Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
DOI: 10.29261/pakvetj/2024.227

REVIEW ARTICLE

Nanoparticles as Potent Allies in Combating Antibiotic Resistance: A Promising Frontier in Antimicrobial Therapy

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ARTICLE HISTORY (24-230)

Received: April 27, 2024
Revised: June 28, 2024
Accepted: June 30, 2024
Published online: August 11, 2024

Key words:
Nanoparticles
Antibiotic Resistance
Frontier in Antimicrobial Therapy
Innovative Treatments
Public Health

A B S T R A C T

Antibiotic resistance presents an escalating threat to global health, undermining the efficacy of conventional treatments against diverse microbial pathogens. The imperative for novel strategies to counter this crisis has become evident in the weakening efficacy of traditional antimicrobial therapies. Nanoparticles (NPs) have emerged as a promising opportunity in the fight against antibiotic resistance. These minute entities embody profound potential, marking the forefront of innovation in combatting resistant microbes. Their infinitesimal scale belies their transformative influence, providing a versatile platform for developing pioneering antimicrobial agents. Varieties such as metallic NPs, leveraging unique physicochemical properties, liposomes tailored for precise drug delivery, and dendrimers alongside polymer-based counterparts engineered for heightened efficacy, collectively promise a paradigm shift in therapeutic approaches. The significance of NPs transcends their diversity. Their adeptness in traversing biological barriers and precisely targeting pathogens underscores their role as potent allies against resistance. Furthermore, their adaptability in modulating drug release kinetics and fine-tuning therapeutic concentrations accentuates their appeal as transformative elements in antimicrobial therapy. Beyond their direct antimicrobial impact, NPs manifest synergistic effects when combined with traditional antibiotics, reinvigorating the potency of existing treatments.

To Cite This Article: Hannan A, Du XX, Maqbool B and Khan A, 2024. Nanoparticles as potent allies in combating antibiotic resistance: a promising frontier in antimicrobial therapy. Pak Vet J, 44(4): 957-967. http://dx.doi.org/10.29261/pakvetj/2024.227

INTRODUCTION

Nanotechnology is swiftly spreading in different fields of human activity, including veterinary medicine (Kandeel *et al*., 2022; Danchuk *et al.,* 2023). An eclectic range of nanomaterials has been applied to veterinary practice, including diagnostic, pharmaceuticals, vaccines, and feed additives. The use of nanoformulations has provided novel approaches to animal disease treatments. For instance, antibiotics delivered on nanoparticles (NPs) showed greater efficiency with lower toxicity and even smaller dosage required compared to standard methods, thus offering a possible solution to antibiotic resistance (Wang *et al.,* 2023; Le *et al.,* 2023).

Nanotechnology focuses on understanding and manipulating materials to extremely small size ranges between 1-100nm, exhibiting distinct physical and chemical features such as highly reactive nature, significant surface/mass ratio, and unusual interactions with physiological systems. In the last few years, the use of nanotechnology in the medical field has been extensively investigated, especially for the delivery of drugs (Zhang *et al.,* 2010; Lee *et al.,* 2019; Yeh *et al.,* 2020). Innovative characteristics of the NPs, like their compatibility with biological systems, anti-inflammatory potential, anti-bacterial activity, targeted drug delivery like tumor targeting, enhanced bioavailability, and absorption, have sparked a rise in the use of NPs in the field of applied microbiology and biotechnology. Nanoparticles are generally grouped based on their shape, size, and chemical properties, such as Carbon-based NPs, Metal-Based NPs, Ceramics NPs, Lipid-based NPs, Semiconductor NPs, and Polymeric NPs (Khan *et al.,* 2019; Khan and Hossain 2022; Altammar, 2023).

Manufacturing medications, vitamins, probiotics, and nutritional supplements is one potential application of

nanotechnology in animal husbandry (El-Sayed and Kamel 2020; Prasad *et al.,* 2021; El-Dawy *et al.,* 2023). Another example is the use of NPs to identify and eliminate infectious agents without surgery. However, even employing nanotechnology limits the range of antibiotic applications due to their nano size. The regular use of antibiotics in animal production can leave a residue that affects the consumers (Fattal *et al.,* 1989; Dong *et al.,* 2009; Umair *et al.,* 2022; Samy *et al.,* 2022; Batool *et al.,* 2023).

Antibacterial drugs are the prime agents for combating infectious diseases (Pacios *et al.,* 2020; Mohamed *et al.,* 2022; Mehnaz *et al.,* 2023; Mhlongo *et al.,* 2023). However, due to their excessive usage and abuse, bacteria have developed antibiotic resistance, which is an alarming issue (Liu *et al*., 2023). Resistance occurs due to natural evolutionary changes that happen during antibiotic medication, resulting in inheritable resistance. Additionally, resistance may develop by passing genes down the generations via transduction, transformation, or conjugation. Therefore, infectious diseases remain one of the biggest health issues in the world since bacteria have evolved to be resistant to commonly used antibacterial drugs. Furthermore, with the emergence of multiple drug resistance, there are other undesirable side effects associated with using typical antimicrobials. High doses of antibiotic therapy are required to overcome drug resistance, frequently leading to unacceptable toxic effects (Windels *et al.,* 2019; Chinemerem *et al.,* 2022). Since the WHO identified the rise of antibiotic resistance due to harmful bacteria as a research priority in 2015, the pharmaceutical sector has faced one of the largest challenges (Balderrama-González *et al.,* 2021). This problem led to the foundation of alternative approaches to treat infectious diseases, and the development of novel antibacterial agents such as nanomaterials is one of them. Different types of antimicrobial NPs and nano-carriers for the administration of antibiotics have demonstrated their efficacy in treating infections, including those that exhibited antibiotic resistance (Hajipour *et al.,* 2012; Akhtar *et al*., 2023).

Antimicrobial resistance (AMR) could be at two levels: cellular or community levels. Cellular resistance can arise from mutated genes or horizontal gene transfers from other micro-organisms. Community-level resistance refers to the ability of a group of bacteria to withstand environmental stress in ways that other cells are unable to do. As a result of such tolerance, an increase in AMR occurs (Cheng *et al.,* 2016). Few other resistance mechanisms could be acquired by bacteria that could be generally categorized into three prime groups: Target modification, antibiotic target mutation, and blocking access to the target (Moo *et al.,* 2020).

Metallic NPs can interact at molecular levels through targeted delivery, allowing improved disease diagnosis, progress evaluation, and treatment (Scioli Montoto *et al.,* 2020; Yetisgin *et al.,* 2020; Mitchell *et al.,* 2021; Anjum *et al.,* 2023). The use of metallic NPs is one of the potential strategies for combating bacterial resistance (Shaikh *et al.,* 2019; Amaro *et al.,* 2021; Khan and Rasool 2023). Metallic NPs have a larger contact area with a microbe due to their smallest size and higher surface/volume ratio. These characteristics increase biological and chemical activity, and as a result, NPs exhibit significant antimicrobial activity. Targeting various structures in bacteria is also a vital characteristic of metallic NPs. Nanoparticles can work by impairing the functions of bacterial cell membranes, such as permeability or respiratory processes.

Additionally, NPs can disrupt their functions by interfering with proteins composed of sulfur and chemicals consisting of phosphorus, i.e., DNA, after invading bacterial cells. That's why it becomes difficult for bacteria to develop resistance to metals because of their complicated mechanisms (van Hoek *et al.,* 2011; Zhu *et al.,* 2022). Although several metal resistance mechanisms have been identified, the most prevalent one is an increased outflow of metal ions from the cell. This is a one-step mutation at a high level. Due to its multiple modes of action, this mutation increases the flow of metal ions out of the cell and decreases the likelihood of metal resistance (Allahverdiyev *et al.,* 2011).

Many types of inter-metallic and mono-metallic NPs are now readily available to defend against microorganisms due to recent advances in nanoparticle technology (Jaji *et al.,* 2020; Martínez *et al.,* 2020). In many biomedical-related applications, such as the delivery of drugs to the coating of antibacterial, mono-metallic NPs such as Au, Ag, and their oxides have been proven to be vital elements. Intermetallic NPs such as Ag-Cu, or Au-Pt-Pd and many others have been employed in the medical field and frequently generated using various synthetic techniques, including micro-emulsion, Redox Process, or sol-gel method.

These NPs can be categorized into two primary groups, mixed and segregated, which are then subsequently divided into further groups based on the configuration of their atoms: alloy, sub-cluster, intermetallic, and core-shell types (Hassan and Ghadam, 2020). Reactive oxygen species (ROS) produced by these NPs cause oxidative stress, one of the most frequent contributors to the antibacterial processes. Bacterial cells are capable of achieving an internal ROS balance, but excessive ROS generation causes damage to proteins and DNA membranes, and also inhibition of enzymes and interfering translation and transcription of DNA result in cell death (Gunawan *et al.,* 2020; Altun *et al.,* 2021).

Emergence of antimicrobial resistance

History of AMR emergence: In 1939, René Dubos, a French microbiologist, isolated the antibiotic tyrothricin (a mixture of gramicidin D and tyrocidine) from the soil bacteria Bacillus brevis. That antibiotic was effective against Gram-positive bacteria (Uddin *et al.,* 2021); however, that antibiotic was highly toxic in humans (Mohr, 2016). In 1890, Paul Vuillemin used the word "antibiose" to describe an agent that prevents the activity of diverse microorganisms (Bentley and Bennett 2003; Dhingra *et al.,* 2020). In the 1940s, Waksman carried out a planned and systematic study of the antimicrobial behavior of soil bacteria, especially Streptomyces spp. Waksman's work started the Glorified Era of antibiotic discovery between the 1940s and 1970s (Durand *et al.,* 2019). He discovered many major antibiotics and antifungals like actinomycin, neomycin, streptomycin, clavacin, and fumigacin (da Cunha and Fonseca 2019). Of these antibiotics, such as streptomycin, neomycin, and

actinomycin, are currently in clinical use (Sykes and Papich 2013; Uddin *et al.,* 2021).

Over 20 antibiotic classes from hundreds of bacterial species and fungi were discovered during that golden period (Nicolaou and Rigol 2018). Several pharmaceutical manufacturers opted for Waksman's culture strategy to develop new molecules. Sadly, very few new antibiotic groups were detected, including tetracyclines, macrolides, nitrofuran, quinolones, and oxazolidinones in 1948, 1952, 1953, 1960, and 1987, respectively, and no novel classes have been added for the last 50 years (Nicolaou and Rigol 2018; Durand *et al*., 2019).

The prompt and reasonably elementary development of several antibiotics within a short time resulted in their over and misuse (Mittal *et al.,* 2020; Padma, 2022; Timmerhuis *et al.,* 2023), leading to the development of AMR by various mechanisms discussed elsewhere in this article. AMR is challenging health and healthcare globally. The saddle of AMR steadily increased over time, and recent reports portray extreme predictions, although global estimates are difficult to derive (Limmathurotsakul *et al.,* 2019).

Previously well-treatable infections require new therapeutic strategies, while already difficult-to-treat diseases have developed extensive resistance, e.g. multidrug-resistant tuberculosis (MDR-TB). In a recent review, Luz *et al.* (2022) analyzed 158,616 articles on AMR over the past 20 years. According to them, there was an 8.5% nominal annual increase in articles on AMR); however, in 2018, 14,547 articles were published on AMR, an increase of 450% compared to 1999. This situation emphasizes how globally important this issue is. There is also a trend in AMR based on organisms. The MDR-TB has been the most prevalent research topic over time, the peak was observed in relative proportion in 2012 (10.8% of all topics), followed by *Staphylococcus aureus*, which displayed a short but prominent peak in 2007–2008 (Luz *et al.,* 2022). Other topics that got scientists attention were AMR in Escherichia coli, MDR Acinetobacter, ESBL (Extended-spectrum beta-lactamases), carbapenem-resistant Enterobacteriaceae (CRE)/carbapenem-producing Enterobacteriaceae (CPE), etc. (Nicolas-Chanoine *et al*., 2019; Bezabih *et al*., 2021; Luz *et al*., 2022; Kim *et al*., 2023).

Antimicrobial resistance's impact on the healthcare sector is increasing, and the consequent lack of availability of appropriate antimicrobials is a global issue. There is a dire need for knowledge related to the environmental and social factors that contribute to AMR, which are crucial for the creation of effective diagnostic as well as therapeutic interventions. The consumption of antibiotics triggers a natural response, which leads to the development of antibiotic resistance (Naeem *et al.,* 2023). The prevalence of antimicrobial-resistant microbes is rising due to several interconnected complicated factors that include their usage in humans and agricultural products as well as from environmental pollution. The human microbiome has been exposed to high amounts of antimicrobials due to their frequent use in clinical treatment (Holmes *et al.,* 2016; Betelhem *et al.,* 2022).

Bacteria may possess intrinsic resistance to specific antibiotics; however, they also can acquire resistance against antibiotics through chromosomal gene mutations and horizontal transfer of genes (Hasan and Al-Harmoosh 2020; Mancuso *et al.,* 2021; Urban-Chmiel *et al.,* 2022). The ability to resist the effects of an antibiotic due to innate structural and functional features is known as the intrinsic resistance of a bacterial species to a particular antibiotic. For example, the biocide triclosan has broad spectrum activity against Gram-positive microorganisms and many Gram-Negative bacteria, but it is incapable of stopping the growth of members of the Gram-Negative genera Pseudomonas (Goudarzi and Navidinia 2019). This is the simplest example of intrinsic resistance in a single species. This was first believed to be caused by active outflow, but more recent research has demonstrated that it is caused by the presence of an allele on the FabI gene which encodes enoyl-ACP reductase enzyme- the substrate for triclosan. Bacteria can acquire or evolve antibiotic resistance in addition to intrinsic resistance which can be mediated by a variety of mechanisms. These mechanisms can be divided into three main categories (Blair *et al.,* 2015).

a. Reducing the intracellular concentrations of the antibiotic due to inadequate bacterial penetration or antibiotic outflux.
b. Modification of antibiotic target through genetic alteration.
c. Post-translational changes in antibiotic target.

Principal forms of antimicrobial resistance

Natural resistance (Intrinsic/Structural): Antibiotic use does not contribute to this sort of resistance rather the structural characteristics of the bacteria are responsible (Hasan and Al-Harmoosh 2020; Genreith-Schriever *et al.,* 2020; Fan *et al.,* 2021). A microorganism naturally possesses this type of resistance. It is related to the general physiology of microbes and is a chromosome-controlled characteristic (Kakurinov, 2014).

Acquired resistance: This type of resistance arises as a result of changes to the genetic makeup of bacteria. The fundamental chromosome or other chromosomal structures like plasmids or transposons are the culprits of this type of resistance. Chromosomal resistance is caused by mutations in the bacterial chromosome that might happen because of specific physical and chemical conditions causing reduced bacterial drug permeation, or even modifications of drug target (Hasan and Al-Harmoosh, 2020). The basic processes that cause bacterial resistance involve modifications in the permeability of the plasma membrane, drug target modification, enzymatic drug suppression, and active efflux of antibacterial agents (Jacoby, 2009).

Enzymatic alteration of antibiotic: Antibiotic-destroying enzymes are produced by bacteria. The sensitive hydrolysable bonding molecules found in antibiotics can be targeted and broken by the enzymes produced via genomic and plasmid DNA. Three primary categories of drug-deactivating enzymes exist (Munita and Arias 2016). Hydrolase mostly consists of β-lactamase. Passivation enzyme which includes erythromycin esterase, chloramphenicol acetyltransferase, and aminoglycoside inactivating enzyme. Modified enzyme, which includes aminoglycoside modifying enzyme.

Drug target site modification: The primary manifestations of this process are the polymyxin-resistant

bacteria and gram-positive microbes. One key reason for resistance to drugs is the modification of the antibiotic receptor site that could render it challenging for antibacterial to adhere to the bacterium. For instance, the gene that codes for mecA encodes PBP2a, a low-affinity interaction peptide that confers susceptibility to all β-lactam antimicrobial agents, from the plasma binding protein of *Staphylococcus aureus* (Azam *et al.,* 2023).

Cross-resistance: Cross-resistance is defined as the occurrence of resistance to all antibiotics from the same class due to a single mechanistic pathway (Périchon and Courvalin 2009). It refers to a particular bacteria's resistance to a particular antibiotic when that microorganism also has resistance to other antibiotics and uses similar or the same mechanisms. This generally occurs when antibiotics have similar structures, such as resistance to erythromycin, or cephalosporin and penicillin (Hasan and Al-Harmoosh, 2020).

Nevertheless, cross-resistance can also occasionally be observed in a whole other class of medications, such as the cross-resistance between erythromycin and lincomycin, which may or may not have genomic origins (Horinouchi *et al.,* 2017; Colclough *et al.,* 2019; Hasan and Al-Harmoosh, 2020). The possibility that microbes encounter with biogenic antimicrobials in sewage, farms, or urban areas could co-select for the development of resistance to therapeutic antimicrobial drugs and play a major role in the emergence of antibiotic-resistant bacteria is becoming more widely known (Aabed and Mohammed 2021; Ali *et al.,* 2021). Resistance to several different antibiotics is provided by an identical molecular pathway known as bacterium crossover resistance. It happens when antibiotics bind to an identical target, have a common mechanism that inhibits cellular development or mortality, or exhibit a conduit to the cell's cytoplasm (Van Duijn *et al.,* 2018). Collateral sensitivity is contrary to crossover resistance when multiple mechanisms lead to an adverse relationship between the susceptibility of organic antimicrobials and susceptibility to antimicrobial agents (Leung *et al.,* 2019).

Multi-drug resistance and other types: Pathogens that have developed multidrug resistance are those that have acquired resistance to antibiotics ensuring that the infection might not be controlled or removed by a single antibiotic. The development of multidrug-resistant (MDR) pathogenic bacteria was the result of improper and excessive use of antibiotics for therapy (Dong *et al.,* 2009; Hasan and Al-Harmoosh, 2020; Mwafy *et al.,* 2023).

The varieties of bacteria are said to as MDR if they exhibit resistance to at least three classes of antibiotics. The varieties that are resistant to all except one or two types of antimicrobial agents are considered to be extremely resistant to medications; in this case, the species in question is referred to as pan-drug resistant (Hasan and Al-Harmoosh, 2020; Terreni *et al.,* 2021). MDR diseases have grown in frequency, particularly in healthcare facilities; in a couple of years, there may be a chance to reach the period known as the "post-antibiotic era," when diseases that initially seemed manageable could quickly evolve into fatal threats (Pelfrene *et al.,* 2021; Catalano *et al.,* 2022).

Initially, upon susceptibility R-plasmids, microbes usually aggregate many genes, every single one of which codes for resistance to one substance, inside a particular cell. Furthermore, the overexpression of genes encoding for multidrug pumps for efflux, which extrude a variety of medications, may potentially contribute to resistance to multiple drugs. Lastly, MDR can be created by adding a chemical moiety to the antibiotic or by enzymatically rendering the medication inactive. In recent years, phage therapy has been suggested. Bacterial viruses known as phages are widely distributed, unique to their host, and capable of attacking MDR isolates of bacteria. The lytic bacteriophage OMKO1 (family Myoviridae) of P. aeruginosa is used in the suggested phage therapy. It binds to receptors on the outermost layer of porin M (OprM) of the multimodal efflux pumps MexAB and MexXY. This might be a novel method of phage therapy in which bacteriophages pick MDR bacteria to make them more susceptible to conventional antimicrobial agents. This treatment can halt or even alter the emergence of antibiotic-resistant bacterial infections in addition to increasing the effectiveness of treatment in the MDR bacteria (Pelfrene *et al.,* 2021; Terreni *et al.,* 2021; Catalano *et al.,* 2022).

The COVID-19 pandemic may be a contributing factor to the developing global issue of multidrug resistance to medications. The problem of resistance to antibiotics (AMR) persists due to diverted funds from antimicrobial management, high prophylactic consumption of antibiotics in COVID-19 patients, and passive effects of worsening economic circumstances that exacerbate poverty and may influence resistance rates.

Pan drug resistance: Resistance to all antibacterial agents is referred to as pan-drug resistance (PDR). The resistance of infectious bacteria to different antimicrobial agents makes pan drug resistant infections caused by bacteria a serious threat to the general population when combined with the overuse of wide-spectrum antimicrobials in healthcare settings (Karakonstantis *et al.,* 2021; Ozma *et al.,* 2022).

Just a small number of antibacterial agents have efficacy against pan drug resistant Gram-negative bacteria, which include *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli Klebsiella pneumoniae*, and *Acinetobacter baumannii*. These bacteria constitute the most prominent ones which exhibit susceptibility to several antibiotics (Karakonstantis *et al.,* 2020).

Mechanisms of antibiotic resistance: Antibiotic resistance can be classified into two basic categories: acquired and natural. Natural resistance can be mediated, whereby proteins that are regularly found in the bacteria are only triggered to resistant concentrations after antibiotic therapy, or innate, where it happens frequently in microorganisms (Cox and Wright 2013).

Mechanisms of AMR can be divided into four primary groups:

a) Reducing drugs uptake
b) Active efflux of drugs
c) Drugs inactivation
d) Modification of drug targets

Reduced drug uptake, inactivating a drug and drug efflux are the mechanism employed in intrinsic resistance

while acquired resistance uses drug target modification in addition to drug efflux and drug inactivation (Willers *et al.,* 2017). There are differences in the types of mechanisms used by gram+ve and gram-ve bacteria due to their structural differences. Gram-positive bacteria are less likely to use drug uptake limiting mechanism because they don't have lipopolysaccharide (LPS) in outer membrane and also lack the ability to utilize some specific drug efflux mechanisms while gram-ve bacteria can employ all major mechanisms for resistance (Reygaert, 2018). Utilizing input of the hydrolysis of ATP in ABC pumps like DrrAB, OtrC, TlrC, and MlbYZ, or gradients of protons in MFS, MATE, SMR, and RND family pumps, antimicrobial efflux pumps extract the antimicrobial agent from the cell (Abdi *et al.,* 2020). The mechanism of resistance used by bacteria is outlined in Fig. 1.

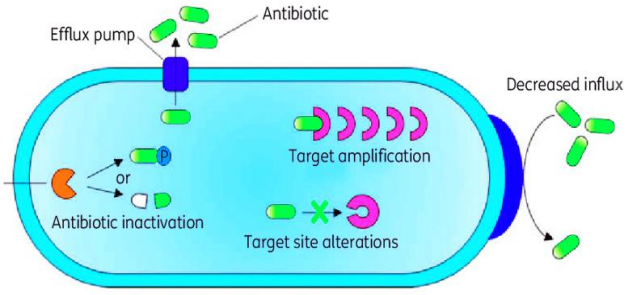

Fig. 1: Diagram outlines the antibiotic resistance methods bacteria use. Multi-drug-resistant pathogens can utilize these methods individually or in combination to resist a variety of antibiotics (Alav *et al.,* 2018).

Drug inactivation: Can reduce the quantity of free antibiotic that is accessible for binding to its internal site by hydrolyzing the antimicrobial agent enzymatically or by forming ineffective metabolites i.e. chloramphenicol, β lactams (Davies, 1994).

Target modification: Encompasses a range of target modifications, including methylation of 23S or 16S rRNA, changes to the peptidoglycan (e.g., glycopeptides), or the formation of alternative low-affinity targets (PBPs) that decrease or entirely inhibit the ability of antibiotics (penicillin) to associate with the receptor (Aslam *et al.,* 2018).

Decreased influx/outer membrane permeability: Antibiotics can effectively penetrate the outermost layer of the membrane via two different routes: typical diffusion porins for hydrophilic antibiotics and a lipid-mediated mechanism for hydrophobic antibiotics. The outermost membrane's lipid and protein constituents strongly influence how sensitive bacterium are to various antibiotics, and drug resistance including changes to these macromolecules is frequent (Nikaido, 1994).

Variations in the microbial cell wall's susceptibility: Gram-negative microbes can primarily cross the outermost layer of bacterium via hydrophilic protein channels. Therefore, alterations that result in altered or reduced production of these channel proteins may lessen the sensitivity of the microbes to different β-lactam antibacterial. It is anticipated that antibiotic resistance will be impacted by mutations in the genomes expressing the outer layer of prions (Goudarzi and Navidinia 2019).

Active antibacterial efflux from bacterial cell: Antibiotic resistance results from microbes not having enough of the antibiotic to have an antibacterial effect. The procedure affects multiple antibacterial and uses energy (Santoni-Rugiu *et al.,* 2019; Uddin *et al.,* 2021; Aslam *et al.,* 2023). Among the most significant efflux exporters are small multidrug resistance (Kermani *et al.,* 2020; Seppälä *et al.,* 2023), multidrug and toxic compound extrusion (Kusakizako *et al.,* 2020; Ku *et al.,* 2022), ATP-binding cassette (Kroll *et al.,* 2020), resistance-nodulation-division (Wang *et al.,* 2021; Zhao *et al.,* 2021), and major facilitator superfamily (Stephen *et al.,* 2023).

Nanoparticles: a novel approach: As an alternative to antibiotics, NPs are now being employed more frequently to target bacteria. The main reason for considering NPs as an alternative to antibiotics is that NPs can successfully avoid microbial resistance. Multiple hazards to public health have emerged as a result of the overuse of antibiotics, including superbugs that are resistant to all known medications and epidemics that are untreatable yet by medicine. The fight against drug resistance necessitates the development of novel, potent bactericidal compounds, and NPs have emerged as a possible solution to this issue (Wang *et al.,* 2017). The antibacterial properties of different types of NPs differ from one another. Nanoparticles can serve as a carrier for better and targeted drug delivery. The relatively smaller size of the NPs makes them ideal for use as antimicrobial therapies (Fernando *et al.,* 2018).

Nanoparticles have been extensively utilized for many years in a number of fields, but with the advancement of nanotechnology, they have recently emerged in the field of medicine. Additionally, the antimicrobial properties of metals against microbes have long been understood and employed. Their anti-infective properties are improved by being formulated as NPs and can be utilized as both carriers for drugs and independent antibacterial agents (Zazo *et al.,* 2017). Numerous methods can be used to characterize metal-based NPs. These techniques offer useful details regarding their structure, physicochemical makeup, and electrical characteristics, all of which are essential for understanding their activity. The most important characteristics of NPs are their size, shape, roughness, and surface energy (Sánchez-López *et al.,* 2020).

Antimicrobial potential of nanoparticles: Even though the specific mechanism of action for nanoparticle's antibacterial activity against microbial infections is not fully understood, it has been observed that NPs can exert their antimicrobial action either directly or by generating a secondary active agent. Damage to the cell wall or plasma membrane, disruption of metabolic pathways, oxidizing the elements within cells, or destruction of DNA are the main factors that cause growth suppression. The size, shape or form, concentration, and NPs interaction with the target microbes determine the mechanism of antibacterial action of NPs. It has been claimed that NPs' antibacterial activity increases with decreasing their size because with

smaller size they have better ability to penetrate membranes of cells (Jamdagni *et al.*, 2018).

Particular characteristics of bacteria describe how they respond when they come into connection with metallic NPs. The primary toxic action of antimicrobials on bacteria is caused by direct contact with the cell membrane so understanding the differences between Gram-positive and Gram-negative bacterial cell walls is critical (Ma *et al.*, 2022). The outer layers of bacteria both Gram-positive and Gram-negative are negatively charged. The thick peptidoglycan layer of Gram-positive bacteria is composed of linear chains that alternate N-acetylglucosamine and N-acetylmuramic acid residues. These chains are connected by a series of 3- 5 amino acids that interconnect one another to create an interlocking network. The majority of Gram-positive bacteria also possess teichoic acids (negatively charged with a significant number of phosphate groups) that rise from their cell walls to their exterior. Contrarily, Gram-negative bacteria possess a thin layer of peptidoglycan, and their structure is a little bit more complicated (Saikachi *et al.*, 2021). Gram-negative bacteria have an outer membrane made of phospholipids and partly phosphorylated LPS, which helps to enhance the negative surface charge of their cell surface. Due to electrostatic forces, negatively charged cell walls in bacteria draw positively charged metallic NPs towards the surface. These metallic NPs build a strong bond with cell membranes and rupture cell walls, which improves the permeability of the cells and interferes with biological activities. Metal ions or NPs produce oxidative stress within cells and ROS cause glutathione oxidation thus hindering bacterial defense against oxidative stress. After that, the metal ions are liberated to interact with cellular components like proteins, and DNA and ultimately impair cellular activities (Sánchez-López *et al.*, 2020). The photodynamic and photothermic effects of NPs have a significant impact as antimicrobial agents, as depicted in Fig. 2. This impact is closely linked to the release of metallic ions and ROS (Balderrama-González *et al.*, 2021).

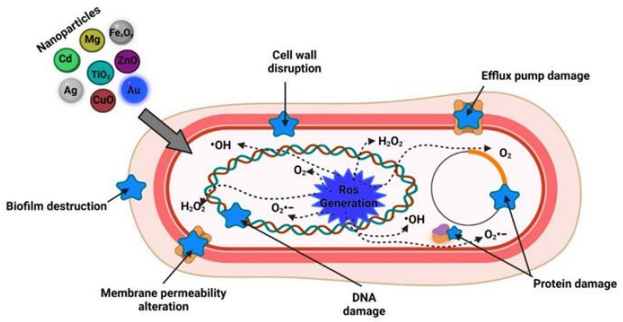

Fig. 2: Mechanism of action for nanoparticles made of inorganic materials.

Interaction between the membrane and cell wall: One of the primary defense mechanisms that microbes have is their cell wall and membrane which are made up of a number of chemicals that aid in facilitating the absorption of NPs (Teichoic acid, the primary substance found in gram-positive microbes, distributes the NPs throughout the network of phosphate molecules, prohibiting them from aggregating. Nonetheless, the dense peptidoglycan barrier and pores of Gram-positive bacteria facilitate the entry of smaller compounds that can harm the cell barrier and ultimately kill the bacterium)

Production of ROS: Bacteria are capable of maintaining equilibrium in the formation of ROS during normal circumstances, one way that NPs can harm bacteria is via the oxidative damage brought on by ROS i.e. hydrogen peroxide (H2O), superoxide radical (O2·−), singlet oxygen (O2), and radial hydroxyl (·OH)

Cell membrane penetration: Nanoparticles break through the cell wall, start emitting ions, and diffusely produce ROS. Emission of metal ions and their binding to the carboxyl and phosphate functional groups in the cell membrane, which have a negative charge (Godoy-Gallardo *et al.*, 2021).

Inhibition of DNA damage and protein synthesis: Nanoparticles disintegrate the enzymes, other proteins synthesized in the bacterial cell membranes, and ribosomal subunit proteins. Similarly, there has been evidence of bacterial DNA destruction, compression, and fragmentation, which has decreased the biological function of genomes (Khorsandi *et al.*, 2021).

Metabolic pathway damage: Nanoparticles go into a cell of bacteria, and their metabolism changes, damaging the cell membrane, creating ROS and ultimately leading to the bacterial death (Yu *et al.*, 2021).

Inhibition of biofilms: By generating metal-ion NPs when they interact with bacterium can alter the pace at which bacteria adhere, damaging biofilms and perhaps inducing metabolic inhibitory processes (Xu *et al.*, 2021).

Types of nanoparticles used as antimicrobial therapy: There are three basic kinds of materials that are employed for drug delivery: Hybrid, inorganic, or organic based NPs. Organic materials, such as polymers and carbon-based, metallic NPs like gold and silver NPS, and metal oxide NPs iron oxide or zinc oxide or copper oxide NPs (El-Hamaky *et al.*, 2023). Hybrid NPs are synthesized by combining both organic and inorganic materials (Gupta *et al.*, 2019).

The NPs of noble metals such as Au, Ag, and Cu have been demonstrated to function as wide spectrum antimicrobials. These metal and metal oxide NPs are typically hazardous due to metal ion discharge, ROS production, or photodynamic effects (Yuan *et al.*, 2018). Chitosan is the most popular natural polymer utilized as a nanocarrier to deliver both antibiotics and non-antibiotic antibacterial medicines. Synthetic polymers are also employed to work as NPs such as PLA, and PCL or PLGA are used to deliver antibacterial drugs (Spirescu *et al.*, 2021).

Fattal *et al.* (1989) investigated that compared to the ordinary control group, rats receiving ampicillin loaded into NPs showed an improved survival ratio. This difference can be attributed to the fact that the previous research needed 40 times less antibiotic to produce the identical outcome with greater dispersion

in tissues, indicating that a lesser amount of antibiotic was needed to produce the identical outcomes (Ianiski *et al.,* 2021; Rawat *et al.,* 2022; Sadr *et al.,* 2023). Nanoparticles with respect to their spectrum and mode of action are given in Table 1.

Medical application of nanoparticles

Nanoparticles as novel drug delivery system: The efficient delivery of the drug to the target site is one of the biggest challenges associated with the treatment of many diseases. Conventional drug delivery methods have significant problems and obstacles, including inadequate distribution throughout the body, limited efficacy, and an inadequate degree of selectivity. To lessen the possible drawbacks of conventional therapy, the latest approach for controlled delivery of drugs was introduced. Controlled drug delivery systems follow the targeted delivery of drugs at required site and protect against the rapid degradation of drug and also decrease the adverse effects. The on-site drug delivery is made possible by combining the drug moiety with the NPs that work as nanocarriers (Devrim and Bozkır 2017). Liposomes, polymeric NPs, solid lipid NPs (SLNP), and dendrimers are some of the kinds of nanocarriers that have been extensively studied as antimicrobial drug delivery systems (Zhang *et al.,* 2010). Antibiotics have been successfully transported via liposomes by reducing drug toxicity and increasing drug effect against microbes by targeted action enhancing the therapeutic efficacy of medications (Devrim and Bozkır 2017).

Liposomes are small-sized spherical-shaped vesicles having an aqueous core covered by a phospholipid's bilayer. Liposomes are made up of natural phospholipids. Their composition makes them less toxic, biocompatible, and biodegradable as compared to other synthetic material based nanocarriers (Yordanov 2014). Polymeric NPs are solid particles composed of multiple biocompatible polymeric matrix that encloses the drug. Their unique polymeric composition makes them stable as compared to liposomes in body fluids. The focus behind formulating polymer - based NPs is on-site targeted drug delivery to maximize therapeutic efficacy and decrease the side effects caused by typical conventional methods (Kalhapure *et al.,* 2015). SLNPs combine the benefits of classic solid NPs alongside liposomes. Through parenteral, topical, ophthalmic, oral, and pulmonary routes of drug administration, SLNPs have shown improved bioavailability and targeted delivery of antimicrobial drugs (Huh and Kwon 2011). Dendrimers are nanosized macromolecules that are biocompatible enhance the efficacy of an active drug and also minimize toxicity. The specificity of their action is determined by their unique molecular structure (Chis *et al.,* 2020). Nanoparticles can easily enter body cells due to their tiny

Table 1: This table summarizes different nanoparticles with respect to their spectrum and mode of action

Mechanism of Action	Type of Nanoparticles	Antimicrobial spectrum	Remarks	References
Release of Metal Ions	Ag (Silver)	Gram-negative bacteria (*Escherichia coli*)	The basic mechanism is ion release by metals, which has been demonstrated by dimension of particles, coating on the surface, and availability of oxygen.	Yuan *et al.* (2018)
	Cu (Copper)	Gram-positive and Gram-negative bacteria	Production of reactive oxygen species and Cu ion release both aided in antibacterial action.	
Generation of reactive oxygen species	Au (Gold) Non-cluster	Gram-positive and Gram-negative bacteria	It has potent antimicrobial action as compared to large sized silver NPs because of excessive ROS production.	
	Cu (Copper)	Gram-positive and Gram-negative bacteria	Production of reactive oxygen species and Cu ion release both aided in antibacterial action.	
	TiO_2 (Titanium dioxide)	Gram-negative bacteria (*Escherichia coli*)	Interaction b/w NPs and bacteria is required for antibacterial action.	
	Al_2O_3 (Aluminum oxide)	Gram-negative bacteria (*Escherichia coli*)	Al_2O_3 produces more ROS as compared to TiO_2 NPs.	
	ZnO Zinc oxide	Gram-positive bacteria (*Staphylococcus aureus*) only	As ZnO nanoparticle size reduced, antibacterial activity gets increased.	
Light-induced photodynamic action	Au (Gold)	Gram-positive and Gram-negative bacteria	Au NPs aggregation help in bacterial imaging by two-photon photoluminescence (TPPL)	
	CuS (Copper sulfide)	Gram-positive and Gram-negative bacteria	ROS generation and heat produced by Near-Infrared irradiation assist in exerting antimicrobial action.	
	TiO_2 (Titanium dioxide)	Gram-negative bacteria (*Escherichia coli*)	Production of ROS by Ultraviolet irradiation at wavelength of 365 nm contributes to the antimicrobial action.	
	ZnO (Zinc oxide)	Gram-negative bacteria (Escherichia coli)	Production of ROS by Ultraviolet irradiation contributes to the antimicrobial action.	
Cell lysis	Ag (Silver)	Gram-positive and some Gram-negative bacteria	Interact with bacterial membranes via electrostatic forces and their accumulation damage the integrity causing cellular fragmentation.	Jamdagni *et al.* (2018)
	Cu (Copper)	Gram-positive and Gram-negative bacteria	Damage to the call membranes, interfering with their integrity leading to cell lysis.	
	ZnO (Zinc oxide)	Gram-positive and Gram-negative bacteria	Invading the cell wall causing rupture of membrane, entering cytoplasm and retard the cell growth.	
DNA/RNA Damage	Ag (Silver)	Gram-positive and some Gram-negative bacteria	The denaturation of bacterial DNA and RNA molecules mediated by ions produced by NPs stop cell division and impairs DNA replication.	
	ZnO (Zinc oxide)	Gram-negative bacteria (*Escherichia coli*)	DNA damage in *E. coli* cells	
	TiO_2 (Titanium dioxide)	Gram-negative bacteria (*Escherichia coli*)	DNA damage in *E. coli* cells	
Interaction Proteins	Au (Gold)	Gram-positive and Gram-negative bacteria	Interfere the normal function of proton pumping ATPase, decreases ATP molecules resulting in reduced metabolism.	
	Ag (Silver)	Gram-negative bacteria (*Escherichia coli*)	Inhibits ATP production	

and controlled size. Nanoparticle-mediated medication delivery has numerous advantages over traditional therapy.

a) Controlled and continued drug release over time provide enhanced therapeutic efficacy.
b) Improved bioavailability and the accurate dose of the drug at the required site.
c) Incorporation of drugs within the core does not require any chemical reaction.
d) Different drugs can be administered to a single site for synergistic effects.
e) The release profile of the drug and degradation behavior can be adjusted by manipulating the size of the nanoparticle (Mahavir *et al.,* 2018).

The pharmacokinetics and pharmacological properties of drugs can be greatly enhanced when they are physically encapsulated, adsorbed, or chemically conjugated into NPs in comparison to their free drug equivalents. The use of NPs for drug delivery has many benefits, including increased drug serum dissolution, increased circulation time throughout the body, sustained and controlled drug release, preferred drug delivery to target organs and tissues, and simultaneous delivery of multiple drug compounds to identical sites for a combined therapeutic approach (Singh *et al.,* 2011).

Tumor targeting: Nanoparticles are capable of providing a desired concentrated dose of medicine in the region of tumor targets because of their improved permeability and retention properties. Also, NPs will limit drug distribution to specific organs, reducing drug contact with healthy tissues (Nikam *et al.,* 2014). Noble metal NPs can migrate into the tumor environment through the openings of the angiogenic vascular system showing targeted action by improved permeability and retention time (Conde *et al.,* 2012).

Medical diagnostics and sensors: NPs are making significant advances in the fields of detection and diagnosis of diseases. These components have been effectively combined with chemical sensors that can identify substances with medicinal relevance (Schröfel *et al.,* 2014). The development of multiplex molecule identification using customizable arrays and the development of novel label-free techniques for recognizing and quantifying a particular interaction using electrochemical techniques are the main goals of nanoparticle-based detection (Emerich and Thanos 2007).

Bioimaging: For the identification and diagnosis of diseases, a variety of bio-imaging techniques, including magnetic resonance imaging, Ultrasound, CT scan, and many other techniques are available. These methods can generate high-quality visuals of internal systems without causing any harm to the patient. Contrast substances are typically utilized in these bio-imaging procedures to distinguish normal tissue from sick tissue as well as to locate the organ or tissue of interest. The primary limitations of the contrasting agents currently used for MRI and CT imaging are their harmful effects, short retention times, and minimal imaging times. Newer substances, such as core-shell NPs have been explored as potential contrast agents since they can give a prolonged image timing and offer biological compatibility (McNamara and Tofai 2017).

Some field applications: Anwar *et al.* (2020) evaluated three types of total six preparations against multidrug resistant *E. coli*. They used three antibiotics coated ZnO nanoparticles (gentamicin coated nanoparticle-GNp; chloramphenicol coated NPs -CNp; and both gentamicin and chloramphenicol coated nanoparticle-GCNp). Sub-clinically positive mastitic milk samples (n=200) of bovine origin were processed for isolation of MDR *E. coli* using microbiological and clinical laboratory and standard institute's protocols. There was significantly ($P<0.05$) the lowest minimum inhibitory concentrations (MICs) and the highest zone of inhibitions (ZOIs) in case of GCNp (10.42±4.51µg/mL and 22.00±1.00mm) followed by GNp (20.79±8.95µg/mL and 20.00±1.00 mm) and then CNp (25.96±8.95µg/mL and 12.33±0.57mm). The study concluded antibiotic coated ZnO NPs significant candidates modulating antibiotic resistance in MDR *E. coli*. Similarly, Nefedova *et al.* (2023) applied NPs of metallic silver (AgNPs) to address the global problem of antibiotic resistance on 200 breeding cows with serous mastitis. According to them, *E. coli* showed decreased sensibility to 31 antibiotics decreased by 27.3%, but after treatment with AgNPs, it increased by 21.2%.

Nanoparticle's safety: NP safety research is lagging behind the application of NPs (Onoue *et al.,* 2014; Missaoui *et al.,* 2018). There is an estimate that about 20% of the NPs are rejected during clinical trials because of safety reasons (Schütz *et al.,* 2013). There could be acute and chronic issues of NP use leading to toxicity and search for their safety. The Acute toxicity judgment of NPs is insufficient to evaluate their safety for many reasons (Missaoui *et al.,* 2021). First, exposure to NPs is an endless daily process, such as workers' exposure during manufacturing or exposure through daily application to patients. Secondly, degraded NPs may take a substantial time, possibly much more than the therapeutic agent's elimination of what they carry. Another important point is that dissolution or degraded products of NPs may also be toxic. Finally, the accumulation and biodistribution of NPs may change with time (Mohammadpour *et al.,* 2019). Such issues need further studies, especially NPs chronic exposure outcomes. These studies should be based on assessing the side effects of chronic NP use in humans/veterinarians both in vitro (industry) and in vivo (clinical setup). Another issue is assessing bioaccumulation in the environment (Oberdörster 2010; Isama 2014; Tang *et al.,* 2015; Mohammadpour *et al.,* 2019). There is a dire need for comprehensive studies to obtain a better grasp of the safety profile of NPs in biological barriers (Lotfipour *et al.,* 2021). In the published literature, there are a few such studies that have been carried out (Zielińska *et al.,* 2020; Yao *et al.,* 2023); more well-designed studies are required to highlight the safety/toxicity of NPs.

Conclusions: Nanoparticles signify a new era in antimicrobial therapy by providing a promising diverse way to combat antibiotic resistance. Because of their small size and wide surface area, they may interact with bacterial pathogens more effectively, which improves their antibacterial efficacy. Nanoparticles can also be designed to selectively target particular bacterial strains or infection sites, minimizing side effects and enhancing

therapeutic efficiency. Due to their versatility, NPs can be used in a variety of ways, including metal and metal oxide NPs, liposomes, dendrimers, and polymeric NPs. Each of these formulations has unique qualities that can be modified to tackle particular antimicrobial challenges. The potential of integrating standard antibiotics with NPs has demonstrated strong synergistic effects providing a broader attacking strategy against antibiotic-resistant microorganisms. Furthermore, rapid and precise antibiotic resistance detection may be revolutionized by nanoparticle-based diagnostic technologies, enabling better patient management and therapy selection.

Authors contribution: AH and AK: Conceptualization. AH and BM: Literature search, collection of articles and draft manuscript writing. AK and XD helped in writing and editing the manuscript. All authors agreed on the final version of the manuscript.

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