Research, Society and Development, v. 14, n. 3, e3214348345, 2025
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Pharmaceutical innovations used to fight multidrug-resistant bacterial infections

Inovações farmacêuticas utilizadas no combate de infecções a bactérias multirresistentes

Innovaciones farmacéuticas para combatir las infecciones bacterianas multirresistentes

Received: 03/02/2025 | Revised: 03/08/2025 | Accepted: 03/08/2025 | Published: 03/12/2025

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Abstract
Pharmaceutical innovation is a fundamental process that involves the development, research and introduction of new drugs and therapies onto the market. This includes the discovery of new molecules, improvements in drug delivery technologies, enhancement of existing formulations and the search for new treatments for various diseases. One of the current challenges in this field is antimicrobial resistance, especially in relation to multi-resistant bacteria. To meet these challenges, innovation in the discovery and development of new drugs is essential. This is crucial for the development of new antibiotics and therapies capable of effectively combating multidrug-resistant bacteria. In addition, strategies to prevent and control antimicrobial resistance are key to ensuring the continued effectiveness of drugs over time. An important approach to gathering up -to-date information and developing better therapeutic options against multidrug-resistant bacteria is to search for the latest literature. In this context, a study was carried out to compile the most recent pharmaceutical innovations used to combat these infections by multidrug- resistant bacteria. The methodology used was a literature review of academic databases, with specific exclusion criteria to e nsure the relevance of the selected studies. This literature review covered several innovative techniques, such as computational modeling, technologies using nanocomposites, gold and silver nanoparticles, natural extracts, among others. These techniques represent promising approaches for the development of new antimicrobial treatments that can be effective against multidrug- resistant bacteria, complementing or replacing conventional treatments.
Keywords: Pharmaceutical innovation; Multidrug-resistant bacteria; Drugs.

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Resumo

A inovação farmacêutica é um processo fundamental que envolve o desenvolvimento, pesquisa e introdução de novos medicamentos e terapias no mercado. Isso inclui a descoberta de novas moléculas, melhorias em tecnologias de administração de medicamentos, aprimoramento de formulações existentes e busca por novos tratamentos para diversas doenças. Um dos desafios atuais nesse campo é a resistência antimicrobiana, especialmente em relação a bactérias multirresistentes. Para enfrentar esses desafios, a inovação na descoberta e desenvolvimento de novas drogas é essencial. Isso é crucial para o desenvolvimento de novos antibióticos e terapias capazes de combater eficazmente as bactérias multirresistentes. Além disso, estratégias para prevenir e controlar a resistência antimicrobiana são fundamentais para garantir a eficácia contínua das drogas ao longo do tempo. Uma abordagem importante para reunir informações atualizadas e desenvolver melhores opções terapêuticas contra bactérias multirresistentes é a busca na literatura mais recente. Nesse contexto, um trabalho foi realizado para compilar as inovações farmacêuticas mais recentes utilizadas no combate dessas infecções por bactérias multirresistentes. A metodologia utilizada foi a revisão da literatura a partir de bancos de dados acadêmicos, com critérios de exclusão específicos para gara ntir a relevância dos estudos selecionados. Esta revisão de literatura abrangeu diversas técnicas inovadoras, como a modelagem computacional, tecnologias utilizando nanocompósitos, nanopartículas de ouro e de prata, extratos naturais, entre outros. Essas técnicas representam abordagens promissoras para o desenvolvimento de novos tratamentos antimicrobianos que possam ser eficazes contra bactérias multirresistentes, complementando ou substituindo tratamentos convencionais.

Palavras-chave: Inovação farmacêutica; Bactérias multirresistentes; Drogas.

Resumen

La innovación farmacéutica es un proceso fundamental que implica el desarrollo, la investigación y la introducción en el mercado de nuevos medicamentos y terapias. Esto incluye el descubrimiento de nuevas moléculas, la mejora de las tecnologías de administración de fármacos, la mejora de las fórmulas existentes y la búsqueda de nuevos tratamientos para diversas enfermedades. Uno de los retos actuales en este campo es la resistencia a los antimicrobianos, especialmente en relación con las bacterias multirresistentes. Para hacer frente a estos retos, es esencial innovar en el descubrimiento y desarrollo de nuevos fármacos. Esto es crucial para el desarrollo de nuevos antibióticos y terapias capaces de combatir eficazmente las bacterias multirresistentes. Además, las estrategias para prevenir y controlar la resistencia a los antimicrobianos son fundamentales para garantizar la eficacia continuada de los fármacos a lo largo del tiempo. Un enfoque importante para recopilar información actualizada y desarrollar mejores opciones terapéuticas contra las bacterias multirresistentes es buscar en la bibliografía más reciente. En este contexto, se llevó a cabo un estudio para recopilar las innovaciones farmacéuticas más recientes utilizadas para combatir estas infecciones por bacterias multirresistentes. La metodología utilizada fue una revisión bibliográfica basada en bases de datos académicas, con criterios de exclusión específicos para garantizar la pertinencia de los estudios seleccionados. Esta revisión bibliográfica abarcó diversas técnicas innovadoras, como la modelización computacional, las tecnologías que utilizan nanocompuestos, nanopartículas de oro y plata, extractos naturales, entre otras. Estas técnicas representan enfoques prometedores para el desarrollo de nuevos tratamientos antimicrobianos que puedan ser eficaces contra las bacterias multirresistentes, complementando o sustituyendo a los tratamientos convencionales.

Palabras clave: Innovación farmacéutica; Bacterias multirresistentes; Fármacos.

1. Introduction

Pharmaceutical innovation is a set of processes involving the research, development and introduction of new drugs, the implementation of new organizational and marketing strategies in the pharmaceutical sector and therapies in the consumer market. This can include the discovery of new molecules, the improvement of drug delivery technologies, the improvement of existing formulations and the search for new treatments for diseases (BNDES, 2005; Pammolli, Magazzini, & Riccaboni, 2011; Santos, 2022).

With the growing profile of infections with multidrug-resistant strains of bacteria in clinical practice, it is increasingly difficult to treat and control these pathogens that develop resistance to multiple antibiotics due to the various selective p ressuresin the environment (World Health Organization (WHO). (2024). In 2021, it was estimated that 4.71 million deaths were associated with antimicrobial resistance (AMR) worldwide, including 1.14 million deaths attributable to bacterial AMR (Naghavi et al., 2024). Therefore, this pandemic exacerbated by the uncontrolled use of antibiotics has become a global public health challenge generating increased morbidity, mortality and costs to health systems (Naylor et al., 2018).

In view of this, innovation in the discovery and development of new drugs is essential to address challenges such as AMR, since pharmaceutical innovation is crucial to the development of new antimicrobials and therapies that can effectively combat multidrug-resistant bacteria (Zhang et al., 2021). In addition, strategies to prevent and control AMR are also key to ensuring that drugs remain effective over time (Shim, 2023).

Thinking of ways to gather the latest information in order to devise the best therapeutic options against multidrug - resistant bacteria, searching the most up-to-date literature is an option when thinking about antimicrobial innovations. To this end, the aim of this study was to compile the latest pharmaceutical innovations used to combat infections caused by multidrug- resistant bacteria, with a view to highlighting the various innovative techniques and/or methods used to complement and/or replace the usual treatments for multidrug-resistant bacterial infections.

The methodology used included a literature review based on academic databases, using key words in English and Portuguese (pharmaceutical innovation, multidrug-resistant bacteria, drugs), dated between 2023 and 2024 in English, Portuguese and Spanish. Exclusion criteria were literature reviews or subjects that did not involve bacteria or other microorganisms, as well as materials that did not address innovations.

This literature review aims to address the various innovative state-of-the-art techniques compared to traditional antimicrobials used in clinical practice, from computational modeling, technologies using nanocomposites, gold and silver nanoparticles, natural extracts, bacteriophage-based therapy, microbiome-derived antimicrobial compounds and CRISPR-Cas- based antimicrobials.

2. Methodology

This study was carried out in the format of a narrative literature review (Rother, 2007; Casarin et al., 2009), of a qualitative nature (Pereira et al., 2018), using information obtained from academic databases using key words in English and Portuguese (pharmaceutical innovation, multidrug-resistant bacteria, drugs), dated between 2023 and 2024 in English, Portuguese and Spanish. Exclusion criteria were literature reviews or subjects that did not involve bacteria or other microorganisms, as well as materials that did not address innovations.

With that in mind, this literature review aims to address the various innovative state-of-the-art techniques compared to traditional antimicrobials used in clinical practice, from computational modeling, technologies using nanocomposites, gold and silver nanoparticles, natural extracts, bacteriophage-based therapy, microbiome-derived antimicrobial compounds and CRISPR- Cas-based antimicrobials.

3. Results and Discussion

Pharmaceutical innovation enters the scenario of creating/improving potential antimicrobial agents in the face of their uncontrolled use since the discovery of penicillin. In addition, a growing challenge facing the medical community is the increase in infections caused by strains of bacteria that are multidrug-resistant to various classes of antibiotics, whether they inhibit cell wall synthesis, depolarize the membrane, inhibit the synthesis of proteins, nucleic acids or metabolic pathways (Shim, 2023). It is therefore estimated that infections by multidrug-resistant bacteria could cause more than 10 million deaths a year worldwide by 2050 (Murray et al., 2022).

Priority microorganisms from the World Health Organization (WHO) and antibiotic resistance threats from the Centers for Disease Control and Prevention (CDC) show urgent threat levels up to watch list or medium priority in health systems. Gra m- negative bacteria are in the urgent and high threat group due to carbapenem-resistance - e.g. *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and species from the *Enterobacteriaceae* family -;

fluoroquinolone-resistance (e.g.*Salmonellae).Salmonellae)*; third generation resistant to cephalosporins and fluoroquinolones (e.g. *Neisseria gonorrhoeae*); vancomycin-resistant *Enterococci*; fluoroquinolone-resistant *Shigella* species. The main Gram-positive bacteria of most concern due to the frequency of cases in populations and the irrational use of antimicrobials are *Staphylococcus aureus*, resistant to methicillin (MRSA) and vancomycin; *Enterococcus faecium*, resistant to vancomycin; group A *Streptococcus* resistant to erythromycin and group B resistant to clindamycin (World Health Organization - WHO, 2019; Centers for Disease Control and Prevention - CDC, 2019).

Therefore, this work was carried out in the form of a narrative literature review, using information obtained from databases such as Pubmed, Scielo and Google Scholar, using the keywords: Pharmaceutical innovation, multi-resistant bacteria, drugs; also using the terms in English (Pharmaceutical innovation, multi-resistant bacteria, drugs), based on articles and materials produced between 2023 and 2024.

Literature reviews, subjects that do not involve bacteria (other microorganisms such as fungi, viruses) or that do not present any kind of treatment innovations, drugs or molecules with antimicrobial capacity were not accepted. The searches were started using inclusion and exclusion criteria. For inclusion, the articles had to be within the period, in Portuguese, Spanish, French and English and the abstracts had to be read selectively.

Among the searches carried out, 81 papers were found with the keywords in Portuguese on google academic and 615 with the words in English. No papers were found in the other databases for the period searched. As a result, 17 papers were selected that met the requirements of the above-mentioned theme.

From the perspective of the selected papers, a variety of methodologies were selected, including computational virtual screening techniques to identify potential antibacterial agents against *S. aureus* strains. Twenty-four molecules were selected based on MIC values and one promising antibacterial agent, tetrahydroxybenzofuran, was adopted as the main molecule. After pharmacokinetic and toxicological analyses, three molecules (LB255, LB320 and LB415) we re identified as promising, with LB320 standing out as having potential for antibacterial activity. The Molecular Docking studies indicated significant results for the promising molecules in both molecular targets. Synthetic accessibility showed that LB320 is easy to synthesize, suggesting that it could be an interesting candidate for future experimental studies (Pinto et al., 2023).

Among innovative molecules, we can consider those from plants, microorganisms and animals as key sources for new discoveries. Research into snake venom is one of the initiatives for use in innovation. A recent study on Bothrops alternatus showed that a fraction isolated from the snake's venom exhibited antimicrobial activity. This molecule is a high molecular mass substance, possibly belonging to the class of L-amino acid oxidases (LAAOs), flavoenzymes that oxidatively deaminate L-amino acids to form α-keto acids, hydrogen peroxide and ammonia. These enzymes are found in venoms of venomous snakes, contributing to toxicity through oxidative stress. The discovery of this effect highlights the importance of further explorin g the properties of this fraction, with additional studies needed to identify and characterize it structurally and functionally in order to better understand the mechanisms underlying the antimicrobial effect (Oliveira et al., 2023).

Among the substances obtained from natural extracts with antimicrobial and antibiofilm activities, the essential oils (EOs) of *Mentha piperita L.* and *Eucalyptus globulus*, as well as their combinations, were tested against *Staphylococcus aureus* and *Enterococcus faecalis*. Methods such as disk diffusion, broth microdilution to determine the Minimum Inhibitory Concentration (MIC) and the checkerboard method were used to evaluate synergistic, additive or antagonistic associations. Innovatively, the results showed that the EOs were able to inhibit the bacteria in the planktonic state, with effective MICs. The combination of EOs showed synergistic or additive activity, depending on the bacteria tested. In addition, the EOs and combinations reduced initial biofilm adherence, indicating potential to inhibit biofilm formation.

These results suggest that the EOs of *E. globulus* and *M. piperita L.*, alone and in combination, have potential as antimicrobial and anti-biofilm agents against these bacterial strains (Ferreira et al., 2023).

Meanwhile, the investigation of the antibacterial activity of ethanolic extracts of Meniran (*Phyllanthus niruri L.*) and Kenikir (*Cosmos caudatus Kunth*) leaves against *Shigella* dysenteriae, tested in different combinations and identified groups of compounds such as saponins, tannins, alkaloids, flavonoids and polyphenols. The results showed that both extracts had antibacterial activity against this pathogen, with the Meniran extract being more effective when used alone. These findings highlight the potential of these extracts as antibacterial agents against this pathogenic bacterium (Rukmana et al., 2023).

Among the approaches to new molecules, research into microorganisms in different environments is crucial to discovering new natural molecules with antimicrobial potential. In this study, a strain of Streptomyces sp. called SCJ was isolated from soil collected in a Moroccan garden and identified using a polyphasic approach. The SCJ strain showed activity against various bacteria and fungi, including multidrug-resistant strains. The ethyl acetate extract of this strain showed significant antimicrobial activity against these microorganisms, with no evidence of hemolytic activity. GC-MS analysis revealed the presence of compounds such as 3,5-Dimethylpyrazole and pyrrolizidine derivatives, suggesting a possible contribution to the antimicrobial activity observed (Rammali et al., 2024).

The use of natural extracts combined with other innovative techniques are also promising proposals. A recent study used the combination of lipid nanoparticles (NL) containing essential oils. Ten NL formulations containing essential oils, vegetable butter and surfactant were developed and evaluated for physicochemical and thermal stability. In vitro tests were conducted to evaluate the activity of the fresh formulations at one year of age, highlighting a formulation with cinnamon essential oil that demonstrated activity against strains of *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The formulation was also studied for in vivo biocompatibility in a chicken embryo model, showing promising results that support further in vivo efficacy tests (Silva et al., 2024).

In addition, other innovative technologies such as cationic phthalocyanines have shown high efficacy in photodynamic activity against various microorganisms, including drug-resistant strains such as *Candida albicans*, *Escherichia. coli*, *K. pneumoniae*, *S. aureus*, vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *S. aureus*. Commonly used as an object of study in the field of nanotechnology, the versatility and stability of the molecules have made them important compounds in various areas of pharmaceutical innovation. The effectiveness of antimicrobial photodynamic therapy (aPDI) was influenced by the concentration of the compound and the dose of light used. New neutral and cationic phthalocyanines were s ynthesized and characterized, showing favorable photophysical and photochemical properties. The cationic compounds demonstrated the ability to generate singlet oxygen in aqueous media, standing out as promising for aPDI against microbial biofilms (Sindelo et al., 2023).

In silico studies have become increasingly promising, and recent work has demonstrated the antimicrobial role of this methodology. In an investigation evaluating the interactions between secondary metabolites from the *Psidium guineense* plant and enzymes with antimicrobial activity against *K. pneumoniae*. Using a computational approach, the binding affinities of the plant's flavonoids with the active site of the PBP1b enzyme were evaluated. The results showed that quercetin, kaempferol and rutin showed binding affinity with the macromolecule, suggesting the ability of these compounds to inhibit the enzyme and potentially degrade the bacterial cell wall. These findings provide theoretical support for antibacterial studies using P. gu ineense and its flavonoids as agents against bacterial infections, especially by acting on the cell wall of bacteria (Duzino, 2023).

The synthesis, characterization and antimicrobial activity of (2R)-3-butin-2-yl 2,3,4,6-tetra-O-acetyl-β-D-glycopyranoside, an O-glycoside derived from carbohydrates with potential biological application, especially as an antibacterial agent, was investigated. The compound was synthesized with high yield and stereoselectivity, showing activity against several bacterial strains, including *E. coli*, S. *aureus* and *K. pneumoniae*, with moderate to good inhibitory concentrations to zones of inhibition with maximum sensitivity profile. In addition, good availability for oral administration and high absorption in the gastrointestinal tract were observed, indicating its potential as a candidate for the development of oral antibacterial agents (Silva et al., 2023).

Considering the possibility of associations between innovative techniques and the use of usual drugs, studies have carried out from this perspective. In this work, coumarins were investigated for their antibacterial and modulating mechanism of action against standard and multidrug-resistant bacterial strains. An in silico pharmacokinetic characterization of the compounds was carried out, followed by in vitro evaluations of antibacterial activity and antibiotic modulation. Coumarin C13 showed antibacterial activity against strains of *S. aureus* and *E. coli*, while other coumarins showed modulating capacity for fluoroquinolone and aminoglycoside antibiotics. Compounds C10, C13 and C14 reduced the minimum inhibitory concentration of antibiotics for multi-resistant strains and C11 potentiated the effect of norfloxacin and gentamicin for Gram-positive and negative bacteria and norfloxacin only for Gram-negative. In addition, coumarins were effective in their role of potentiating the effect of norfloxacin by a dual mechanism: inhibition of the efflux pump by direct interaction with the protein (C9, C10, C11 and C13) and greater interaction with the membrane (C10 and C13). These results provide a detailed perspective on the potential of coumarins as efflux pump inhibitors, highlighting the specific mechanism of action and molecular interactions with the target protein (Martin, 2023).

With coumarin compounds in mind, Abdelaziz et al. (2023) analyzed compounds synthesized and evaluated as new coumarin-N-heterocyclic hybrids for their anticancer and antimicrobial activities. The hybrids showed moderate to good antiproliferative activity against cancer cell lines, with compounds 7a-d and 10c standing out. The molecular docking results revealed a marked affinity of the compounds with the key protein SER 79. In addition, the hybrids showed broad-spectrum antibacterial and antifungal activity, with MICs ranging from 3.2 to 66 µM against bacteria and from 0.0011 to 29.5 µM against fungi. In silico analysis indicated that these hybrids have high gastrointestinal absorption, low blood-brain barrier (BBB) permeability and the ability to penetrate the cell membrane. These results highlight the potential of these hybrids as promising candidates for the development of anticancer and antimicrobial agents (Abdelaziz et al., 2023).

With liposomal systems in mind, which are already being used as more effective and less toxic drug options, this work also investigated the antibacterial activity and inhibition capacity of the NorA, Tet(K), MsrA and MepA efflux systems by sesquiterpenes, including nerolidol, farnesol and α-bisabolol, individually or in liposomal nanoformulation, against multidrug- resistant strains of S. aureus. The isolated sesquiterpenes showed antibacterial activity and inhibition of the efflux pump. Farnesol showed the lowest Minimum Inhibitory Concentration (MIC) against strain RN4220, while nerolidol significantly reduced the MIC of EtBr, indicating effective inhibition of NorA. The liposomal formulations had less promising results, except for liposome/farnesol, which reduced the MIC of EtBr against some strains. More research is needed to understand the mechanisms of action of the compounds tested in inhibiting bacterial resistance systems (Santana, 2023).

Among other innovative methodologies, both bacteria, *S. aureus* and *E. coli*, showed sensitivity to the silanized titanate nanotube, with satisfactory inhibition halos sensitive at higher concentrations (100 and 50 mg L-1). The nanometric size of the titanate nanotube allows greater penetration into cell membranes, while the silane groups present induce antibacterial properties. Varying the concentration of the nanotube affects the formation of inhibition halos, with a ratio of 1:4 (50 mg of NBC -COOH and 200 mg of NtsTi-Si(CH2)3NH2) being the most effective. As for the zinc oxide

nanoparticles, they showed an anticancer effect on ovarian cells and antibacterial action on *S. aureus* and *E. coli*, with an inhibitory concentration of 50% at 27.45 μg/ml and inhibition diameters ranging from 20.16 ± 0.16 to 27 ± 0.57 mm for S. aureus and 25.66 ± 0.33 to 31 ± 0.33 mm for E. coli . The green synthesis of ZnOnps is a promising alternative, being low-cost, non-toxic and environmentally friendly, paving the way for alternative therapies against ovarian cancer and bacterial infections (Cruz, 2023).

Zinc oxide nanoparticles (ZnOnps) have remarkable biomedical properties as anticancer and antibacterial agents. This study investigated the behavior of ZnOnps synthesized by green methods on ovarian cancers and their antibacterial activity against *S. aureus* and *E. coli*. The ZnOnps showed an inhibitory concentration of 50% at 27.45 μg/ml and inhibition diameters between 20.16 ± 0.16 and 27 ± 0.57 mm for *S. aureus*, and 25.66 ± 0.33 to 31 ± 0.33 mm for *E. coli*. ZnOnps also showed a statistically significant antagonistic effect compared to traditional antibiotics. The green synthesis of ZnOnps is an easy, economical, non-toxic and environmentally friendly approach. The cytotoxic action on ovarian cancer cells and antibacterial properties suggest their potential as an alternative therapy for ovarian cancer *S. aureus* and *E. coli* infections (Mousa, 2023).

Nanobiotechnology is revolutionizing the use of various materials, including metallic nanoparticles (NPs). The biosynthesis of NPs using plant extracts is a simple, effective and low-cost approach. This study aimed to develop a sustainable methodology for the synthesis of gold nanoparticles (AuNPs) using the aqueous extract of Anacardium occidentale leaves and to evaluate their antimicrobial activity. The AuNPs showed antibacterial potential, inhibiting the growth of *S. aureus* by interacting with the microorganism's membrane. The plant extract was effective in synthesizing AuNPs with antimicrobial activity against *S. aureus* (Figueira, 2023).

Transmission electron microscopy analysis revealed that the gold and silver nanoparticles, including those added to the decoction, exhibited varied geometric shapes, such as spherical and triangular, with average particle diameters between 18.007 and 33.875 nm. The antibacterial activity of the silver and gold nanoparticles associated with *Spondia mombin L.* was evaluated by broth microdilution, with analyses carried out after 0 and 24 hours on strains of *P. aeruginosa*, *S. aureus*, *E. coli* and *K. pneumonie*. The results were statistically analyzed using analysis of variance and Tukey's test ($p < 0.05$). Bactericidal activity was observed only with the silver and silver nanoparticles associated with the decoction, while the gold nanoparticles associ ated with *S. mombin L.* showed no bacterial activity. The silver nanoparticles associated with the decoction of *S. mombin L.* showed significant effects on bacterial activities, with total inhibition of Gram-positive and Gram-negative bacteria observed at a concentration of 50 mg/mL-1 (Santos, 2023).

In this study, ternary complexes of [Cu(Phen)(L-methionine)H2O]Cl-1.5H2O and [Cu(Phen)(L-asparagine)H2O-Cl]H2 O were synthesized. The properties of these complexes were investigated by X-ray diffraction (XRD), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and Raman and FT-IR spectroscopies. The crystal structure of the [Cu(Fen)(L- asparagine)H2O-Cl]H2O complex was elucidated by single-crystal XRD, revealing triclinic symmetry with space group $P\bar{1}$. In addition, biological studies showed antibacterial activity of the complexes against Gram-positive and Gram-negative bacteria. Both complexes showed potential as enhancers of commercial antibiotics, with a minimum inhibitory concentration (MIC) only 3x higher than the standard drug Gentamicin for the Gram-positive bacterium *Streptococcus pneumoniae* (Rodrigues, 2023).

With more modern methodologies in mind, the use of bacteriophages as innovative forms has shown good results. In a study aimed at investigating the efficacy and safety of intravesical use of bacteriophage-based medication in patients with chronic recurrent cystitis, a prospective parallel-group clinical trial was conducted with 75 patients randomized into

three groups. The first group received intravesical treatment and rectal suppositories with bacteriophages, the second group only intravesical treatment, and the third group only rectal suppositories. The treatment lasted 12 weeks, with evaluations b efore the start and after 14, 30 and 90 days of therapy. The results were evaluated using blood, urine and bacteriological tests to determine the sensi tivity of the pathogens to antibacterials and bacteriophages, as well as using the Polymerase Chain React ion (PCR) method to identify the pathogens. In short, bacteriophages have shown efficacy and safety in the treatment of bacterial infections, with the abi lity to destroy target bacteria without harming the homeostasis of the human microbiota. The diversity of genetically modified viruses with tropism for bacteria and incorporated into medicine resistant strains of pathogens, unlike broad -spectrum antibiotics (Krakhotkin, 2025).

Antimicrobial compounds derived from the microbiome is also another promising novelty in pharmaceutical innovation. The compound lugdunin (cycloheptapeptide composed of alternating D,L-amino acids and a thiazolidine heterocycle) is an antibacterial agent derived from the microbiome with good activity against various Gram-positive bacteria in vitro and in animal models of nasal colonization and skin infection. The mechanism of action of lugdunin is related to the depletion of bacterial energy resources by rapidly depolarizing the cytoplasmic membranes of different bacterial species and acidifying the cytoplasm of *Staphylococcus aureus*, including the methicillin-resistant isolate (MRSA), within minutes due to the activity of the protonophore (Berscheid et al., 2024; Ruppelt et al., 2024). Another study showed that the molecule epifadin, which is produced by the nasal *Staphylococcus epidermidis* IVK83, is able to eliminate *Staphylococcus aureus* during cocultivation in vitro and in vivo. This shows that the epifadin-producing commensal *S. epidermidis* can help prevent nasal carriage by *S. aureus* (Salazar et al., 2024).

Recent studies have investigated another tool in pharmaceutical innovation: CRISPR -Cas (Clustered Regularly Interspaced Short Palindormic Repeats) systems. These can be used as antimicrobials to fight infections caused by bacteria. CRISPR antimicrobials have been used against multidrug-resistant and virulent strains of *Klebsiella pneumoniae*. The researchers evaluated the effectiveness of different CRISPR nucleases, comparing those that target DNA with those that target RNA. They found that DNA-targeting nucleases outperformed RNA-targeting nucleases in the tests. The AsCas12a nuclease showed robustness in targeting different strains, and the study also identified several ways in which pathogenic bacteria can escape the antimicrobial action of CRISPR. These escape mechanisms vary widely, making it difficult to optimize lethal efficacy. However, they observed that certain guide RNAs (gRNAs) showed different levels of efficacy between strains, which was associated with the interaction between improper gRNA folding and DNA repair mechanisms specific to each isolate. Finally, they demonstrated that Cas12a-based antimicrobials can be used to eliminate *K. pneumoniae* when encoded in phagemids delivered by T7 -like bacteriophages. The findings provided a basis for the future development of CRISPR antimicrobials as a personalized approach to fighting antimicrobial-resistant infections (Vialetto et al., 2024). Another study showed that 106 isolates of *K. pneumoniae* were identified by the genes of the CRISPR-Cas system using PCR. This research concluded that if the CRISPR/Cas modules are not present in the strains, the bacteria could acquire foreign DNA, including antimicrobial resistance genes. Those *K. pneumoniae* isolates with a CRISPR-Cas system were less likely to carry antibiotic resistance genes than those without this defense system (Montazeri et al., 2024).

4. Conclusion

Considering the studies covered, the search for antimicrobial agents is a dynamic and multifaceted area, with a diverse range of approaches and research sources. From advanced computational techniques to the exploration of natural

extracts and the synthesis of new compounds, each method offers valuable and promising insights for the innovative development of antimicrobial therapies.

The virtual screening of compounds such as tetrahydroxybenzofuran highlights the importance of computational methodologies in identifying potentially therapeutic molecules. Similarly, research into antimicrobial agents of natural orig in, such as essential oils, opens the door to alternative and complementary therapies against resistant bacterial strains.

The discovery of new molecules from sources such as snake venoms and soil microorganisms underline the importance of exploiting biodiversity in the search for bioactive compounds. Similarly, the synthesis of coumarin -N-heterocyclic hybrids and ternary copper complexes demonstrates the potential of medicinal chemistry in the creation of new therapeutic agents.

In addition, the development of innovative technologies, such as metal nanoparticles and antimicrobial photodynamic therapy, opens up new perspectives in the fight against bacterial infections, offering effective and specific approaches.

The clinical evaluation of the intravesical use of bacteriophages in patients with chronic recurrent cystitis represents a significant advance in the therapeutic application of antimicrobial agents, highlighting the importance of translational rese arch in transforming scientific discoveries into tangible benefits for human health. Pharmaceutical innovations involving antimicrobial compounds derived from the microbiome and antimicrobials derived from the CRISPR system are also promising biological tools for improving drugs against multidrug-resistant bacteria.

In short, the combination of diverse approaches and collaboration between different scientific fields are essential to address the growing challenge of antimicrobial resistance and ensure the development of effective therapies against bacterial infections.

Conflict of Interests

The authors declare that there is no conflict of interest.

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