CHAPTER 5

MICROBIAL RESISTANCE AND BIOPROSPECTION: TRENDS AND CHALLENGES

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ABSTRACT: This article analyzes the interrelationship between microbial resistance and the sustainable use of biodiversity, exploring its implications for global health and environmental conservation. Initially, the crucial role of antimicrobials in modern medicine is highlighted, while highlighting the emerging challenges associated with bacterial resistance. Antibiotic resistance is examined from the perspective of intrinsic and acquired mechanisms, including horizontal gene transfer between bacteria. On the other hand, the article explores the richness of biodiversity, especially in the Brazilian context, and its importance for biotechnological research. Initiatives such as BIOTA-FAPESP and the SISBIOTA Program are highlighted as examples of integrated approaches to mapping and conserving biological diversity, while promoting sustainable socioeconomic development. Furthermore, bioprospecting is presented as a promising strategy for discovering new therapeutic agents in natural organisms. The potential of Brazilian biodiversity as a source of new medicines is emphasized, highlighting the need for conservation approaches that balance economic exploitation with environmental preservation. Finally, the article argues that biodiversity conservation can play a crucial role in combating microbial resistance, offering therapeutic alternatives and reducing dependence on conventional antimicrobials. This integrated approach highlights the importance of collaboration between scientists, policymakers and local communities in the search for sustainable solutions to global health and environmental challenges.
KEYWORDS: Microbial resistance, Biodiversity, Antimicrobials, Bioprospecting, Sustainability.

RESISTÊNCIA MICROBIANA E BIOPROSPECÇÃO: TENDÊNCIAS E DESAFIOS

RESUMO: Este estudo analisa a inter-relação entre a resistência microbiana e o uso sustentável da biodiversidade, explorando suas implicações na saúde global e na conservação ambiental. Inicialmente, destaca-se o papel crucial dos antimicrobianos na medicina moderna, enquanto ressalta os desafios emergentes associados à resistência bacteriana. A resistência aos antibióticos é examinada sob a ótica dos mecanismos intrínsecos e adquiridos, incluindo a transferência horizontal de genes entre as bactérias. Por outro lado, o artigo explora a riqueza da biodiversidade, especialmente no contexto brasileiro, e sua importância para a pesquisa biotecnológica. Iniciativas como o BIOTA-FAPESP e o Programa SISBIOTA são destacadas como exemplos de abordagens integradas para mapear e conservar a diversidade biológica, ao mesmo tempo em que promovem o desenvolvimento socioeconômico sustentável. Além disso, a bioprospecção é apresentada como uma estratégia promissora para a descoberta de novos agentes terapêuticos em organismos naturais. O potencial da biodiversidade brasileira como fonte de novos medicamentos é enfatizado, ressaltando a necessidade de abordagens de conservação que equilibrem a exploração econômica com a preservação ambiental. Por fim, o artigo argumenta que a conservação da biodiversidade pode desempenhar um papel crucial no combate à resistência microbiana, oferecendo alternativas terapêuticas e reduzindo a dependência dos antimicrobianos convencionais. Essa abordagem integrada destaca a importância da colaboração entre cientistas, formuladores de políticas e comunidades locais na busca por soluções sustentáveis para os desafios globais de saúde e meio ambiente.
PALAVRAS-CHAVE: Resistência microbiana, Biodiversidade, Antimicrobianos, Bioprospecção, Sustentabilidade.

INTRODUCTION

Antimicrobial resistance, which has been observed since the advent of antibiotics, is a result of the excessive and inappropriate use of these medications. This has led to the emergence and increase of pathogenic microorganisms that are resistant to all available classes of antibiotics, whether natural, semi-synthetic, or synthetic. This reality not only complicates the treatment of diseases in humans but also affects plants and animals, highlighting the urgent need to discover new therapeutic agents to address this health crisis (BEJARANO; PÉREZ; SÁNCHEZ-MORA, 2018).

In this context, the widespread use of antibiotics has resulted in the emergence of microorganisms known as superbugs, representing a significant challenge to public health. These bacteria have developed survival mechanisms in the host, which can be attributed to natural selection as conceptualized by Charles Darwin. These mechanisms include gene transfer, mutations, and biofilm formation (HOPMAN et al., 2019). Thus, the first cases of penicillin resistance were recorded in 1961, and over time, resistance to various antibiotics began to emerge. Currently, we are living in the era of prudent antimicrobial use, characterized by intensive efforts to find alternatives to the excessive use of these medications (PRESCOTT, 2017).

Consequently, strategies to mitigate bacterial resistance, such as the responsible use of antibiotics, the prevention of bacterial infections, and the control of the spread of resistant microorganisms, are fundamental. Moreover, it is crucial to maintain continuous and active efforts in the search for new metabolic compounds that are effective against a variety of pathogenic microorganisms. In this scenario, scientific studies aim to identify biological diversity and explore new natural products with antimicrobial potential (DA COSTA & JUNIOR, 2017).

Bioprospecting is defined as the exploration of genetic resources in nature with the aim of contributing to future research and development of products. In the pharmaceutical field, this practice is crucial as it drives the biotechnological advancement of medications. This is due to the fact that the pharmaceutical sector depends on the investigation of new molecules for the production of medicines, with a significant portion of currently available substances resulting from this type of research (DA SILVA et al., 2024).

Thus, in view of the growing global concern with the increase in antimicrobial resistance and the urgent need to find new therapeutic solutions, it is essential to explore the trends and challenges related to these themes, as the study can provide valuable insights for the development of more effective prevention and treatment strategies, in addition to highlighting the potential of bioprospecting in the discovery of new antimicrobial compounds.

MICROBIAL RESISTANCE

Since their identification, antimicrobial drugs have played a crucial role in promoting human health and have been essential for improving the quality of life. However, doctors often misuse these antimicrobial agents, which are among the most widely used medications. Thus, the indiscriminate and excessive use of antibiotics has led to the development of antimicrobial resistance and the emergence of multidrug-resistant strains (RAM) in pathogens, reaching alarming levels in various regions of the world, especially in developing countries (AYUKEKBONG; NTEMGWA; ATABE, 2017).

Antibiotics are compounds of natural or synthetic origin whose primary function is to combat infections caused by microorganisms, targeting specific microbial components such as the cell wall, protein synthesis, and nucleic acid synthesis, among other mechanisms. To counter these specific attacks, bacteria develop strategies of antimicrobial resistance. This process occurs when bacteria develop different mechanisms to neutralize the action of the antibiotic, usually through DNA mutations or the transfer of plasmids (CARNEIRO, 2019; SCALDAFERRI, 2020).

There are several chemical classes of antibiotics, which can be organized according to their specific target within the bacterial cell. These include: cell wall synthesis inhibitors (Penicillins, Cephalosporins, and Polypeptides); protein synthesis inhibitors (Aminoglycosides, Pleuromutilins, Tetracyclines, Macrolides, Streptogramins, Oxazolidinones, and Glycylcyclines); agents causing damage to the plasma membrane (Lipopeptides); nucleic acid synthesis inhibitors (Rifamycins, Quinolones, and Fluoroquinolones); and competitive inhibitors of essential metabolite synthesis (Sulfonamides) (TORTORA; FUNKE; CASE, 2017).

According to Spellberg (2016), antibiotic resistance (RAM) is undoubtedly one of the main challenges of the 21st century for all major economic, political, and regulatory entities, including the International Monetary Fund (IMF), the World Bank (WB), the World Health Organization (WHO), and the Group of Eight (G8). RAM presents the greatest problems and challenges, representing a significant threat to public health (through chemotherapy failure), social concerns and crises, animal health, and environmental issues, thus constituting a severe global problem.

There are various reasons why the indiscriminate use of antibiotics is observed, including inappropriate prescriptions, whether due to lack of necessity or the choice of broad-spectrum medications, along with incorrect periods and doses, which could be adjusted according to the specific situation of the patient. Another contributing factor to this scenario is the lack of doctor-patient communication, leading to treatments that could be brief becoming prolonged problems, sometimes even irreversible (ESTRELA, 2018).

Bacterial resistance can develop through intrinsic and acquired mechanisms (ABRANTES; NOGUEIRA, 2021; DALMOLIN, 2022). Intrinsic or natural resistance is genetically transmitted, meaning it has morphological and enzymatic characteristics that naturally confer resistance to a specific antibiotic and is part of the bacteria's innate characteristics. Acquired resistance, as the term indicates, is developed through external influences, through genetic mutations that reduce drug sensitivity or horizontal gene transfer (MUNITA; ARIAS, 2016; OLIVEIRA, 2020).

Due to the diversity of antibiotic action mechanisms, bacteria have developed various resistance strategies. In general, bacterial resistance to antibiotics can occur in three ways: 1) changes in cell membrane permeability, which can block the antibiotic's entry into the cell or allow the antibiotic to be expelled from the cell (by active efflux); 2) acquisition of the ability to degrade or inactivate the antibiotic; or 3) the emergence of mutations that alter the target of an antibiotic, rendering it ineffective (LIMA; BENJAMIM; SANTOS, 2017).

The genes responsible for resistance to modern antibiotics have been present in bacteria for centuries or millennia. To acquire antibiotic resistance, there is a dynamic exchange of genetic material between bacteria, occurring even between those of different species, as well as between living and inactive bacteria. This genetic exchange occurs through mechanisms such as conjugation (which involves the transfer of plasmids and transposons through direct contact between bacteria, or the transmission of genetic copies through needle-like structures), transduction (where the exchange of genetic material is mediated by bacteriophage viruses), and transformation (in which the bacterium acquires exogenous DNA from the environment, including from other already dead bacteria) (KHAN; MILLER; ARIAS, 2018).

Antibiotic resistance arises through pre-existing genetic characteristics, transmitted among bacteria by various mechanisms, which can be categorized into four main types: first, the activity of efflux pumps; second, changes in cell membrane composition, altering permeability; third, through mutations that can prevent the entry of antibiotics due to changes in the antibiotic's action site; and lastly, by producing enzymatic inactivators (Figure 1) (DA COSTA, A., & SILVA JUNIOR, 2017; BELLO; DINGLE, 2018).

According to Silveira et al. (2006), pathogenic strains have been able to resist highly effective antibiotics from various chemical classes by using these mechanisms either alone or in combination. The levels of resistance among common bacterial pathogens are alarming; for example, the average rates reported in 76 countries, of 42% for *Escherichia coli* resistant to third-generation cephalosporins and 35% for methicillin-resistant *Staphylococcus aureus*, represent a significant concern (GLASS, 2022).

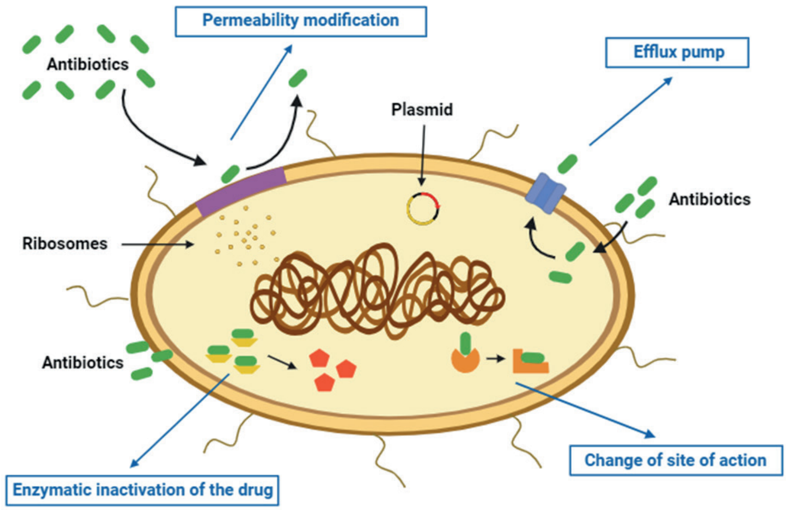

Figure 1. Main defense mechanisms of bacteria against antibiotics.

According to recent statistics, approximately 700,000 people die annually due to infections related to antimicrobial resistance, and it is estimated that this number will increase to 10 million per year by 2050 globally. These numbers are considered alarming and reaffirm the urgency in the search for new antimicrobials. However, considering that traditional antibiotics are still effective in treating various infections, the main focus of new therapeutic agents is to confront multidrug-resistant pathogens and provide a preventive advantage against emerging pathogenic conditions, which expands the search for complementary and alternative medicine, as that it has the capacity to offer treatments with fewer side effects, a broad spectrum of activity against various diseases, high tolerability, low level of toxicity, more affordable cost and pharmacokinetics that allow clinical efficacy without the need for chemical changes (ANAND, 2020) .

BIOPROSPECTION AND SUSTAINABLE USE OF BIODIVERSITY

Biodiversity or biological diversity is the term used to represent the variety of crucial ecological elements that encompass a range of spatial scales, from genetic levels to species and communities (CAIN; BOWMAN; HACKER, 2018). Therefore, biological diversity refers to the variability of living organisms in all their forms, including terrestrial, marine, and other aquatic ecosystems, as well as the ecological complexes they are part of. This encompasses the diversity within species, between species, and within ecosystems as a whole (BRASIL, 1998).

Brazil is globally known for containing the richest biodiversity on the planet, housing five major continental biomes, the most abundant diversity of continental life, with a significant proportion of endemic species, and possessing between 15% and 20% of the world's entire biological diversity, including the largest tropical forest, the Amazon, and two of the nineteen global hotspots, the Atlantic Forest and the Cerrado (PRATES; IRVING, 2015). According to Ribeiro et al. (2019), given this status as a megadiverse country, Brazil has a significant commitment regarding the understanding, application, and preservation of biodiversity. This implies considering the fundamental values of life, the associated ecosystem services, and their interaction with social well-being perspectives, as well as opportunities to drive sustainable economic development through this knowledge.

Based on this premise, in 1999, the São Paulo Research Foundation (FAPESP) founded the Research Program on Characterization, Conservation, Restoration, and Sustainable Use of Biodiversity (BIOTA-FAPESP), with the main purpose of mapping and examining the biodiversity of microorganisms, animals, and plants in the State of São Paulo, as well as promoting the development of natural products with added value that can boost the bioeconomy at a regional level and on a broader scale (FAPESP, 2022). The high-quality results from the beginning of BIOTA-FAPESP inspired the creation of similar initiatives by federal research funding agencies. Such is the case of the SISBIOTA Program, supported by the National Council for Scientific and Technological Development (CNPq) in partnership with several state research funding agencies, established in 2010. This initiative promoted collaboration among different natural product research groups throughout Brazil, facilitating the optimization of available resources and equipment, as well as having a positive impact on local communities, which hold traditional knowledge, through the sharing of benefits derived from the sustainable exploitation of biodiversity, following the principles of bioeconomy (SILVA, 2022).

Given Brazil's relevance in the global importance of biodiversity conservation, in conservation areas where human interaction is allowed, traditional knowledge can play a crucial role in environmental planning, species protection, and the promotion of sustainable development. Thus, traditional knowledge emerges as an effective tool for the planning and protection of these regions, enriching science by providing practical approaches grounded in ecosystem understanding, contributing to the understanding of environmental changes (BORGES; PEIXOTO, 2009; BRITO; MARÍN; CRUZ, 2017).

According to Mateo et al. (2001), bioprospecting can be defined as a systematic search for organisms, genes, enzymes, compounds, processes, and components derived from living beings in general, collectively known as genetic resources, that have the potential to contribute to the development of a product. This is notable for its potential in the development of new medicines obtained directly or indirectly from natural products.

Currently, the market for herbal medicines is continuously growing, driven by the wide range of applications of extracts and bioactive compounds derived from plants with medicinal and therapeutic properties. These are characterized by containing active principles that can be employed in the formulation of products related to a variety of pharmacological responses, such as anti-inflammatory effects, wound healing, pain relief, treatment of parasitic diseases, reduction of inflammation, combating anemia, antibacterial properties, among others (PEDROLLO et al., 2016; SILVA; OLIVEIRA, 2017; EFFERTH et al., 2021).

Therefore, it is essential to develop conservation strategies and promote research on native species, aiming to replace the pressure caused by extractivism with sustainable management practices. This would allow studies related to the use of plants in medicine production, analysis of the chemical composition of native species, investigation of their potential biological activities, and the diversity of species to be explored as a source of sustainable opportunities (JOLY, 2011; STEHMANN; SOBRAL, 2017; SILVA; DOTTO; REBELO, 2022).

CONCLUSIONS

Given the complexity and challenges cited by the misuse of antibiotics and the consequent emergence of antimicrobial resistance, it is essential to conclude that, to face this serious problem, it is essential to adopt preventive and corrective measures in all spheres of society, including awareness, investments in research and development of new antimicrobials, and responsible prescribing practices. Furthermore, exploring alternatives to conventional medicine can offer complementary therapeutic approaches and contribute to preserving the effectiveness of traditional antibiotics. Given the growing impact of antimicrobial resistance on public health, it is imperative to act now to ensure a future where antibiotics remain an effective tool in promoting human health.

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