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Mini Review

Physicochemical Methods as an Alternative Approach to Overcome Antimicrobial Resistance

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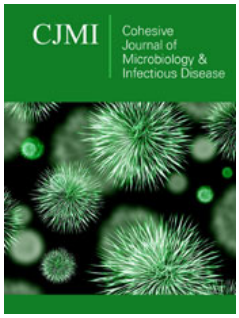

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Abstract

Antibiotic resistance-or, to put it more broadly, Antimicrobial Resistance, or AMR-keeps evolving and extending past all boundaries. Consequently, treating infectious diseases has grown more difficult or even unfeasible, leading to higher mortality and morbidity. Despite the standard antimicrobial therapy's failure, no new class of antibiotics has been developed in the last few decades. As a result, a number of cutting-edge substitute strategies for dealing with these drug-resistant pathogenic microbes have been discovered. The aim of this review is to compile and evaluate the various physio-chemical approaches that are being used or suggested as possible substitutes for conventional antibiotics. These substitute techniques might influence how multi-drug resistant bacteria are treated in clinical settings including humans.

Keywords: Bacteria; Antimicrobial; Antibiotics; Antimicrobial resistance; Multi-drug resistant

Introduction

For many years, the goal of developing and commercializing various antimicrobials has been the same: to treat and eradicate mild to serious infectious disease. Numerous antimicrobials, including several improvements on the revolutionary antibiotic penicillin itself, were discovered as a result of the coincidental discovery of penicillin in the late 1920s. New antiviral medications have also been developed as a result of research to treat diseases like AIDS and other conditions that were previously incurable. Antifungal (sometimes called anti-mycotic) and anti-parasitic drugs have also become essential weapons in the fight against infections. The development of Antimicrobial Resistance (AMR) in response to antimicrobials has significantly reduced the usefulness of these drugs, despite the fact that they have been essential in enhancing our health and lengthening our lives. The main effect of AMR is that infections become more challenging to treat and dramatically raise the risk of disease transmission, serious illness, and death when antimicrobials lose their effectiveness. Notably, AMR is present in all forms and dimensions. Many organisms are becoming Multi-Drug Resistant (MDR), making treatment even more difficult. However, organisms that are pan- and extensively Drug-Resistant (XDR and PDR), which are nearly hard to treat with conventional medicines, are of grave concern. Antibiotics and other antimicrobial drugs are getting less and less effective due to Antimicrobial Resistance (AMR) and treating infections has grown more challenging or even unfeasible, according to official WHO reports [1].

AMR has a major impact on the pharmaco-economic costs. For instance, the Infectious Disease Society of America (IDSA) released a study detailing the expensive burden of Antimicrobial Resistance (AMR) among Medicare beneficiaries in the United States. The study revealed that, in 2017, infections resulting from bacteria resistant to different antibiotics cost the country $1.9 billion in medical expenses, and 10,000 deaths among beneficiaries. Prior to this, the 2014 UK Review on Antimicrobial Resistance, which was chaired by Lord Jim

O'Neill, revealed that 700,000 people die each year from resistant infections. If proactive measures are not taken to stop the rise in drug resistance, this number is predicted to rise to 10 million deaths annually by 2050, at a cost of $100 trillion in lost economic output [2]. According to the first-ever complete evaluation of the worldwide burden of Antimicrobial Resistance (AMR), which was based on a statistical analysis of the data available in 2019 from 204 countries, 1.27 million of the 4.95 million deaths linked to bacterial AMR are thought to be caused by AMR. Resistance-related AMR fatalities were expected to be lowest in Australasia and higher in sub-Saharan Africa [3].

AMR is a worldwide public health concern that lurks across national borders and poses a silent threat to people in high-, medium-, and low-risk countries. There will be an impact on the environment, food production, poverty, health security, and the UN Sustainable Development Goals (SDGs), which highlights the need for a multisectoral One Health plan to reduce AMR [4]. Furthermore, the effects of AMR bacteria spreading from food animals may have a significant influence on public health as well as animal health in a "One Health" setting [5]. New approaches are being developed to prevent and treat MDR, XDR, and PDR infections in light of the impact AMR bacteria are having on global health and the requirement for novel antibiotics. In fact, even so-called "antibiotics of last resort" are starting to lose their efficacy in clinical settings [6]. The goal of this review is to thoroughly discuss the physicochemical methods employed to overcome AMR.

Physicochemical Methods

Atmospheric Pressure Non-Thermal Plasma (APNTP)

A relatively new method for assessing the antibacterial properties of antimicrobial drugs is called non-thermal Atmospheric Pressure Plasma (ANTP) [7]. The effectiveness of the APNTP approach was demonstrated by the inactivation of a microbe in the in vitro experiments. Given that it is relatively easy to use, operates economically, and has just a few, moderate side effects that are currently known, it offers a promising alternative to existing antibiotic regimens [8]. Additionally, Ermolaeva et al. [9] evaluated the field of plasma treatment for wound healing, root canal therapy in dentistry, air sterilization, and bacterial deactivation, especially in circumstances where traditional antibiotics typically fall short [9]. While the exact mechanisms underlying APNTP-mediated bacterial deactivation remain unclear, it seems to function by generating products such as electrically charged particles in a plasma gas phase, Ultraviolet (UV) radiation, and reactive nitrogen and oxygen species [10]. Reactive oxygen species believed to be implicated in the killing of bacteria include peroxide, ozone, atomic oxygen, superoxide, singlet oxygen, and hydroxyl radicals [11]. The oxidative injury to the nucleic acids, lipid peroxidation and UV radiation caused by ROS (mostly in fatty acids near the cell surface), and the chemical alteration and degradation of proteins (mainly by hydroxyl (-OH) radicals) are the main mechanisms by which the aforementioned techniques work. Other studies have shown that ROS is most likely the cause of bacterial cell death [12]. The physical harm to the cells is caused by charged particles' electrostatic forces, namely electrostatic disruption. Furthermore, direct exposure to electrically charged particles during electroporation might cause physical injury to the cells [13]. It was shown that Gram-negative bacteria were considerably more vulnerable to APNTP than Gram-positive bacteria, indicating that APNTP-induced damage to cell walls and membranes may play an important part. Cold plasma may have been able to render clinically relevant bacteria inactive. It was shown that APNTP inhibited microbial growth in suspension and biofilms. It was also demonstrated utilizing the cold plasma approach that Pseudomonas aeruginosa biofilm may be inactivated in vitro. One advantage of APNTP might be its capacity to inactivate bacteria without posing a threat to mammalian cells. Although efforts to determine the appropriate dose of ANTP have not yet been made, it is possible to combine ANTP with antibiotic therapy [11,14].

Sonodynamic antimicrobial chemotherapy

Utilizing the combination of ultrasonic waves and a sonosensitizer, which work synergistically, Sonodynamic Antimicrobial Chemotherapy (SACT) essentially destroys bacteria by producing an inaudible sound at a frequency of less than 20kHz [15,16]. In SACT, the target location is sensitized using a non-toxic sonosensitizer, relatively low-intensity ultrasound, and molecular oxygen. Micro-bubbles are produced when the target cells and ultrasonic wave contact with molecular oxygen [14]. It has been shown that using ultrasounds in addition to conventional antibiotics, such as ciprofloxacin and levofloxacin, can inactivate Escherichia coli due to enhanced absorption and the production of cytotoxic ROS [17]. Despite the fact that ultrasound is known to improve medication absorption within bacterial cells [18]. Additionally, due to its ability to enter thick tissues and its good properties for localized targeting, SACT is fundamentally acknowledged as a better therapy with fewer adverse effects [14]. The advantage of ultrasonography from a therapeutic standpoint is its remarkable ability to penetrate tissue with minimal energy loss. This is a desired quality, and it must be thoroughly evaluated [19]. Both organic and inorganic desensitizers are recognized. However, many inorganic sonosensitizers have better physicochemical properties, but their non-biodegradation and potential biosafety risks prohibit their use in clinical settings. On the other hand, the advantages of organic sonosensitizers' simple metabolism and distinct structure make them appropriate for therapeutic use [20].

Photoinactivation

Bacterial cell death is induced by visible light, a photosensitizer-chromophore, and ROS generated from molecular oxygen. In essence, photodynamic antimicrobial chemotherapy, often known as photoinactivation, or PACT, is a possible technique for eliminating harmful microbes. It has been demonstrated that PACT affects bacterial strains that are sensitive to antibiotics, as well as those that are Gram-positive and Gram-negative. This strategy has generated a great deal of interest in science as an alternative to prevent AMR. Some significant advantages of PACT over conventional antibiotics in medical applications are its localized wound administration, low toxicity, resistance, and adverse effect rates. Unlike antibiotics,

Photodynamic Inactivation (PDI) at sub-inhibitory dosages has not resulted in a rise in antibiotic or photodynamic resistance [14,21]. To become a competitive alternative to antimicrobial treatment, PACT underwent several developments. For example, the antimicrobial deactivation caused by the attachment of porphyrins to nanoparticles. Using the small size of porphyrins and porphyrin-nanoparticle conjugates, the photosensitizers can self-assemble to attach to the bacterial cell wall, resulting in cell death. Improving PACT's application in dermatology and infectious disease prevention is crucial, especially when it comes to treating acne and other skin infections in general. Oyim et al. [21] have noted that the diversity of bacteria poses a challenge to the possible application of PACT in the treatment of infections-related diseases [21].

More research on the systemic approach is still required to fully evaluate the PACT systems' in vivo stability and treatment strategy, even if the topical/local technique for animal model evaluations has been carefully examined. It is essential to fully understand and modify their mode of action in order to maximize their sensitivity and selectivity. In particular, most of the studies left out information about toxicity; hence, future research has to incorporate toxicity studies. Toxicological characteristic assessment will be essential in building confidence in PACT technique prior to submitting the final products for regulatory recommendations. The inability of light to penetrate deeply into mammalian cells severely limits the PACT as well, mostly due to competition with endogenous colors and pigments like melanin with the sensitizer for light absorption. This is a particular issue in cases of localized infections in which bruising or inflammation may cause the injury site to become noticeably discolored, or in ethnic cultures where skin is highly pigmented by nature. Permitted sensitizers are now able to absorb electromagnetic radiation in the visible region of the electromagnetic spectrum, limiting light penetration to a few millimeters and limiting the ability of antibacterial photodynamic therapy to eradicate bacteria located deeper within infected wounds [14,21].

Other physicochemical means

Numerous studies have been conducted on the antibacterial qualities of metals and their oxides. Metal oxide nanoparticles including Ag (Silver), TiO2 (Titanium Oxide), Fe3O4 (Iron Oxide), ZnO (Zinc Oxide), and CuO (Copper Oxide) exhibit very potent antibacterial activities. Most metal oxide nanoparticles exhibit antibacterial properties by releasing Reactive Oxygen Species (ROS), while some are solely advantageous due to their physical composition and metal ion discharge. Following the European Union's (EU) ban on using antibiotics as growth promoters, the use of copper or zinc in aquaculture and food animals was advocated. However, the use of copper or zinc degrades the environment and could accelerate the co-selection that leads to the establishment of antibiotic resistance. In the EU, ZnO cannot be used as a veterinary medicinal product at concentrations higher than 150ppm [14,22].

Conclusion

Antibiotic resistance is a global problem that is continuously expanding and erasing national borders. This is a multi-parameter challenge rather than a single issue. To combat AMR at the local, national, and worldwide levels, diverse cooperation and coordinated actions are needed. In order to shape law, implement it, and provide ongoing updates for dissemination about the distribution and usage of antibiotics for both humans and animals, political commitment may be crucial. Precautions must be made to prevent overusing or misusing antibiotics, and unethical promotion of antibiotics must be avoided. Editing, silencing, and inactivating resistance genes are among the novel targets and tactics that have been sought to increase the efficacy of antibiotics. Importantly, the majority of cutting-edge alternatives do not promote antibiotic resistance. A number of innovative approaches are being examined in an attempt to counteract both established and new resistance.

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