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NANOTECHNOLOGY BASED APPROACHES FOR MITIGATING ANTIMICROBIAL RESISTANCE

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ABSTRACT

The threat posed by antimicrobial resistance (AMR) to world health is serious. Due to the depletion of the supply of traditional antibiotics, new and alternative antimicrobial techniques must be researched. Antimicrobial peptides (AMPs) have the potential to be used in biomedical applications as alternative medicinal and diagnostic agents. Over 3000 AMPs have been found so far, but only a small number of them have been given the go-ahead for clinical studies. Due to their systemic toxicity, sensitivity to protease breakdown, short half-life, and quick renal clearance, their therapeutic uses are restricted to topical use. They were the worst enemy of doctors once infectious illnesses struck. In the past, even the smallest illnesses might cause death. Sometimes a fever might be fatal from an illness, no matter how little. Antibiotics, the ultimate defence against bacterial infections, were quickly developed by the researchers. Diseases were defeated by mankind. The joy of this achievement was quickly replaced with a fearful foreboding. Due to the bacteria's development of antibiotic resistance, the ultimate weapon of humanity was to use blunt force against them. Once more, the germs began to

spread diseases that were fatal and evocative of the terrible times humanity was attempting to escape. The capacity of bacteria to persist in the presence of antibiotic treatments is known as antimicrobial resistance, or AMR**.** This implies that the medications that used to be able to kill the germs with ease are now unable to do so. All of this resulted from the bacteria being resistant to antibiotics due to antibiotic abuse. However, thanks to nanotechnology, we will soon be able to move past our dread of antimicrobial resistance and its fatal consequences. If sufficiently studied, nanotechnology offers a number of uses that can quickly assist.

KEYWORDS: Nanotechnology, drug resistance, nanoparticles, antimicrobial peptides, antimicrobial resistance, nanocarriers and drug delivery systems.

INTRODUCTION

Antibiotic resistance is on the rise, which is extremely dangerous for global public health. Antibiotic-resistant microorganisms are increasingly resistant to conventional antibiotic treatments.[1,2] Scientists are looking to nanotechnology for creative answers to this problem. Antibacterial resistance can be combated by the use of nanotechnology, which involves altering and designing materials at the nanoscale (1 to 100 nanometers). We will examine several nanotechnology-based strategies and their potential to reduce antimicrobial resistance in this chapter.[3]

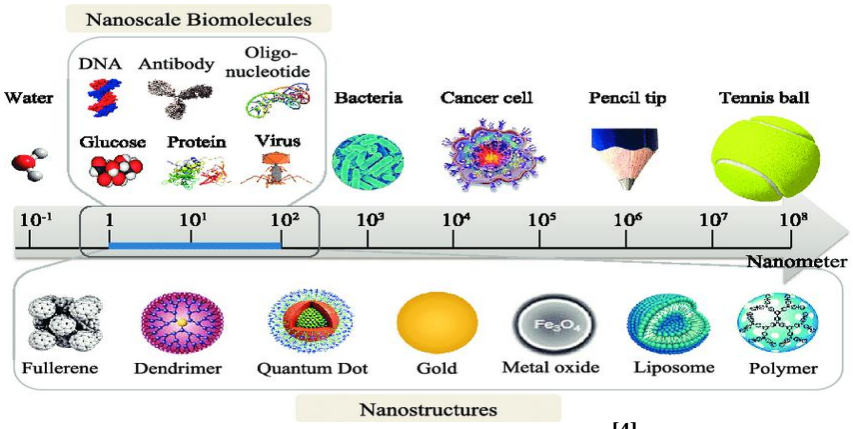

Fig. 1: The Nanoscale world.[4]

Antimicrobial agents from nanoparticles

Utilising nanoparticles as antibacterial agents is one of nanotechnology's most promising uses. Silver, gold, and zinc oxide nanoparticles all have built-in antimicrobial characteristics. These nanoparticles can damage cell membranes, obstruct metabolic functions, and trigger oxidative stress in bacteria when they come into touch with them. Particularly silver

nanoparticles have demonstrated significant antibacterial effectiveness.[5,6] They can enter bacterial cells thanks to their small size, where they can interact with proteins and DNA to impair vital biological processes. They are therefore an effective weapon against bacteria that are resistant to medication.[7]

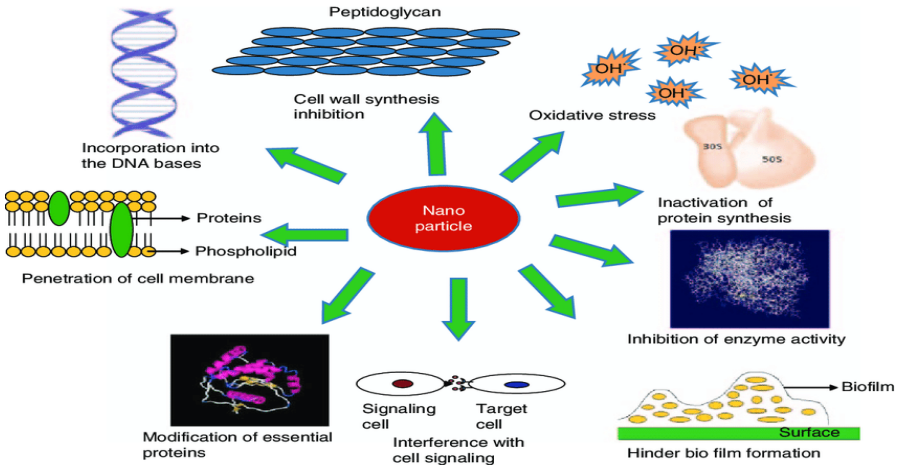

Fig. 2: Antibacterial mechanisms of nanoparticles.[8]

Specific drug delivery

Drug delivery can be done precisely thanks to nanotechnology, which provides a solution to the issue of drug resistance. Antibiotics can be packaged and released selectively at infection locations using nanoparticle engineering.[9] This method of targeted drug administration offers the following benefits.

i. **Reduced systemic exposure:** Systemic exposure is reduced by administering antibiotics directly to the infection site. This lessens the possibility of unwanted effects and helps keep antibiotics effective.[10]

ii. **Increased effectiveness:** By concentrating antibiotics at the location of the infection, a greater dose is delivered to the bacteria. When dealing with strains that are resistant to antibiotics, this is extremely crucial.

iii. **Reduced development of resistance:** Targeted drug administration can stop the development of resistance by preventing inadequate antibiotic concentrations at the infection site.[11,12]

Nanoscale Diagnostics and Imaging

For a treatment to be successful, antibiotic-resistant bacteria must be accurately and quickly identified. Imaging and diagnostic technologies based on nanotechnology have become effective allies in this effort. Quantum dots are tiny semiconductor particles that, when exposed to outside energy sources, emit particular light wavelengths.[13,15] They may be combined with aptamers or antibodies that have been designed to bind just to bacterial cells. Quantum dots affixed to bacterial cells create a distinctive fluorescence pattern when light, enabling the precise and sensitive identification of bacterial strains.[16]

Microbiological coatings

The creation of antimicrobial surface coatings is another interesting application of nanotechnology. These coatings discharge antimicrobial nanoparticles, forming a barrier that prevents bacterial colonisation and the development of biofilms.[17,19]

Medical equipment: To lower the risk of healthcare-associated infections, antimicrobial coatings can be added to medical equipment like implants and catheters. These coatings reduce the growth of antibiotic-resistant strains by blocking bacterial adhesion and biofilm formation.[20,21]

Fabrics: Antimicrobial fabrics coated with nanotechnology are being utilised more frequently in hospital settings. In hospitals and other healthcare institutions, these fabrics can lessen the spread of microorganisms that are resistant to antibiotics.[22]

Safety issues: The toxicity of nanoparticles raises serious safety issues. The safety of nanoparticles employed in medical applications for patients and healthcare personnel is still being studied.[23,25]

Regulatory obstacles: The regulatory approval procedure for medicines and products based on nanotechnology can be complicated. To speed up the market entry of these breakthroughs, regulatory processes must be simplified.

Cost-Effective manufacturing: It can be difficult to scale up the manufacturing of nanoscale materials and devices while keeping costs low. To overcome this difficulty, continual research and development activities are needed.

Adaptation to evolving resistance: It is essential to continuously monitor and track resistance patterns in order to modify nanotechnology-based solutions to new bacterial threats. Researchers need to be alert to changes in resistance profiles and sensitive to them.[26,29]

The role of antimicrobial agents

It is commonly known that microbes and infectious diseases are related.

Therefore, it is essential for the treatment of microbial diseases to use compounds that can eliminate, stop, or limit the proliferation of these pathogens. Following Sir Alexander Fleming's discovery of Penicillium notatum in 1928, a number of additional antimicrobial agents were found, and their antimicrobial action mechanisms have also been extensively studied.[30,32] Figure 1 depicts a few antimicrobial drugs and their modes of action.

The origin, composition, spectrum activity, and other antibacterial agent classifications are dependent on these factors as well. The development of microbial resistance has been documented for nearly all of these antibiotics, despite the fact that these substances were once thought to be very effective against certain germs.[33] The rate of discovering new antimicrobial agents has also decreased, which has made the situation worse.

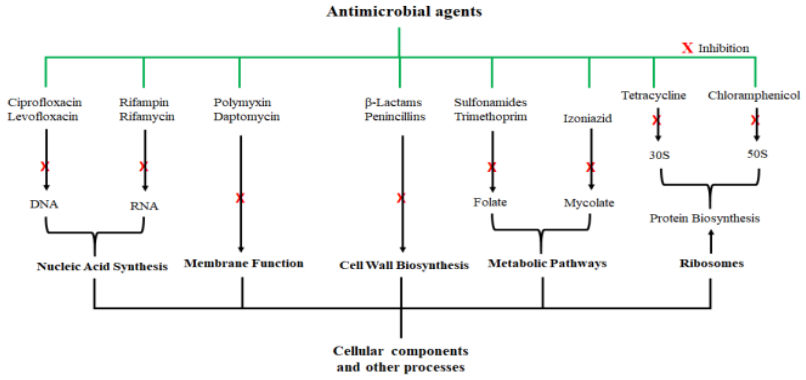

Fig. 3: Examples of antibacterial Substances and How they work. These substances are divided into groups based on the cells or molecules they are intended to affect.[34]

Mechanism of Action of AMPs

AMPs employ various mechanisms of action to exert their antibacterial effect on pathogenic microorganisms. The nature, structure, and content of the AMPs' sequence are significantly responsible for their processes. Amphiphilicity, charge, and secondary structures of AMPs have all been connected to their many modes of action, indicating that the way in which

AMPs interact with or damage microbial membranes is through one of these mechanisms. As a result, AMPs' interaction with microbial membranes is crucial for both their antibacterial effect and their therapeutic use. Other modes of action for AMPs, including as direct killing and immunological regulation, have been identified in addition to membrane rupture. The aggregation, barrel-stave, creation of toroidal pores, and carpet model are the most prominent mechanisms by which the AMP might target the microbial membrane, as shown in Figure 4. These methods have all been well addressed elsewhere.[35]

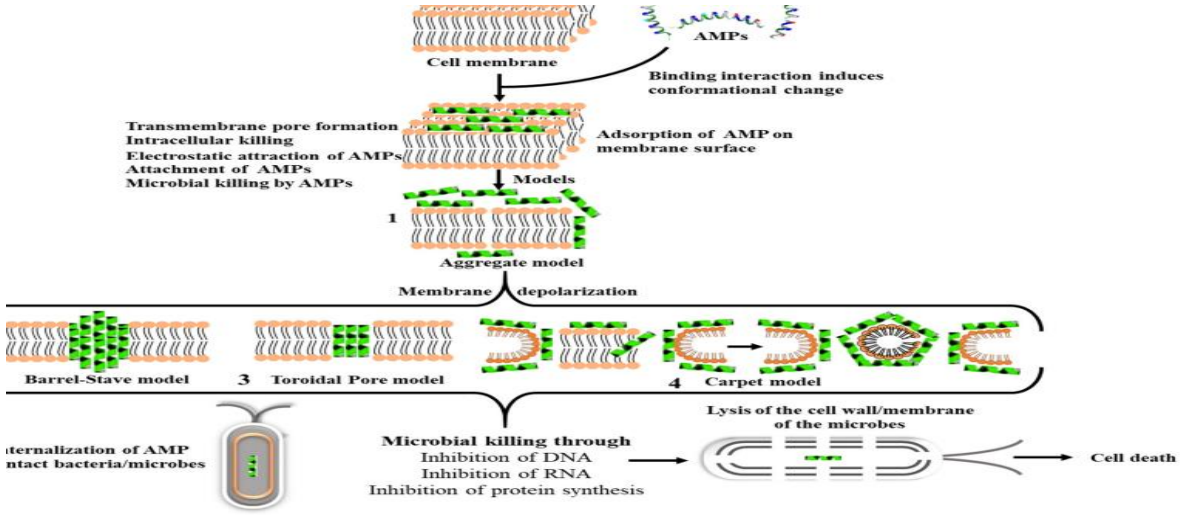

Fig. 4: The mechanism by which AMPs Target and Damage the bacterial membrane, causing bacterial cell lysis, is described.[36]

Nanocarriers of AMPs

AMPs are currently being examined as a possible antibiotic substitute in an effort to stop AMR or get around medication resistance. One of the potential drug delivery strategies is provided by nanomaterials,[37,39] particularly polymeric and MNPs, as shown in Figure 5. Aside from the fact that some nanomaterials have antimicrobial properties and can prevent the growth of microbes.

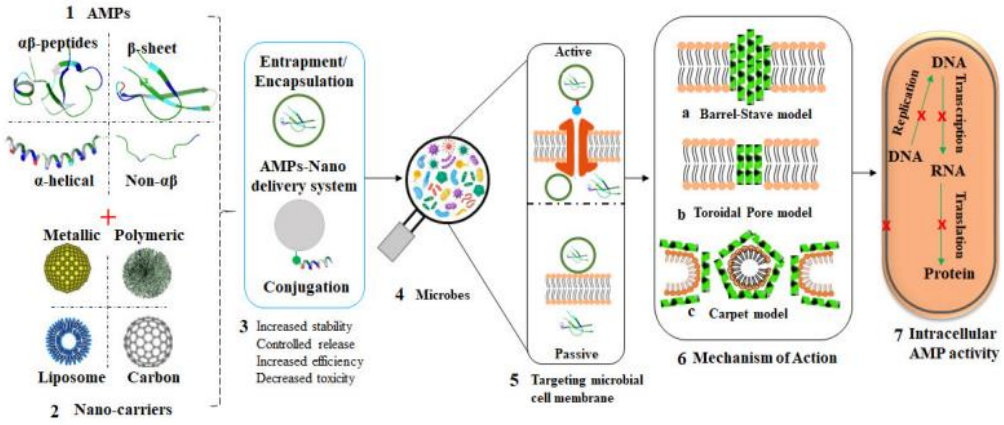

Fig. 5: A description of AMP-loaded nanocarriers and how they work. According to their structural makeup, AMPs can be divided into four groups (1); various nanocarriers have been investigated as efficient AMP carriers (2); various AMP nanoformulations can be made through various chemistries between peptides and nanocarriers (3); microbes are exposed to these AMP nanoformulations via passive or active transportation (4); this causes bacterial membrane attack by the AMPs through various AMP-dependent mechanisms (5); and ultimately, bacterial death (7).

Through a variety of mechanisms, they can also act as carriers for antibiotics or AMPs, which can help them get past the defence mechanisms of the microbes and strengthen their antimicrobial effects. Antimicrobial compounds can be functionalized into these materials to cure and prevent microbial infections as well as increase the efficiency of conventional medications.

Nanotechnology approach

Liposome

MDR is also becoming a significant issue in the treatment of cancer. Inhibiting specific resistance mechanisms, such as P-glycoprotein (PGP) mediated drug efflux, with small molecule drugs or other treatment methods has been one broad method to resolve this issue.[5,6] Due to their effective drug encapsulation in stable, non-reactive carriers; current liposomal anthracyclines have found therapeutic usage in the treatment of cancer. Additionally, there is evidence suggesting a possible benefit in specific clinical circumstances including resistant tumours. This problem is anticipated to be solved by the intra-nuclear release of anticancer medications enabled by nuclear-targeted liposomal based drug delivery system.[39,40]

Metal based Nanoparticles (NPs)

Pure metals such as gold, silver, iron and their compounds like oxides make up metal-based NPs. Reactive oxygen species generation and impaired membrane function are their main mode of toxicity. Several MDR bacterial infections have been successfully treated with this type of NPs. The most reputable metal antimicrobials are silver-based nanoparticles.[41] Although the precise mechanism of action for silver NPs are yet to establish, there are two commonly accepted modes of action, including breakdown of membranes by leached silver ions and ion-mediated killing.

Carbon based nanoparticles

NP made from carbon includes; grapheme nanotubes and carbon quantum dots have demonstrated their anti-bacterial competence. Subsequently using carbon NPs leads to minimal physical and chemical harm is also unavoidable as a result of their bactericidal effects. Exact antibacterial action of these compounds not yet determined yet-but one recent study has reported the effectiveness of multi-walled carbon nanotubes by reducing the development of biofilms by *Klebsiella oxytoca*, *Pseudomonas aeruginosa* and *Staphylococcus epidermidis.*[42,43]

Polymeric nanoparticles

There are two types of polymeric NPs; natural and artificial. Cationic and pH-switchable antimicrobial NPs are made with natural polymers. Antimicrobial peptide action can be mimicked by synthetic polymeric NPs. Polymeric micelles are incorporated in nanocarriers to improve the solubility, stability, effectiveness, and pharmacokinetic characteristics of pharmaceuticals.[44] Dendrimers are typical polymeric molecules that have a central core, radiating branch-like structures and an outer surface with functional groups. Multiple studies have reported that *Pseudomonas aeruginosa* biofilms can be successfully inhibited by glycopeptide dendrimers.

Smart nanoparticles

Smart nanomaterials can change their properties in response to stimuli like pH, bacterial toxins (Endogenous), light, temperature and ultrasound (External). These characteristic enables them to exercise their antimicrobial action. For instance, in response to the acidic environment of *Pseudomonas aeruginosa* biofilms,[45,46] hybrid micelles made of poly(ethylene)glycol, poly(Aspartamide), 2-(diisopropylamino) ethylamine, azithromycin and cis-aconityl-D-tyrosine may contract in size, reverse surface charge and release drug load.[47]

Hydrogel based approach

A significant family of macromolecular antimicrobial agents, antimicrobial hydrogels have been demonstrated to be beneficial in both the prevention and treatment of multidrug-resistant infections.[18] With the help of developments in synthetic chemistry, it is now possible to modify the structure and functionality of molecules to produce broad spectrum antibacterial activity. The potential uses now include a wide spectrum, from coating medical devices and implants, sterilization and wound dressing to antimicrobial creams for the prevention and treatment of infections with MDR.[48,49]

Approaches for mitigating microbial biofilm related drug resistance

Depending on the following characteristics of NPs which includes; physiological state, cell density, quorum sensing abilities, presence of extracellular matrix, upregulation of drug efflux pumps, point mutation, over expression of resistance genes and presence of persister cells biofilms are crucial in chronic and healthcare-associated infections and are more resistant to antimicrobials than their planktonic counterparts.[50]

Antimicrobial photodynamic treatment, antimicrobial lock therapy, antimicrobial peptides, electrical techniques, and antimicrobial coatings are a few reported potential medicines for reducing biofilm. These strategies have qualities that make them effective at addressing the looming antimicrobial resistance (AMR) threat. New biomaterials and methods to attack biofilms have recently been developed as a result of advancements in the field of micro- and nanotechnology, either individually, in combination, or as antimicrobial delivery systems.[51,52]

Phytosome based nanoparticles

Natural substances like phytochemicals and essential oils (EOs) can act as antimicrobial agents. In order to prevent the growth of bacterial and fungal biofilms, a combination therapy involving an antimicrobial drug and a low molecular weight natural product, such as terpene derivatives, has shown encouraging results. Secondary metabolites including terpenes and their derivatives, which are frequently present in EOs, have been demonstrated to have antibacterial properties against both susceptible and resistant microorganisms.[53,54] Particularly, EOs have been reported to be an effective antibacterial, antioxidant, and insecticidal agent, considerably reducing the development of bacteria, yeasts, and moulds as well as the production of microbial biofilms.[55]

Niosome

Because they include non-ionic surfactants and are soluble in water, niosomes are an excellent choice for delivering high doses of medication, particularly anti-biotics with extremely low damage to healthy cells. Recently, theniosomes have been employed as nanocarriers to increase antibacterial activity, and this study used them to do just that while reducing antibiotic resistance.[56,57] To boost the anti-bacterial and anti-cancer activities of selenium nanoparticles (SeNPs), its green production and loading into noisome were carried out.

CONCLUSION

The greatest innovation in the medical field to combat illness was the development of antibiotics. But doctors and other medical community members began to overlook the appropriate application of these medicinal gems. The incorrect usage of antibiotics quickly caused microorganisms to develop resistance to them, rendering them useless against them. Antimicrobial resistance is now upending the foundation of global health security and has the potential to do so in the near future. Scientists are now concerned that we may be heading back towards a time when illnesses predominated. It will be similar to the difficult times that people had in the past before antibiotics were discovered. For the time being, there is a glimmer of optimism. The same promise that antibiotics once bestowed onto humanity has been restored with the discovery of nanoparticles. The only means by which humanity can prepare for the terrible future in which antibiotics will no longer be able to treat illness is through the antibacterial activity of nanoparticles and the synergistic effects that may be achieved through their utilization.Approaches based on nanotechnology have a lot of potential for combating antimicrobial resistance. We can create targeted therapies, diagnostic tools, and preventive measures by using the special features of nanoparticles, which has the potential to completely change the antibacterial treatment industry. Accepting these cutting-edge approaches is essential to protect public health and guarantee the ongoing efficacy of antibiotics in the face of mutating drug-resistant bacteria. One of the most important developments in the ongoing struggle against one of the most important global health issues of our day is the incorporation of nanotechnology into antibacterial techniques.

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