazol. Essas drogas podem ser usadas para uso tópico, bem como no tratamento e profilaxia de infecções invasivas. A ampla utilização dessas drogas tem levado a uma forte seleção de cepas resistentes a elas, que está crescendo cada vez mais. A necessidade de produção de novos antimicrobianos requer diferentes estratégias, dentre as quais destacamos a importância da bioprospecção de metabólitos secundários de bactérias e fungos ambientais com potencial atividade antimicrobiana.

Palavras-chave: Fungos, Candida, tratamento.

1 DEVELOPMENT

Infections caused by bacteria and fungi resistant to antimicrobials are one of the main public health problems in the world [1]. These microorganisms are associated with high rates of morbidity and mortality and also with high hospital costs. Their emergence and spread are closely related to the excessive and inappropriate use of antimicrobials in medical and veterinary practices and in animal production [2].

Antimicrobials are compounds of chemical, natural (from fungi or bacteria) or semi-synthetic origin, which terminate or inhibit microbial growth with minimal or no harm to the host [3]. The use of antibiotics in the clinic was arguably the greatest medical advance of the 20th century. Today, these compounds remain the most important resource in the global management of infectious diseases. The increasing occurrence of antimicrobial resistance in human pathogens has raised global concern as antibiotics
continually lose their effectiveness in clinical and community settings. Despite increasing resistance and changes in drug discovery programs in the private sector, the antibiotic market remains strong [4]. In addition to treat infectious diseases, antibiotics have made many modern medical procedures possible, including cancer treatment, organ transplants, and open-heart surgery [5].

Persistent resistance of cells to antimicrobials is mainly due to their ability to form biofilms, which prevents antimicrobials from binding to their targets and affect the pathogenic agents. The mechanisms underlying persistent profile remain unclear, although toxin-antitoxin systems are believed to be involved in their formation, inhibiting metabolic activity [6].

Bacteria have well-differentiated mechanisms by which they escape and develop resistance to antibiotics. Generally, bacteria avoid the effects of antibiotics through mechanisms that work synchronously with each other. These mechanisms include drug inactivation by enzymes such as β-lactamases and aminoglycoside/fluoroquinolone acetyltransferases, target modification such as DNA gyrase and topoisomerase for fluoroquinolone resistance, and decreased drug uptake through efflux upregulation and porin downregulation. These three main mechanisms can be either intrinsically encoded in the bacterial chromosome or through spontaneous mutations in existing chromosomal genes. Furthermore, transformation or conjugal acquisition of foreign resistance plasmids, in other words, plasmids harboring resistance genes, can confer antimicrobial resistance in hitherto susceptible bacteria [7].

In recent decades, fungal infections have become a major problem in clinical practice, with immunocompromised patients being easily susceptible. Notably, systemic fungal infections are generally associated with high mortality. In addition, there are increasing reports of fungal infections in healthy populations due to the increased incidence of fungal pathogens such as Candida auris, an emerging pathogen with resistance to available antifungal agents. Although systemic fungal infections account for at least 10% of hospital deaths, there are limited drug targets for fungi due to their conserved metabolism [8].

For the treatment of Candida spp., there are few classes of antifungals available for treatment, the classes being: azole derivatives, polyenes and echinocandins [9]. The class of azoles includes imidazole derivatives (ketoconazole, miconazole, clotrimazole), triazole derivatives (fluconazole, itraconazole and voriconazole) and posaconazole. These
drugs can be used for topical use as well as in the treatment and prophylaxis of invasive infections. The wide use of these drugs has led to a strong selection of strains resistant to them, which is increasingly growing [10,11]. Among the different classes of antimicrobials, Polyene class drugs are known as those highly related to high toxicity, specifically nephrotoxicity [12]. This toxicity of polyenes is due to their affinity for cholesterol, which is the human homologue to the fungal cell membrane component ergosterol [13]. The most used drugs of this class are: Nystatin and Amphotericin B. Nystatin, when administered parenterally, generates high toxicity, but it is not absorbed through the skin or the gastrointestinal tract, so it can be administered orally or topically in the treatment of superficial candidiasis without consequent side effects, whereas Amphotericin B is only administered via the oral or intravenous [14]. The Echinocandin class includes the antifungals caspofungin and micafungin, which act by inhibiting the synthesis of the β-D-glucan synthase enzyme, which is important for the formation of the fungal cell wall. These substances are less likely to cause toxic damage to the eukaryotic cell, which does not have a cell wall in its structure, and therefore does not interfere with the inhibition process. These agents have a fungicidal action against most Candida strains and can be used in the treatment of invasive candidiasis (Fig.1) [15].

Antifungal resistance mechanisms are classified as primary or secondary, and may be intrinsic or acquired mechanisms that interfere with the drug action at the active sites. For example, in yeast, echinocandin resistance is mediated by target site modifications resulting from point mutations. In Candida species, the induction of efflux pumps that pumpazole antifungals out from the fungal cell, leading to a decrease in drug concentrations inside the cell, are responsible, among others, for the decrease in Candida susceptibility or resistance to azole antifungals [16].

The discovery of new antimicrobials strongly depends on innovative solutions, being recommended the discovery of antimicrobials at an early stage, due to the relative lack of success in bringing synthetic antibiotics to the clinic. The best strategy for the development of a new generation of antimicrobial drugs is the obtaining microbial natural products, as these compounds are unmatched in their chemical diversity and effectiveness as antimicrobials scaping products of resistance mechanisms [17].
Figure 1. Mechanism of action of some classes of antifungals (Echinocandins, Polyenes, Azoles and Pyrimidine Analogue). Azoles is a lanosterol 14α-demethylase inhibitor. Polyenes acts by binding with ergosterol. Echinocandins inhibits the 1,3-B-glucan synthase and Pyrimidine analogue, in turn, inhibits the DNA/RNA/protein synthesis.

Microbial biodiversity is poorly understood, especially in specific habitats such as plant interiors and extreme habitats. In general, these numbers are conservative and underestimated. However, microbial biodiversity is responsible for the production of hundreds of medicines, such as vaccines, enzymes and antibiotics, which move tens of billions of dollars around the world. Biochemical diversity and endophyte diversity represent a large number of still unknown genes. More and more genetic functions are being discovered, especially for environmental restoration and industrial purposes. Therefore, the use of bacteria and fungi has opened new areas of biotechnological exploration, which requires the separation, characterization and determination of microbial biodiversity in different habitats [18].

Antibiosis among microorganisms was described well before the discovery of penicillin, by Luis Pasteur, where he proposed that microorganisms could secrete material to kill other bacteria. The first clinical use of an antibiotic was reported in the 1890s, where Emmerich and Löw used an extract of *Pseudomonas aeruginosa* (then known as *Bacillus pycyaneus*) to treat hundreds of patients and this extract, called pyocyanase, was
used until the 1910s. Pyocyanase was active against several pathogens and incorrectly considered an enzyme. Instead, the active components of pyocyanase were likely a mixture of pyocyanin, a quorum-sensing phenazine, and 2-alkyl-4-hydroxyquinolones [19].

In 1930, Selman Waksman defined an antibiotic as a compound made by a microbe to destroy other microbes. She identifying soil-dwelling filamentous Actinomycetales ('actinomycetes') as prolific producers of antimicrobial compounds. Waksman discovered several antibiotics produced by soil-dwelling actinomycetes, including neomycin and streptomycin, the first active agent against tuberculosis. Waksman's pioneering work identified the genus *Streptomyces* as a prolific producer of natural antibiotics, or secondary metabolites, which are compounds not necessary for the normal growth, development, or reproduction of an organism in the laboratory. Most of these antibiotics are still in clinical use, but their effectiveness has been hampered by increasing microbial resistance. Most antibiotics in clinical trials today are derived from known classes of synthetic antibiotics, rather than the search for new classes of antibiotics [20].

Since the pharmaceutical industry (PI) focused on synthetic chemistry with high-throughput screening back in the 1990s, natural products have been less explored as a source of new antimicrobials. PI has been working on already known antimicrobials, leading to the development of second and third-generation compounds by chemical structural improvement and semi-synthetic structures based on natural compounds. However, with technological advancements, the techniques of genome sequencing have become accessible resources. Data show that microorganisms with large genomes (actinomycetes), can produce even more secondary metabolites than previously known. Pointing again toward microorganism-derived products as an important source of antimicrobials [21-24].

Secondary metabolites of microorganisms have historically played an important role as antimicrobials. Microbes are exploited as biofactories of bio-derivatives such as peptides, enzymes, and various other particles with bioactive properties. They are found in the most diverse conditions and natural sources. Be it microorganisms present in the soil, and water, and present a plethora of micro biodiversity to be explored [25]. Besides microbes are isolated from soil, which is widely studied. The marine microbes have gained visibility in research because they present a great genetic variability to withstand
the imposed conditions of their habitat. Leads produce different bioactive metabolites [26,27]. The most common approaches to obtain new biosynthetic agents are based on searches in isolated habitats, and that impose conditions for this microbe to evolve genetically and possess unique chemical structures with possible bioactivity (Fig.2) [28-30].

The search process for secondary metabolites can be optimized through technologies associated with the genome of these microorganisms. Knowledge about the microbial biosynthetic gene clusters (BGCs) is important in this process. BGCs possess all the necessary genes to encode different enzymes important in the generation of new metabolic secondaries [31]. (Kautsar et al., 2020) This knowledge associated with the use of technologies such as recombinant DNA and Genome shuffling may point to the future of exploratory engineering in microbes with biosynthetic potential, being known as the bacteria of the genus Streptomyces, or new microorganisms from different natural sources (Fig. 2) [32-34].

Figure 2. Schematic of metagenomic and metabolomic analyses based on a mix of microorganisms collected from the environment (soil, ocean, and others). Based on these two methodologies it is possible to identify new molecules with microbial activities that can be exploited by the pharmaceutical industry as an alternative to the resistance of microorganisms to existing drugs.
2 CONCLUSION

The need to produce new antimicrobial drugs requires different strategies, among which we highlight the importance of bioprospecting for secondary metabolites of environmental bacteria and fungi with potential antimicrobial activity.
REFERENCES


