

Short communication

The Growing Threat of Antibiotic Resistance: Addressing the Urgency

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. 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 minimize the chance of bacterial resistance. Research is ongoing in exploring practical ways to combat antibiotic resistance, including investigating antibacterial properties of medicinal plants and testing the effect of AMPs. 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

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 as 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)

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. (4) 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. (5) 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.(6)

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. (7)

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.(8) There is a dire need for new solutions and discoveries to preserve our current antibiotic armamentarium so we can combat the evolving bacterial resistance.(7)

Phage therapy, a method that uses bacteriophages or bacterial viruses to kill bacteria has been there since more than a century and provides one of the most trusted choices in place of antibiotics. (9) Unlike antibiotics that can attack more than one bacteria and create more chance for resistance to prevail, 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. (10) They have less Side effects compared to antibiotics.(11)

Plants have natural antibacterial because they contain compounds like polyphenols, essential oils, and alkaloids, often referred to as phytochemicals, that have an inherent ability to stimulate antimicrobial activities. (12) According to an estimate, there exist more than 30,000 antibacterial substances in plants, making them a viable option to use instead of antibiotics.(13) Apart from denaturing membrane proteins, disintegrating cell membrane 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.

Antimicrobial proteins (AMPs) from eukaryotes, can also be a good substitute to 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(14). 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. (15)

Multiple researches have been carried out to explore practical ways to combat antibiotic resistance. For instance, in a recent study, researchers investigated antibacterial properties of ten medicinal plants of South Africa against five multi-drug resistant bacteria namely, *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Streptococcus pyogenes*. The active extracts of the selected plants showed 66.34% inhibitory effect on anti-

adhesion of bacteria and 31.82% inhibitory effect on biofilm development of bacteria, thus validating their anti-pathogenic potentials.(16)

Another similar study tested the effect of using *Hydnophytum formicarum* tuber and *Vatica diospyroides* Symington cotyledon, two plant-derived substances together with an 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 diospyroides* reduces the required concentration of ampicillin by a considerable 8-fold.(17)

In another important study, intravesical bacteriophages were used to treat urinary tract infections in patients undergoing transurethral resection of prostate. 97 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 to how can the phage therapy be modified to exhibit greater effectiveness.(18)

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. Higher 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.(19)

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 9 months later.(20)

Conclusion

Antibiotic resistance is accelerating at an alarming rate and needs to be tackled before it depletes the global reserves of antibiotics. Through various studies and clinical trials, as discussed, multiple alternatives have been discovered such as phage therapy, plant-derived medicines, and AMPs that have proven effective in different types of bacterial infections such as those of urinary tract, respiratory tract, etc., in comparison to antibiotics and if worked upon, can offer a wider range of activity.

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Declarations:

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.