

Emerging frontier approaches for the treatment of antimicrobial resistance



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1. Introduction

Antimicrobial resistance (AMR) represents a far-reaching and substantial danger to public health. The emergence of AMR leads to complications in treating infections, contributing to a rise in mortality rates. The broad occurrence of AMR, along with the excessive utilization of antimicrobial drugs, creates a substantial challenge for the restoration of human and animal populations. Urgent attention is required to devise innovative treatments and therapeutics that can effectively address the emergence and spread of resistant strains. Research indicates that AMR gene development and dissemination are primarily linked to overreliance on health drugs, improper use in veterinary medicine, agricultural practices, and vaccine hesitancy. Thankfully, promising approaches have surfaced to combat resistance effectively. These methods encompass antiviral therapy, passive immunization, antimicrobial peptides, vaccines, phage therapy, as well as botanical and liposomal nanoparticles. Each of these innovative techniques aims to alleviate the strain on antibacterial drugs, representing cutting-edge approaches in the field. This review article focuses on the importance of employing these advanced therapeutics to combat AMR. To effectively tackle AMR, a comprehensive strategy is essential. This involves harnessing current cutting-edge therapeutics, advancing antimicrobial susceptibility testing and diagnostic techniques, and ensuring prompt clinical responses to contain AMR's spread. Furthermore, there is a need for research to explore new pharmacodynamic properties of antimicrobials and develop methods to maintain host homeostasis after AMR-caused infections. Addressing AMR calls for a multifaceted approach, involving the appropriate use of advanced antimicrobial drugs in conjunction with diverse cutting-edge therapeutics. In summary, AMR represents a pressing global health challenge. However, by employing current state-of-the-art therapeutics, advancing diagnostic and treatment methods, and continuously conducting research, we can aspire to reduce its impact and safeguard the health of both human and animal populations.

2. New antibiotic discovery

2.1. Genome-scale screening technique

Genome mining uncovers new antibiotics through biosynthetic gene clusters (BGC). Tools like anti-SMASH and PRIS identify BGCs. Strategies include ribosome engineering, CRISPR-Cas9, and small molecule elicitor use. Examples include lactocillin, halophile, taromycin A, and piperidine A/B (1-4).

2.2. Semisynthetic engineering

An innovative strategy is employed to enhance existing glycopeptide and lipopeptide antibiotics, resulting in the formation of improved drugs with broader activity (PK) (5). This semisynthetic engineering process utilizes both enzymatic and chemical methods to synthesize novel medications (6). Notably, three vancomycin derivatives, namely telavancin, dalbavancin, and oritavancin, have been successfully produced using this approach (7). Examples of successful applications of this method encompass azithromycin and clarithromycin (erythromycin derivatives), minocycline, doxycycline (tetracycline derivatives), rifampicin, and tigecycline (rifamycin derivatives) (6).

2.3. Innovative retro-biosynthetic algorithm technique

An innovative retro-biosynthetic algorithm proves to be a valuable tool for new antibiotics (8). The compounds Griselimycins and telomycins show promising interactions with specific proteins (9). Computational strategies, such as the hit compound technique, play a key role in the identification of antimicrobial compounds. The open-access facility CO-ADD significantly contributes to the discovery of antimicrobial drugs (10). Notably, initiatives like CARB-X and IMIENABLE actively support the ongoing fight against AMR (11). Prioritizing the challenges posed by AMR and seeking effective broad-spectrum formulations remain crucial goals. Researchers are actively exploring alternative methods to combat AMR through innovative discoveries.

2.4. Intestinal microbiota

The intestinal microbiota serves as a battleground for tackling multidrug-resistant bacteria effectively. Utilizing the intestinal microbiota presents a promising approach in this endeavour. Two potential strategies are preserving the microbiota and employing faecal microbial therapy (FMT). FMT involves the transplantation of beneficial probiotics to combat pathogens (12).

2.5. Antibiotic adjuvants

Preserving antibiotics is vital amid the search for new ones. Adjuvants can block resistance and boost current drugs, improving outcomes. Combining aminoglycoside and penicillin shows synergy against enterococcal infections. Adjuvants enhance drug efficacy when used together, providing a promising approach to fight resistance. Research explores new adjuvants like polyamino-isoprenyl derivatives, farnesyl spermine, and pegylated azelaic acid (13-15).

3. Novel therapy approaches for the treatment of antimicrobial resistance

3.1. Monoclonal antibodies

Monoclonal antibodies (mAb) are considered potential agents to kill bacteria. Humanized monoclonal antibodies (mAbs) are created to reduce immunogenicity. These specialized mAbs function by neutralizing pathogens through complement-mediated responses, eliminating exotoxins, inducing the production of antivirulent antibodies, or directly targeting and killing bacteria. Clinical trials have demonstrated the effectiveness of mAbs, either used alone or in combination with antibiotics, in treating various diseases (16-18).

3.2. Quorum-sensing inhibitors

Antivirulent therapy uses QS inhibitors to deplete bacterial toxicities without hindering pathogen growth (19). QS inhibitors disrupt cell-to-cell communication, reducing adaptive immunity and pathogenicity (20, 21). Quorum quenching is carried out through sequestration, competition, and signal destruction.

3.3. Vaccination

Vaccines play a significant role in addressing AMR. They reduce infection rates caused by difficult-to-treat bacteria and lower the need for antibiotics, decreasing selective pressure for resistance development (22). Specific vaccines have effectively eliminated certain pathogens and reduced antibiotic usage, preventing resistance evolution (23). Pneumococcal and Hib conjugate vaccines have shown success in reducing MDR infections (24, 25). Respiratory virus vaccines combat resistant influenza, curbing antibiotic use for flu treatment (27-28). Vaccination-based strategies offer the potential in combating AMR.

3.4. Antimicrobial peptides

Antimicrobial peptides (AMPs) are small, cationic molecules produced by fungi, bacteria, plants, and vertebrates, including humans (29). They display broad-spectrum activities against various microorganisms, making them promising therapeutic agents (30). AMPs differ in structure, consisting of ribosomal proteins or nonribosomal compounds (31). Their mechanism of action involves membrane disruption, enzyme inhibition, cell division disruption, macromolecular synthesis inhibition, or autolysis induction.

3.5. Algae-mediated treatment

Domestic and agricultural wastewaters play a significant role in the emergence of antibiotic-resistant bacteria and genes due to the incredible use of antibiotics in human and animal health (32). Antibiotic-resistant bacteria and genes are commonly found in wastewater treatment plants (WWTPs) due to the presence of domestic wastewater. Conventional treatment processes like preliminary, primary, and secondary treatments are used to remove traditional pollutants, but specific methods like UV254, ozonation, and chlorination have been investigated to degrade antibiotic-resistant genes (33-36). Microalgae, particularly green algae, have shown potential in efficiently removing contaminants from wastewater and are important for small- to medium-scale municipal wastewater treatment (37). Although green algae have been used for antibiotic treatment, their impact on antibiotic-resistant bacteria and nontarget organisms needs further exploration (38). Eco-friendly biotechnology must be efficient in waste removal while having a low environmental impact. Selective pressure on antibiotic-resistant bacteria by green algae and potential negative effects on nontarget organisms must be examined. The impact of the target antibiotics and effluent after algal treatment was also assessed using rotifers (38, 39). Studies have reported successful algae-mediated treatments for the removal of antibiotic-resistant genes. Reductions in plasmid transformation and induced ciprofloxacin resistance have been observed with freshwater algae treatment (40, 41). Comparisons between algal-based systems and conventional wastewater treatment have shown a greater reduction in antibiotic-resistant bacteria in the former (42). However, further research is needed to fully understand the potential and environmental implications of using green algae in wastewater treatment.

3.6. Bacteriophage therapy

Bacteriophages act as a biocontrol to combat AMR, and their interest has been renewed due to antibiotic resistance (43). Phage therapy utilizes specific lytic bacteriophages as another option to antibiotics, targeting pathogen receptors and causing cell lysis (44). Live phages effectively treat infectious strains and show promise in managing respiratory and systemic diseases (45). Phage therapy offers advantages over antibiotics, including targeted killing of antibiotic-resistant and MDR organisms with minimal side effects on normal flora (46). However, efforts are required for bacteriophage isolation and genetic modifications. Genetically engineered

phages were created to combat E. coli by multiplying and killing the bacteria without causing cell lysis. This approach minimizes inflammatory effects, unlike antibiotics and live lytic phages, which release more endotoxin (47). However, phage therapy cannot fully replace antibiotics due to intrinsic limitations. It is not effective against deeply intracellular pathogens and cannot be administered intravenously due to host immune responses. Therefore, phage therapy is more suitable for easily accessible infections such as pneumonia and wounds. Additionally, there are challenges related to controlling and storing phages, and a proper regulatory framework is needed (48). To address specificity issues, phage cocktails are being developed, combining multiple phages to target various strains in a single infection (49). This allows for enhanced efficacy as one phage can compensate for the inhibition of another. Researchers are also exploring the use of phage endolysins, such as N-RephasinSAL200, as another option to living phages for targeting bacteria (50). Phage therapy has shown promise in combating MDR urinary tract infections by not only lysing bacteria but also inhibiting biofilm formation through polysaccharide depolymerase induction (51).

3.7. Antimicrobial resistance and COVID-19 pandemic

The COVID-19 pandemic has disrupted antibiotic stewardship efforts and led to increased antibiotic usage worldwide. The use of azithromycin and hydrochloroquinone has surged, and hospital admissions have risen, increasing the risk of hospital infections. A study in India showed a 40% increase in antimicrobial-resistant bacterial pathogens due to excessive antibiotic use. This can lead to the transmission of multi-drug-resistant strains. Biocidal agents used outside hospitals may also promote drug-resistant strains. Healthcare workers need to be vigilant, and medical devices should be appropriately maintained to prevent healthcare-related infections (52).

3.8. Nanoparticles

Nanotechnology shows promise in combating antimicrobial resistance (AMR) by using nanoparticles (NPs) with bactericidal activity and acting as drug carriers for antibiotics and AMPs. Metallic NPs damage bacterial membranes and proteins, while functionalized NPs enhance drug efficiency. CAL02 liposomal NPs are studied for severe pneumococcal pneumonia. Nanocarriers deliver inhibitors to target cancer cell resistance. Hydrogels with antibiotics and NPs are explored for AMR control, needing further study (53-56).

3.9. Phytochemicals

Combination therapy with botanical and nutritional approaches, using phytochemicals and plant extracts, is effective against infections and can combat resistance development in microbes. Plant secondary metabolites disrupt microbes through various strategies, making them valuable for enhancing immune response and combating antibiotic resistance (57-59).

4. Conclusions

The long-term outlook for antimicrobial resistance (AMR) is unpredictable. Reflecting on the early days of antibiotic discovery, scientists are both impressed by the positive impact of drug development and concerned about the rise of resistance. A French microbiologist once predicted that certain bacteria would always remain sensitive to penicillin, but now we are facing difficulties in treating common infections due to AMR.

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