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NEW ALTERNATIVES FOR REPLACING THE USE OF ANTIBIOTICS AND COMBATING ANTIBIOTIC RESISTANCE: A REVIEW

NOI ALTERNATIVE PENTRU ÎNLOCUIREA UTILIZĂRII ANTIBIOTICELOR ȘI COMBATEREA ANTIBIOREZISTENȚEI: RECENZIE

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ABSTRACT | REZUMAT

Antibiotic resistance has become one of the most serious public health challenges in recent decades, with major implications for the treatment of bacterial infections. The mechanisms by which bacteria develop resistance are varied and include genetic mutations, the transfer of resistance genes between bacteria, and the formation of biofilms, which protect bacteria from the action of antibiotics. Also, the use of antibiotics in veterinary medicine and food products contributes to the selection of bacterial pressure, increasing the risk of resistant infections. Thus, research into new therapeutic alternatives is essential, although antibiotics have been a fundamental pillar of modern medicine. It is therefore crucial to explore and develop alternatives that not only complement but also replace the use of traditional antibiotics. This article aims to review the latest advances in various emerging strategies for combating antibiotic resistance.

Keywords: antimicrobial resistance, antimicrobial peptides, antibodies, bacteriophage, probiotics

Antibiorezistența a devenit una dintre cele mai grave provocări ale sănătății publice în ultimele decenii, având implicații majore asupra tratamentului infecțiilor bacteriene. Mecanismele prin care bacteriile dezvoltă rezistență sunt variate și includ mutații genetice, transferul de gene de rezistență între bacterii și formarea biofilmelor, care protejează bacteriile de acțiunea antibioticelor. De asemenea, utilizarea antibioticelor în medicina veterinară și în produsele alimentare contribuie la selecția presiunii bacteriene, sporind riscul de infecții rezistente. Astfel, cercetarea de noi alternative terapeutice este esențială, deși antibioticele au fost un pilon fundamental al medicinei moderne. Prin urmare, este crucial să explorăm și să dezvoltăm alternative care nu doar să completeze, ci să și înlocuiască utilizarea antibioticelor tradiționale. Acest articol își propune să examineze cele mai recente progrese în diverse strategii emergente pentru combaterea antibiorezistenței.

Cuvinte cheie: antibiorezistență, peptide antimicobiene, anticorpi, bacteriofagi, probiotice

Antimicrobial resistance (AMR) is a major public health concern worldwide (42, 54). Infections caused by antibiotic-resistant pathogens negatively affect human and animal health, as they increase the risk of treatment failure and lead to more severe disease cases (2, 14, 18, 20). In recent decades, the misuse of antibiotics, not only in humans but also in animals used for food production (meat, milk, eggs), has led to the emergence and dissemination of antibiotic-resistant bacteria.

Among the causes that have contributed to the development of antimicrobial-resistant microorganisms are the use of subtherapeutic doses of antibiotics in food-producing animals as growth promoters and therapeutic doses for controlling and treating infectious diseases (23, 24).

The transmission of resistant bacteria from food-producing animals to humans through direct contact, handling, or consumption of their products poses a substantial threat to human health (1, 12, 43). Diseases caused by antibiotic resistance currently result in approximately 1.2 million deaths worldwide (37). However, if no measures are taken to control the spread of antibiotic resistance, the estimated number of deaths could rise to 10 million, with an economic loss exceeding 100 trillion dollars by 2050 (36, 39). In the United States, over two million infections with antibiotic-resistant bacteria occur annually, with economic losses of approximately 20 billion dollars (39).

Special attention is also given to foodborne illnesses caused by *Campylobacter, Salmonella, E. coli O 157, Listeria monocytogenes, Staphylococcus aureus,* and *Clostridium perfringens*, as they can affect one in six people each year, leading to approximately 128,000 hospitalisations and 3,000 deaths, with costs amounting to around 90 billion dollars (5, 47). Many of these pathogens are included in the global priority pathogens list of antibiotic-resistant bacteria provided by the National Institutes of Health (NIH) and the World Health Organisation (WHO) (38, 55). Therefore, there is a critical need to control AMR pathogens (35).

This article aims to highlight new non-antibiotic approaches that can be used to reduce antimicrobial use and, consequently, cases of antibiotic resistance.

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COMBINED THERAPY WITH DUAL ANTIMICROBIAL AGENTS AND DRUG-ADJUVANT COMBINATIONS

Bacterial resistance has developed for nearly all available antibiotics, often due to prolonged drug exposure (8). Therefore, selecting antibiotics with optimal pharmacokinetics that enable rapid and efficient delivery to the target site is essential. When such antibiotics are unavailable, alternative strategies are necessary. One of these strategies involves combining two or more antibiotics to leverage a synergistic effect, increasing bacterial susceptibility to treatment (28). In dual antimicrobial therapy, there are three main mechanisms:

1. Inhibition of the same target through different pathways;
2. Targeting different locations within single pathway;
3. Acting on the same pathway and target (40).

A compelling example is the RIPE regimen (Rifampin, Isoniazid, Pyrazinamide, Ethambutol) used against *Mycobacterium tuberculosis*, where four drugs act through distinct mechanisms:

- Rifampin disrupts RNA polymerase;
- Isoniazid blocks the synthesis of fatty acids in the cell wall;
- The exact mechanism of pyrazinamide remains unknown;
- While ethambutol inhibits key enzymes in the cell wall synthesis process.

This approach highlights how targeting multiple pathways can limit bacterial resistance (10, 51). Another example, Bactrim (trimethoprim and sulfamethoxazole), targets different steps in the folic acid synthesis pathway, enhancing efficiency. Synercid combines quinupristin and dalfopristin, both binding the 50S ribosomal subunit, with their combined bactericidal activity significantly surpassing that of each component alone (10, 26). Drug-adjuvant combinations also combat antibiotic resistance. Adjuvants enhance the effectiveness of an antibiotic by directly counteracting resistance mechanisms, inhibiting efflux pumps, or disrupting bacterial signalling (28). For instance, Augmentin combines amoxicillin with clavulanic acid to counteract β-lactamase enzymes, enhancing amoxicillin's potency against resistant bacteria. However, not all β-lactamases are susceptible to this inhibition, leading to the development of advanced inhibitors like BLI-489 and LK-157, effective against bacteria with a broad spectrum of β-lactamases (7). Avibactam, an adjuvant to ceftazidime, helps suppress AmpC β-lactamase in Pseudomonas aeruginosa, increasing efficacy from 65% to 94% when combined with ceftazidime (31, 36). While dual therapies and drug-adjuvant combinations expand therapeutic options and efficiency, they may increase the risk of side effects and drug interactions (29).

ANTIMICROBIAL PEPTIDES (AMPss)

As antibiotic resistance escalates, antimicrobial peptides (AMPs) offer a promising alternative. AMPs, positively charged and essential for immune defence across a wide range of organisms, exhibit broad-spectrum activity against bacteria, viruses, and fungi (6, 8, 30). Their mechanism of action, which targets bacterial cell membranes, rarely leads to resistance, making them valuable in therapy. Many AMPs, such as gramicidin, polymyxins, and daptomycin, are FDA-approved for antibacterial use, and their structural diversity supports various antibacterial mechanisms (44, 46). AMPs bind to bacterial cell wall components, such as polysaccharides in Gram-negative bacteria and lipoteichoic acid in Gram-positive bacteria, damaging the membrane and leading to cell death (8, 18, 34). Their versatility also allows for easy modifications to combat emerging resistance, broadening their clinical applicability (26). AMP-based drugs such as Cubicin, Oritavancin, Dalbavancin, and Telavancin, used against various resistant bacteria, highlight the therapeutic efficacy of AMPs in infections (31).

MONOCLONAL ANTIBODIES (MABs)

Monoclonal antibodies (MABs), produced by B cells, are known for their precision and minimal side effects. Traditionally used in cancer and autoimmune disease treatments, MABs have recently gained attention for bacterial infections (32). FDA-approved MABs such as Bezlotoxumab, Raxibacumab, and Obiltoxaximab have shown results in treating bacterial toxins in diseases like *Clostridium difficile* infections and anthrax. For example, Bezlotoxumab reduces reinfection rates in patients with *C. difficile* by neutralising enterotoxin B (4, 49). While the clinical applications of these MABs are under development, they hold real potential in adjunctive or prophylactic roles, especially in high-risk patients (56).

BACTERIOPHAGES

Bacteriophages, viruses that target bacteria, have re-emerged as an alternative therapy for multidrug-resistant (MDR) infections (16, 45, 52). Phages can be used to deliver antimicrobial agents or disrupt bacterial metabolism (7). Lytic phages, which reproduce inside bacteria and subsequently lyse them, produce enzymes such as virolysins to break down bacterial cell walls (53). Current research focuses on optimising phage therapy for clinical use, particularly against MDR bacteria. A promising area includes phage-derived endolysins, which specifically degrade bacterial cell walls, as demonstrated in studies like that of Wu et al., showing improved survival in sepsis cases involving *Acinetobacter baumannii* (55). Drugs such as SAL 200 and Exebacase, derived from endolysins, have entered clinical trials and shown efficacy against bacteria like *Staphylococcus aureus* (13, 22, 56).

PROBIOTICS

Probiotics are beneficial microorganisms that,

when administered in sufficient quantities, provide health benefits (9). These microorganisms, often classified into genera such as *Bifidobacterium, Lactobacillus, Saccharomyces,* or *Bacillus,* exhibit antimicrobial effects through various mechanisms: they produce bacteriocins with antibacterial properties, strengthen mucosal barriers to block bacterial adhesion and intestinal entry, eliminate toxins, correct imbalances in gut microbiota, and modulate immune responses by stimulating protective cytokines and reducing inflammatory cytokines (17, 50).

Over the last century, numerous studies have demonstrated the positive impacts of probiotics, from directly inhibiting pathogens to improving host immune function, thereby influencing pathogen survival. Research by Piewngam et al. explored the potential of *Bacillus* strains as probiotic therapy against *Staphylococcus aureus*. In their study, *Bacillus subtilis* was found to release lipopeptides called fengycins, which inhibit *S. aureus* by disrupting its quorum-sensing agr system, essential for its survival (39). In a separate study, Lee et al. investigated the bacteriocin HW01 from *Pediococcus acidilactici* and found it effective against Pseudomonas aeruginosa biofilm formation, reducing motility, virulence factor production, and biofilm formation, though it did not affect free bacterial cells (27). Further research involving 140 *Lactobacillus* strains identified 13 capable of preventing K*lebsiella pneumoniae* biofilms, with one strain, *Lactobacillus plantarum* CIRM653, even breaking down existing biofilms. In studies conducted by Vieira et al., *Bifidobacterium longum 5* has been shown, to reduce the severity of *K. pneumoniae* infection in mice, reducing mortality by 50% through a mechanism involving activation of the immune response and reduction of bacterial load in the lungs (51). Additionally, Sikorska and Smoragiewicz demonstrated that bacteriocins from various *Lactobacillus* strains prevented MRSA biofilm formation (47). These studies underscore the efficacy of probiotic bacteriocins in combating bacterial pathogens. While laboratory and clinical model results suggest that probiotics could be viable antibiotic alternatives, further research is needed to refine dosages and ensure cellular viability in treatment (41).

NANOMATERIALS AND NANOPARTICLES

Recent research highlights the utility of nanomaterials, including nanoparticles (NPs) and nanodrug carriers, in treating infections, particularly those caused by multidrug-resistant (MDR) pathogens. The lethal impact of NPs on microbial cells is achieved through:

1. Damaging the cell membrane and inhibiting permeability regulation due to direct attachment to the bacterial cell wall;
2. Blocking electron transport and oxidative phosphorylation;
3. Altering bacterial metabolism by interfering with enzymes, DNA, and ribosomes, leading to protein and enzyme deactivation, prevention of DNA replication, and alteration of gene expression levels:
4. Inhibiting biofilm development;
5. Inducing oxidative stress through the release of reactive oxygen species (ROS); and
6. Triggering host immune responses (19) (Fig. 1).

Nanoparticles can enhance the efficacy of existing antibiotics or offer unique bactericidal effects independent of antibiotics. In the former case, nanomaterials can transport antibiotics into bacterial cells, bypassing cellular barriers to deliver the drugs directly into the bacterial cytoplasm. This controlled release reduces the required doses, minimises side effects, and optimises the drug's pharmacokinetics and cost efficiency (15, 17). Research has investigated optimal NP-antibiotic combinations against MDR microorganisms. NP interactions are either physical (e.g., hydrophobic or electrostatic) or chemical, such as the conjugation of functionalised nanoparticles (e.g., hydrogen, aldehyde, or sulfhydryl groups) with antibiotics (21). In their independent bactericidal role, nanomaterials typically have positively charged polymer coatings that electrostatically interact with the negatively charged bacterial cell wall, disrupting the membrane and preventing biofilm formation. Fused metal nanoparticles (e.g., silver, gold, copper) can physically damage cell walls, induce oxidative species, and disrupt bacterial structures, effectively reducing cell viability (56). Studies on nanoparticle-antibiotic conjugates demonstrate promising antimicrobial efficiency against MDR bacteria. For example, gold nanoparticles inhibited drug-resistant strains such as *Staphylococcus aureus, Escherichia coli,* and *Vibrio cholerae* (26). Zinc oxide nanoparticles showed similar success against *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis,* and *Staphylococcus aureus*, while additional studies demonstrated the antimicrobial properties of titanium dioxide against *S. aureus* and *E. coli* (28). These findings illustrate that nanoparticle-based agents are effective against MDR pathogens, offering high precision in targeting antibiotics and reducing dosage requirements (21).

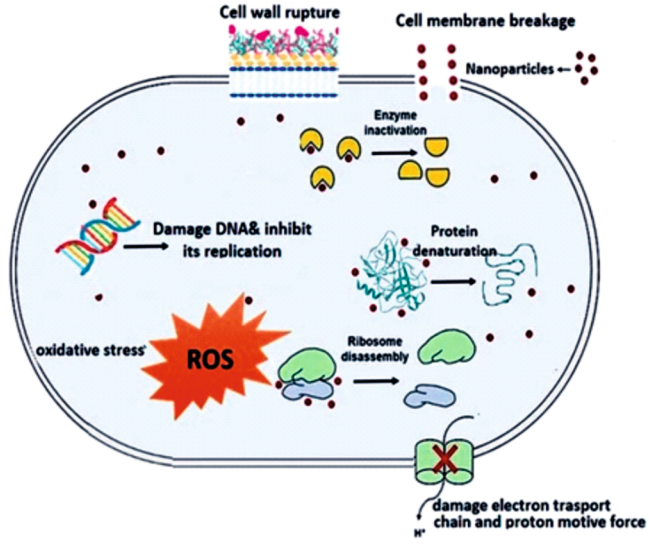

Fig. 1. The mechanism of action of Nps on bacterial cells (19)

CANNABINOIDS

In the search for novel antibiotic alternatives, the antimicrobial properties of cannabinoids have reemerged as viable therapeutic options. Recognised as early as the mid-20th century, the antimicrobial properties of cannabinoids derived from cannabis plants are being re-evaluated in light of the ongoing antibiotic crisis and the historical success of natural products in drug development (11, 25). Recent studies have explored the antimicrobial potential of both synthetic and plant-derived cannabinoids, which interact with CB1 and CB2 receptors (46).

Research on exogenous cannabinoids, such as tetrahydrocannabinol (THC), demonstrates their effectiveness against pathogens, including *Listeria monocytogenes* and *Staphylococcus aureus* (48). Cannabidiol (CBD), another cannabinoid, has exhibited both bacteriostatic and bactericidal effects against pathogens such as *methicillin-susceptible and resistant Staphylococcus aureus and Streptococcus* (3, 25). Luz-Veiga et al. also found that CBD inhibited *Pseudomonas aeruginosa* and *Escherichia coli* (33).

Cannabinoids can inhibit biofilm formation, minimise metabolic activity within biofilms, and prevent bacterial survival in the biofilm environment, making them effective against MDR pathogens. Additionally, cannabinoids show synergistic potential with antibiotics; for instance, CBD combined with ampicillin demonstrated enhanced eradication of MRSA biofilms and amplified the effects of antibiotics like erythromycin, vancomycin, and colistin against pathogens such as *E. coli* and *MRSA* (3). Although cannabinoids have also shown potential in combating fungal pathogens, further research is needed to fully understand their antifungal applications (11). Cannabinoids show promise as broad-spectrum antimicrobial agents.

CONCLUSIONS

New therapeutic strategies, such as antimicrobial peptides, monoclonal antibodies, bacteriophages, and nanoparticles, are proving their utility as alternatives to traditional antibiotics in combating resistant infections. Food fraud and the presence of antibiotic residues in food products due to inadequate regulations complicate global food safety, as different countries struggle to standardise and monitor antibiotic levels in agriculture. New treatments, including combination therapies and drug–adjuvant associations, have proven effective against certain resistant bacteria by combining two antibiotics or enhancing the efficacy of an antibiotic through adjuvants.

Antimicrobial peptides (AMPs), monoclonal antibodies, bacteriophages, and nanoparticles represent viable alternatives to replace the use of antibiotics. Although studies conducted so far certify their effectiveness in infections, further research on large samples is needed to fully understand their therapeutic potential.

Cannabinoids and probiotics are being explored for their antimicrobial properties and potential to treat resistant bacterial infections, offering an alternative way to combat antibiotic resistance while maintaining health.

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