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THE ROLE OF NANOTECHNOLOGY IN COMBATING ANTIMICROBIAL RESISTANCE, A REVIEW OF CURRENT STRATEGIES AND FUTURE PERSPECTIVES

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Abstract

Background:
Antimicrobial resistance (AMR) has emerged as one of the most critical global public health threats, compromising the effectiveness of antibiotics and undermining decades of progress in the treatment of infectious diseases. The rapid rise of AMR threatens the prevention and treatment of bacterial, viral, fungal, and parasitic infections. Inappropriate prescribing and overuse of antimicrobial agents have accelerated the development of resistance mechanisms, including efflux pumps, enzymatic drug inactivation, reduced membrane permeability, biofilm formation, and genetic mutations.

Objective:
To review the role of nanotechnology in combating antimicrobial resistance, focusing on the mechanisms, therapeutic applications, challenges, and future prospects of nanoparticles.

Methods:
A comprehensive review of the recent literature was conducted to examine the antimicrobial properties of metal and metal oxide nanoparticles, including silver (AgNPs), zinc oxide (ZnO NPs), and titanium dioxide (TiO_2 NPs). The review focuses on their mechanisms of action, synergistic effects with conventional antibiotics, and applications in overcoming multidrug-resistant pathogens.

Results:
Nanoparticles exhibit strong antimicrobial activity by disrupting microbial membranes, generating reactive oxygen species (ROS), penetrating biofilms, and enabling targeted drug delivery. They also enhance intracellular drug retention, inhibit the transfer of resistance genes, and restore the effectiveness of conventional antibiotics against resistant pathogens.

Conclusion:
Nanotechnology offers a promising and innovative approach to combating antimicrobial resistance by overcoming conventional resistance mechanisms, with

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the potential to improve the treatment of resistant infections despite challenges in clinical translation and safety.

Introduction

Resistance is the ability of bacteria to survive, inhibit the action of, or overcome the effects of antimicrobial agents that are intended to prevent their growth or eliminate them. (Jubeh *et al.,* 2020; Breijyeh *et al.,* 2020). Antibiotic resistance in bacteria often results from unnecessary and inappropriate use of antibiotics. In the 19th century, contagious diseases reported as the potential cause of death among humans (Munir et al., 2020; Ahmed *et al.,* 2020). The discovery of antibacterial drugs in the first half of the 20th century was a remarkable breakthrough, leading to a significant reduction in deaths caused by infectious diseases. However, this success was short-lived. Over the past several decades, microorganisms have progressively developed resistance to existing antibiotics due to the irrational use, misuse, and overexploitation of antimicrobial agents, creating a renewed global challenge in the fight against infectious diseases. (Cohen, Levy *et al.,* 2000; Huh and Kwon 2011).

AMR has become one of the biggest public health problems in the world in the 21st century. It diminishes the treatment efficacy of the medicine which is used for treatment of different infection diseases caused by different infectious organism like bacteria, viruses, parasites and fungi, and make these infections more challenging to prevent and treat (Poole 2002).

AMR is particularly concerning due to the resistant of bacteria to antibiotics (Frère and Rigali 2016). Over the decades, pathogens like bacteria cause severe infections to become resistant to varying degrees to new antibiotics. Faced with this reality, steps must be taken to curb the growing global healthcare crisis (Organization 2014).

WHO emphases the importance of increasing global cooperation to combat and control AMR (Aslam, Asghar *et al.,* 2024). WHO developed global strategy to reduce the evolution of the AMR microorganisms in 2001(Organization 2012).

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Figure 1. (A) Figure presenting the measures helps in the reducing of AMR. (B) illustrate the strategies that fight with AMR globally (modified from Dr. Razzaque's paper) (Razzaque, 2021; Aljeldah, 2022).

Antimicrobial Resistance mechanisms

Remove the antibiotic from bacteria cell

Bacteria have several efflux pumps in their cell membrane which are used for the transportation of different compounds across the cell membrane. These molecules include nutrients and signaling molecules. And some of these efflux pumps help in reducing the antibiotics by removing the antibiotic from the cells (Bretscher 1985; Smith, Zhang *et al.,* 2017). In several conditions, permanent changes to DNA of the bacteria cause bacteria to overproduce specific pumps, leading to increased resistance. (Moo, Yang *et al.,* 2020; Shriram, Khare *et al.,* 2018).

Decrease permeability of the membrane that surrounds the bacterial cell

Several alterations to the membrane of the bacteria can reduce the permeability which leads to decrease the influx of the antibiotics into cell. This mechanism of decreasing the permeability of the membrane leads to enhancement of the AMR (Marshall and Kadangs, 2014).

Destroy the antibiotic

Certain enzymes of the bacteria can neutralize the antibiotics. Enzyme like beta-lactamase, help in the destruction of the beta-lactam ring of the penicillin which is the important antibiotic used for the treatment of infections (Fernandes, Amador *et al.,*

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2013). Recently, bacteria synthesized the extended spectrum β-lactamases enzyme (ESBL) produced by several bacteria which is major challenge in the bacterial treatment. They reduced the broad-spectrum beta-lactam antibiotics uses. And like Carbapenems are sometime uses as last resort in the Treatment of the ESBLs bacteria (Maisch, 2009).

Antibiotic modification:

Several bacteria occasionally form enzymes which add distinct chemical groups to antibiotics. These groups attachment do not allow the binding of antibiotics to its targets in the cell of bacteria (Dobrovanov, Nazarchuk *et al.,* 2022).

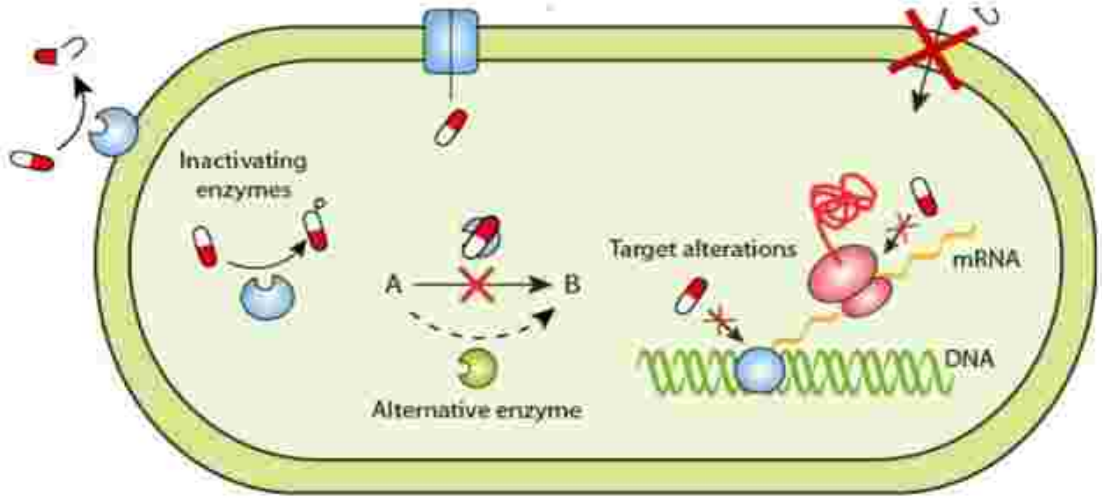

Figure 2. Figure shown Antibiotic resistance approaches (Sharma, Johnson *et al.,* 2016)

Alternate protein expression

Certain bacteria have capability to produce alternative proteins that are replaced with normal proteins that are targeted by antibiotics. This property of the bacteria enables them to survive and resist targeted antibiotics. *Staphylococcus Aurus* is one example of the alternative protein production which involves the acquiring of mecA resistance gene and synthesizing novel penicillin-binding protein (Magana, Ioannidis *et al.,* 2015). These proteins are required for bacterial cell wall synthesis and are targets of β-lactam antibiotics. The affinity of these penicillin-binding proteins is low for beta-lactam antibiotics which lead to make the resist to the antibiotics. This resistance is based on Methicillin-resistant *Staphylococcus Aureus* (MRSA) (Kashani *et al.,* 2018; Schmelcher *et al.,* 2018).

Reprogram target.

Occasionally, certain bacteria are modified versions of protein or structure (variant) such as vancomycin-resistant bacteria form distant wall of the bacteria cell than sensitive bacteria. Due to reprogramming, the targeted antibiotics are incapable of interacting with cell wall (Walsh 2000).

Use of Nanotechnology in Drug Resistance

Recently, the development in the field of nanotechnology has proven the significance of nanoparticles and metals. Antimicrobial properties have gained considerable recognition as effective inhibitors of pathogen growth (Hajipour *et al.,* 2021; Fromm *et al.,* 2012). To overcome the resistance phenomenon of microorganisms, nanoparticles exhibit various functions, such as enhancing the accumulation of antimicrobial drugs in cells or inhibiting the formation of biofilms (Bharti, 2024; Song, Liu *et al.,* 2021). Various metals and metal oxide nanoparticles, such as silver oxide (Ag 2 O), titanium dioxide TiO2, zinc oxide (ZnO), copper oxide (CuO), gold (Au), magnesium oxide (MgO), silicon (Si), and

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calcium oxide (CaO) have effective antibacterial activity. (Dizaj *et al.*, 2014; Lotfipour *et al.*, 2014). Recently, developed nanoparticles to decreases and combat resistance of bacteria, multi drug resistance (MDR) and biofilm. These nanomaterials are engineered structures, and their size is from 1-100 nm. Nanoparticles and nanomaterials are uses in different medical applications like in diagnosis of diseases, therapeutic agents and diagnostic imaging system, medical equipment, drugs delivery system (Horikoshi and Serpone, 2013).

Lipid-Based Nanoparticles

Solid lipid nanoparticles (SLNs) are smallest particles developed from solid fats, mostly their size from 50-1000 nanometers. SLNs are used to carry and deliver the drug to target area effectively and accurately into the body. The drug is held by their solid fats core part and unique substances named surfactants and co-surfactants maintain the particles and stables. SLNs are helpful in the diagnosis and treatment of several diseases like Infections, brain disorders, diabetes, skin diseases and particularly several censors. This treatment is performed effectively by carrying and delivering the drug to the target area and decrease the side effects (Bayón-Cordero *et al.*, 2019; Alkorta *et al.*, 2019; Müller *et al.*,2000; Mäder *et al.*, 2000; Makowski *et al.*, 2019; Silva *et al.*, 2019). The properties specific nanocarrier of SLNs depend on the solid core composition which are usually compose of mono-diglycerides, fatty acid, triglycerides, waxes and fatty alcohol (Bayón-Cordero *et al.*, 2019; Alkorta *et al.*, 2019). This review does not discuss all SLNs agents, but it is notable that choosing of the best SLNs based on the drug type and their expected uses (Scioli Montoto *et al.*, 2020; Muraca *et al.*, 2020). They remain solid at room temperature and carry drug effectively with controlled drug releasing (Scioli Montoto *et al.*, 2020; Muraca *et al.*, 2020).

In addition, the highly biocompatibility and biodegradability property must be ensured which can use to encapsulated lipophilic and hydrophilic drugs (Eloy *et al.*, 2014; de Souza *et al.* 2014). Enhancing their solubility, stability and bioavailability, multiple drug administration mode, oral to nasal, parenteral, transdermal and ocular. Specifically oral SLNs is promising drug. this is because encapsulated drugs are shielded and protected from the acidic pH of the stomach and from digestive enzymes in the gastrointestinal system which maintain their stability and prevent from degradation (Dumont *et al.*, 2018; Bourgeois *et al.*, 2018) (Scioli Montoto *et al.*, 2020; Muraca *et al.*, 2020).

Nonetheless, there are some disadvantages of the SLNs like loading of low drug and plausible leakages of drugs in storage (Bayón-Cordero *et al.*, 2019; Alkorta *et al.*, 2019).

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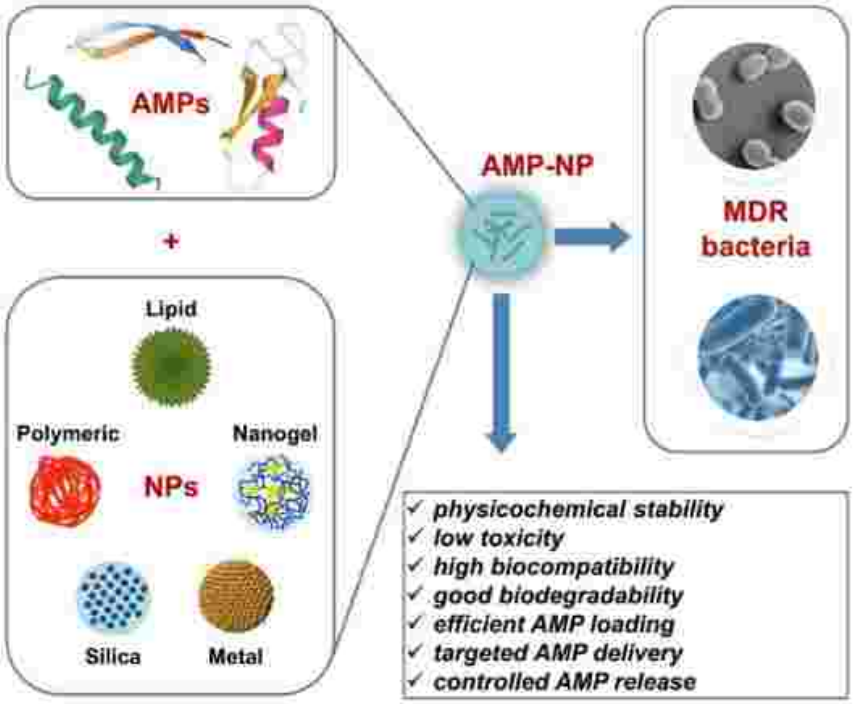

Figure 3. Several drug delivery systems (nanosystems) like silica-based, lipid-based, metal based, lipid based and nanogel systems are used for antimicrobial peptides (AMP) transport. The encapsulated APM in the nanosystems increases their antimicrobial actions against MDR infectious organisms while enhancing stability, increases biocompatibility, enhancing biodegradability, and reducing their toxicity. An optimal nanosystems must ensure effective loading of AMP, accurate delivery, sustained and controlled drug releases (Imperlini *et al.,* 2023; Massaro *et al.,* 2023).

Inorganic Nanoparticles

These are classified into metals nanoparticles, and formed by metal oxide (Liong *et al.*, 2010; Lu *et al.*, 2008). They are characterized by their own antibacterial activities (Tsikourkitoudi *et al.*, 2022; Henriques-Normark *et al.*, 2022). Due to their unique antibacterial activities, Inorganic NPs either use separately or may be loaded with antibiotic and exhibit dual mechanisms of actions (Ameh, Gibb *et al.*, 2022).

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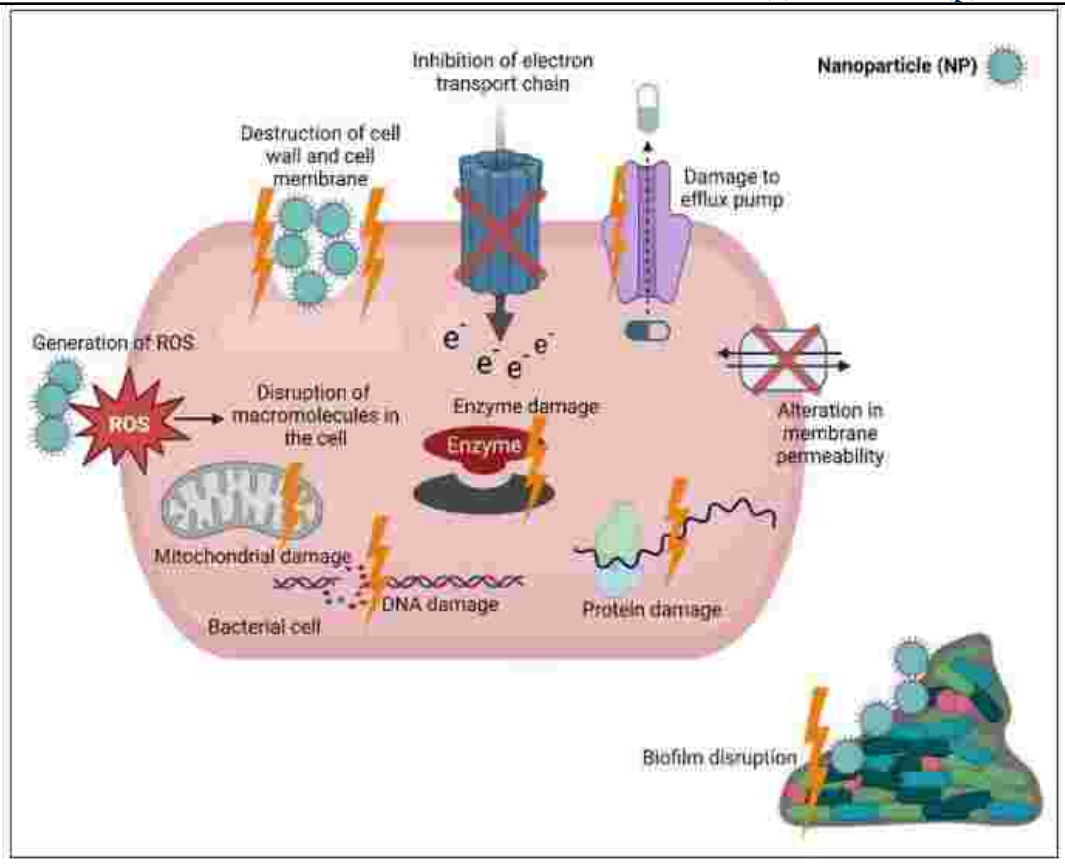

Figure 4. Nanoparticles fight and kill bacteria by different mechanisms, causes oxidative stress by generating reactive oxygen species (ROS), which lead to damage cellular components like mitochondria, enzymes, DNA and proteins.

They also enhance the permeability of the membrane, inhibit the efflux pump of bacteria and electron transport chain (ETC), and causes disturb and prevent the formation of the biofilm (Hetta *et al.,* 2023; Ramadan *et al.,* 2023; Battah *et al.,* 2023; Abd Ellah *et al.,* 2023).

Conclusions

NPs are nano-weapons against bacterial resistance to traditional antibiotics. Furthermore, metal and metal oxide NPs are effective against MDR and both gram negative and gram positive. However once co-administrated with antibiotics, they increase distribution drugs to the targeted area of action. Also enhance the activity of the antibiotic by their own effects and decreases broad spectrum antibiotics adverse effects. Several nanoparticles (metals and metal oxide) show combined effects when they administrate with antibiotics. By using nanoparticles (NPs) along with antibiotics is promising approach to combat with antibiotics resistance. Matal's nanoparticles have specific properties which make them effective for antimicrobial treatment. Therefore, these nanoparticles may become suitable substitutes for traditional antibiotics.

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