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The Growing Threat of Antibiotic Resistance: Addressing the Urgency

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Authors' contributions

This work was carried out in collaboration among all authors. The conceptualization was done by HSR and HF. The literature and drafting of the manuscript were conducted by BSR, SDZZ, SII, HH and HF. The editing and supervision were performed by HSR and HF. All authors read and approved the final manuscript.

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Short Communication

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ABSTRACT

Antibiotic resistance has become a critical public health issue due to the overuse and misuse of antibiotics. Despite ongoing efforts to develop stronger antibiotics, bacterial resistance continues to evolve, leading to a global crisis. Effective antibiotics are becoming scarce, and diseases that were once treatable are now becoming uncontrollable. There is a need for new solutions to preserve the current antibiotic arsenal and combat bacterial resistance. Narrow-spectrum antibiotics which do not contribute to multidrug resistance could be a solution instead of broad-spectrum antibiotics.
One potential solution is phage therapy, which uses bacteriophages to target specific bacteria without harming healthy cells. Plants are another potential solution because they contain natural antibacterial compounds like polyphenols and alkaloids. Antimicrobial proteins (AMPs) from eukaryotes can also be a good substitute for antibiotics because they do not require a receptor and

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minimize the chance of bacterial resistance. A clinical trial on women with recurrent UTI was performed. The results of which revealed that overall methenamine hippurate is effective in reducing the intake of antibiotics. Whole genome sequencing is a rapidly evolving method through which resistance pathways are identified to tackle resistance. Developing metallophores is an area of great potential and metal complexes are more likely to advance towards becoming a clinically approved replacement to antibiotics. The development of new solutions is critical to prevent the spread of antibiotic-resistant bacteria and ensure that bacterial infections remain treatable.

Keywords: Antibiotic resistance; phage therapy; antimicrobial proteins; phytobiotics.

1. INTRODUCTION

Antibiotics were discovered at a time when severe bacterial infections were only treated with surgical drainage or spontaneous cure, due to which they were also referred to as "wonder drugs [1]. Medications which are used to treat and prevent bacterial infections are termed antibiotics. On the other hand, antibiotic resistance results from a change in bacteria in response to antibiotic use. It causes the evolution of bacteria to a form in which it ceases to react to drugs making the infection severe and causing death [2].

Salvarsan was the first antibiotic deployed in 1910. Human lifespan is increased by 23 years just because of the drastic change that antibiotics brought to modern medicine. When penicillin was discovered in 1928, it started a golden age of discovery of antibiotics from a natural product, which was at its peak during the mid-1950s, but since then, there has been a significant decline in the discovery of antibiotics because of the growth of drug resistance in various human pathogens, which led to the current ongoing crisis of antimicrobial resistance [3].

In 2020, anti-microbial resistance was one of the top ten global health threats facing humanity as stated by WHO [4]. Antimicrobial resistance poses a danger to global public health, causing at least 1.27 million deaths globally and approximately 5 million fatalities in 2019. Each year, more than 2.8 million infections in the US are resistant to antibiotics. As a result, more than 35,000 individuals pass away [5]. Antibiotic resistance is widespread worldwide, indicating that effective antibiotics are running out to treat common diseases such as hospital-acquired infections, urinary tract infections (UTI), sepsis, sexually transmitted infections, and diarrhea [6]. According to the WHO information sheet on antimicrobial resistance, the resistance to ciprofloxacin, an antibiotic for treating UTI, varied from 8.4% to 92.9% and 4.1% to 79.4% for Escherichia coli and Klebsiella pneumoniae, respectively [7].

Bacterial resistance has been evolving for the last 50 years despite efforts by scientists to create stronger antibiotics, largely due to the overuse and misuse of antibiotics. Due to this ongoing crisis, the treatment of various pathogens, including methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococci, is now controversial [8].

According to a recent study, in a Waste Water Treatment Plant (WWTP) a total of 6.4 x 105 copies/mL resistant genes for tetracyline were found in biosolids whereas 6.4 x 103 copies/mL in the efflent. This indicates growing antibiotic resistance in ecological components near WWTPs which could be a serious risk of exposure to the local community [9].

There are three mechanisms through which antibiotic resistance takes place. The first way is using a group of membrane-associated pumping proteins for antibiotics efflux from the bacterial cell. The other way is modifying the target on which the antibiotic acts. This can occur through mutating ribosomal RNAs or such key binding elements or biosynthetic pathways reprogramming, as in the glycopeptide antibiotics resistance case. The third way is the modification of enzymes which targets to destroy antibiotics [10]. There is a dire need for new solutions and discoveries to preserve our current antibiotic armamentarium so we can combat the evolving bacterial resistance [8].

Multiple researches have been carried out to explore practical ways to combat antibiotic resistance. Antimicrobial proteins (AMPs) from eukaryotes can be a good substitute for antibiotics mainly due to their non-receptor mechanism of killing, positive charge and high levels of expressions, particularly in tissues in close contact with the environment such as intestines, skin, urinary tract, lungs, eyes, etc [11]. They are naturally found in all species and can easily be extracted from insects, animals, plants and even fungi where they can be used as effective drugs. Where bacterial AMPs require a receptor, eukaryotic AMPs do not, and thus minimize the chance for bacteria to develop resistance [12].

Another major reason for bacterial resistance is development of broad-spectrum antibiotics where one formula is used to treat a variety of bacteria. Possible solution to this is generation of narrow-spectrum antibiotics which do not contribute to multidrug resistance [4].

Plants are naturally antibacterial because they contain compounds like polyphenols, essential oils, and alkaloids often referred to as phytobiotics, that have an inherent ability to stimulate antimicrobial activities [13]. According to an estimate, there exist more than 30,000 antibacterial substances in plants, making them a viable option to use instead of antibiotics [14]. Apart from denaturing membrane proteins, disintegrating cell membranes or inhibiting bacterial cell division, plant-based derivatives are also important because some of them have the ability to prevent the translation of antibiotic-resistant genes in the bacteria.

For instance, in a recent study, researchers investigated the antibacterial properties of ten medicinal plants of South Africa against five multi-drug resistant bacteria, namely, E. coli, pseudomonas aeruginosa, staphylococcus aureus, klebsiella pnuemoniae, and streptococcus pyogenes. The active extracts of the selected plants showed a 66.34% inhibitory effect on the anti-adhesion of bacteria and a 31.82% inhibitory effect on the biofilm development of bacteria, thus validating their anti-pathogenic potentials [15].

Another similar study tested the effect of using Hydnophytum formicarium tuber and Vatica diospyroides Symington cotyledon, two plant-derived substances, together with antibiotic ampicillin, on bacteria, namely E. coli and Staphylococcus aureus. The results indicated synergy in reducing the growth of bacteria, particularly through their impact on bacterial cell membranes. The effect was seen to be more pronounced in comparison to when these plant extracts were used separately. It was also found through this study that the use of Vatica diospyorides reduces the required concentration of ampicillin by a considerable 8-fold [16].

To further explore the effectiveness of plant-based derivatives in place of antibiotics, another study deployed the use of herbal drug EPs 7630 in 25 patients and the antibiotic Amoxicillin in the other 25 patients of uncomplicated acute bacterial rhino sinusitis. Greater improvement after treatment was seen in patients given the herbal drug for nasal obstruction, mucosal edema, facial pain, etc., as compared to those given the antibiotic. Similarly, fewer types of bacteria grew on culture from middle meatal samples in Eps 7630 than Amoxicillin, reflecting on its low tendencies of causing resistance [17].

Alternatives are also being explored for antibiotic resistance especially in common conditions such as UTI. Methenamine hippurate hydrolyzes to formaldehyde when subjected to an acidic environment. A clinical trial on women with recurrent UTI was performed to determine if methenamine hippurate could be used instead of low dose antibiotics. The results revealed that overall methenamine hippurate was found to be effective in reducing the intake of antibiotics. It also provided similar levels of treatment satisfaction [18].

Phage therapy, a method that uses bacteriophages or bacterial viruses to kill bacteria, has been there for more than a century and provides one of the most trusted choices in place of antibiotics [19]. Unlike antibiotics that can attack more than one bacteria and create more chances for resistance to prevailing, one phage only targets one bacteria at a time, lowering such risks. Besides, phages can also be used to treat antibiotic-resistant bacteria, further expanding their spectrum of activity [20]. They have fewer Side effects compared to antibiotics [21].

In another important study, intravesical bacteriophages were used to treat urinary tract infections in patients undergoing transurethral resection of the prostate. Ninety-seven patients were included in the primary analysis, out of which 37 were given antibiotics, whereas the remaining were treated with bacteriophages. The patients treated with antibiotics were found at an advantage, but those given bacteriophages also showed remarkable progress. Moreover, the latter also had a noticeable safety profile, thereby making the therapy non-inferior to the antibiotics. This study is essential as it provides key insights into how phage therapy can be modified to exhibit greater effectiveness [22].

Another groundbreaking research on a similar topic explored the use of phage therapy to treat multi-drug resistant Pseudomonas aeruginosa infection in a 26-year-old patient with cystic fibrosis awaiting a lung transplant. The patient underwent bacteriophage therapy and within 100 days after the therapy ended, the patient neither experienced cystic fibrosis exacerbation nor developed pseudomonal pneumonia again. She also successfully received a lung transplant nine months later [23].

Whole genome sequencing is a rapidly evolving method through which resistance pathways are identified to tackle resistance. Due to developments and discoveries in the field of genetic sequencing, humanized monoclonal antibodies are gaining credibility. Injecting them instead of antibiotics show promising results in curing the infection, however their high costs remain a drawback [24].

The potential of metals as antimicrobial agents in antibiotic resistance has also been tapped. They can either be used as nanoparticles, free ions or also as metal complexes to combat the bacteria. Metallophores are used as channels where they take over the transport system of the bacteria and bring about convenient delivery of the packaged ions into their systems. Developing metallophores is an area of great potential where they can be made to bind strongly to the ions but also release them immediately when subjected to certain triggers. Hence, presently, metal complexes are more likely to advance towards becoming a clinically approved replacement to antibiotics [25].

2. CONCLUSION

Antibiotic resistance is a growing global health crisis caused by the overuse and misuse of antibiotics. Despite efforts to create stronger antibiotics, bacterial resistance has been evolving for the last 50 years. Antimicrobial resistance poses a danger to public health, causing millions of deaths each year. Narrow-spectrum antibiotics and antimicrobial proteins from eukaryotes can be a good substitute for antibiotics. Plants contain compounds that stimulate antimicrobial activities, making them a viable option to use instead of antibiotics. More research needs to be done to combat bacterial resistance, and the discovery of new solutions is crucial to preserve our current antibiotic armamentarium.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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