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Application of Nanotechnology for Antibacterial Drug Delivery: A Review

Sajjad Mohsin Irayyif, Alwan Al Qushawi, Reham Najem Abdulridha
College of Dentistry, Waist University, Republic of Iraq

Aula Hassoon Obaid
Collage of Medicine, University of Fallujah, Al-Anbar, Iraq

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Annotation: Metal-based nanoparticles have been thoroughly examined for many biological purposes. The WHO states that metal-based nanomaterials have shown efficacy against prioritized pathogens besides diminutive size and specificity for microorganisms. The nanoparticles made from metals exhibit non-specific methods of bacterial toxic effects, as they do not interact with a particular receptor in bacterial cells. This characteristic complicates the development of bacterial resistance and expands the range of antibacterial efficacy. Consequently, most effectiveness studies on nanoparticles made from metals have shown encouraging outcomes against both Gram-positive and Gram-negative bacteria. This paper aims to thoroughly assess the current advancements in using significant metal nanoparticles as antibacterial agents. Particular attention is devoted to silver nanoparticles, but other nanoparticles often used in ant biotherapy, such as gold, zinc oxide, copper, and copper oxide, are also examined. This review's originality stems from the comparative

analysis of various metal nanoparticles, encompassing their manufacturing techniques, physicochemical characterization, pharmacology, and the toxicological risks associated with their application as antibiotics. Their role has been emphasized in advancing different, more vital pharmaceuticals aimed against multi-resistant different types of bacteria.

Keywords: Nanotechnology; Nanomaterials; Bacteria; Medical field.

Introduction

Bacteria developed as some of the first living species on Nature and demonstrated significant adaptability all through time. The discovery of antibiotics in the 20th century was seen as one of humanity's most critical medical triumphs. The inception occurred with the discovery of Salvarsan, one of the first pharmaceuticals effective in treating the infectious illness of syphilis without exhibiting toxicity to patients [1]. However, it was only with the fortuitous discovery of antibiotics through Alexander Fleming in 1928 that antibiotic studies started, culminating in its zenith during the 1950s and 1960s, an era referred to as the "golden age" During 1930 and 1962, approximately 20 different kinds of antibacterial were developed; nevertheless, the emergence of resistant bacterial strains has made identifying new antibacterial chemicals more difficult for the medicine industry [2].

Bacteria resistant to antibiotics are a primary cause of the diminished effectiveness of antimicrobial medicines. Bacterial resistance arises from alterations in microorganisms' capacity to withstand antibacterial treatments, either via their inactivation or by diminishing their therapeutic effectiveness. As time passes, such resistances arise easily in bacteria due to genetic modifications. Misuse and overuse of antibacterial significantly promote such alterations. This results in prolonged infection durations, increased death rates, and additional cost strain on healthcare systems [3]. Resistance to antibiotics can result from genetic modifications in bacteria. Additionally, gene transfer occurs between bacteria or viruses via DNA modification, involving the absorption and integration of fragmented DNA; exchange, which refers to the transmission of bacteria genes mediated by a virus; and the conjugation process, which is the exchange of genetic material between a donor and another bacterium. Resistance to antibiotics manifests via various mechanisms, comprising enzymatic activities of β-lactamases, acetyltransferases, and aminoglycoside-modifying proteins. Altering the capacity of membranes to obstruct the ingress of antimicrobial agents is a standard response system, in addition to modifications in bacterial objectives [4, 5].

Because golden age, different types of antimicrobial agents successful against *Staphylococcus aureus* or other types of bacteria that are resistant to meth (MRSA), have been identified. Nevertheless, several analogues from recognized classes and antibacterial mixes have been introduced. Figure 1 depicts the historical establishment of resistance for some antibiotics alongside drug change and the evolution of sensitivity in organisms [6].

Nanotechnology pertains to the design and use of devices and provides at the nanoscale (1–1,000 nm), using concepts for manipulating compounds at atomic and molecular concentrations. The

advantages of nanoparticles primarily arise from the unique characteristics of substances at the microscopic level, which often diverge from their macroscopic qualities. [7]. The alteration in a material's characteristics is mainly due to the increased surface area-to-volume ratio, which makes them highly reactive, affecting their mechanical and electrical properties. At the nanoscale level, quantum phenomena dictate the physical properties of substances, resulting in considerable alterations in their electromagnetic and optical characteristics [8].

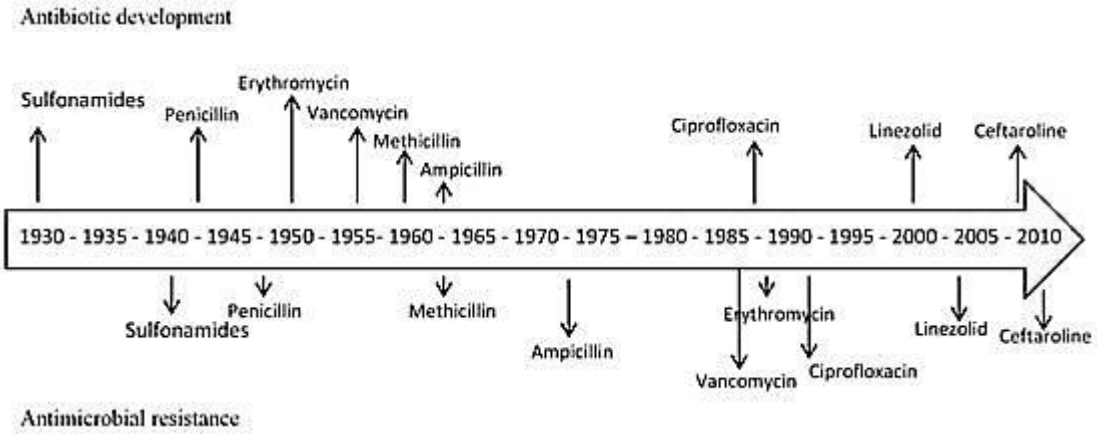

Figure 1. Antibiotic history of the emergence of bacteria that are resistant throughout time [7].

Overview of Metal Nanoparticles

Nanotechnology has significantly impacted several scientific disciplines and advanced the realms of different fields of chemistry, medicine, and others. Due to its capacity to manipulate mechanical and catalytic characteristics of materials, nanotechnology has yielded significant advantages across several scientific disciplines. Nanotechnology has significantly advanced several domains, including synthesis, food production, storage, and biology. Nanotechnology has become significant in medicine because it prevents illnesses, diagnosis, and therapy [9].

The primary drawback in nanotechnology is the restricted size of these materials, which enables them to infiltrate any biological system. Furthermore, insufficient research has been undertaken to provide commentary on the length of time these compounds may persist in the environment or the long-term ramifications, including the accumulation of such elements in ecological and biological systems. Consequently, these nanomaterials' short-, medium-, and long-term impacts remain inadequately comprehended [10].

In several studies, inorganic nanoparticles have shown cytotoxic, genotoxic, and possibly carcinogenic effects, capable of inducing apoptosis and reducing cell growth. Several studies indicate that nanoparticles' toxicity depends on their size and charge. Specific categories of nanoparticles from inorganic substances demonstrate toxicity to humans and bacteria, with their toxicity dependent upon dose and the kind of cell. Inorganic nanoparticles are classified into metal nanoparticles and metal oxide nanomaterials. Research has been conducted on metal oxide nanoparticles and nanoparticles made of metals for their antibacterial properties [11].

Owing to the distinctive antibacterial capabilities of individual metallic nanoparticles, including Ag and other metals, they have been extensively investigated in several studies. Conversely, metal oxide nanomaterials such as TiO_2, Fe_3O_4, ZnO, and CuO are recognized for significant against bacterial efficacy. The principal antimicrobial action of nanostructures generates reactive oxygen species (ROS). Most nanomaterials exhibit efficacy due to their chemical composition and capacity to release metal ions into our surroundings [12].

A metal nanoparticle (MNP) is a small metal with dimensions ranging from 1 to 100 nm in length, width, and size. Such nanomaterials may be synthesized, changed with diverse organic functional compounds, and connected with materials. Small nanoparticles can be used in medicine and

biotechnology to carry genes and drugs. Metallic nanoparticles possess unique characteristics, and the principal characteristics of MNPs include a substantial surface area-to-volume ratio relative to their bulk counterparts. This attribute enhances the relationship between biological and metal-based states, resulting in unique electronic arrangements, plasmon stimulation, quantum confining, short-range ordering, a larger amount of pores, an essential amount of little sites for coordination such as corners and edges, an important number of dangling bonds, and consequently, remarkable physical characteristics and the ability to accommodate many more electrons [13].

The notable advantages of metallic nanoparticles include enhanced Rayleigh scattering, surface-enhanced Raman scattering, increased plasma absorption, biological system imaging, and the ability to ascertain chemical information on metallic nanoscale substrates. Conversely, metallic nanoparticles provide several drawbacks, including particle instability, impurities, biological toxicity, explosion risk, and synthesis challenges. Bacterial resistance poses a significant obstacle to research aimed at developing novel antibiotic medicines. Metal nanoparticles emerge as prospective antibiotic agents, demonstrating significant antibacterial properties in many investigations. The antibacterial mechanisms of metal nanoparticles include forming reactive oxygen species, cation release, damage to biomolecules, depletion of ATP and contact with membranes [14].

Main Mechanisms of Metal-Based Nanoparticles

Bacteria possess distinct properties that elucidate their interactions with metal nanoparticles. Since the principal toxicological effect of antibiotics on microorganisms is from direct contact with the outer layer of the cell, it is essential to understand the differences in the cell walls of the two types of bacteria [15].

The two types of bacteria possess a negatively charged surface. Bacteria with the Gram-positive designation possess a robust peptidoglycan layer composed of straightforward sequences of alternating N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) residues, interconnected by different pairings of 3 to 5 amino acid residues, so creating an intense network. Furthermore, negatively charged teichoic acids, characterized by excessive phosphate groups, project from the cell wall to the outer layer of most Gram-positive bacteria. Conversely, Gram-negative bacterial strains possess a more intricate structure. Besides the thin peptidoglycan layer, Gram-negative bacteria possess a phospholipid-based exterior membrane that incorporates partly phosphorylation lipids (LPS), enhancing the negative charges on the interior membrane's membrane [16].

Microbial walls, characterized by a negative charge, bind electrically charged nanoparticles to their exterior through electrostatic forces. In contrast, positively charged nanoparticles made from metals establish a strong bond with membranes, breaking cell walls and increasing leakage. Furthermore, nanomaterials may liberate metal ions from the extracellular milieu, penetrating the cell and interfering via medical applications. Within the cell, nanoparticles may stimulate the generation of ROS [16, 17]. Oxidative stress induces glutathione oxidation, inhibiting the bacterial antioxidant defence system against ROS. The metallic particles then engage with the structures of biology, such as DNA, affecting cellular functioning. Metal ions may establish robust connections with nitrogen, oxygen, and sulphur, which are prevalent in synthesized chemical materials. Due to the often-non-specific interaction between metal ions and biomolecules, metal-based nanoparticles usually demonstrate a wide range of activity [17].

Production of Metal and Metal Oxide Nanostructures

The small particles do not constitute an innovative science. The natural production of nanoparticles made from metals by some microorganisms has been recorded as a means of substantial element detoxification. However, the versatility of this technology has only been shown in recent years, with the metal of nanomaterials utilized in pharmaceuticals synthesized [18]. The flexibility has piqued the curiosity of technological belonging, which has initiated an ongoing quest for novel

compositions that are used and production techniques. While the study has recently broadened to involve fewer prevalent metals, silver, gold, copper, iron, and zinc are the predominant materials used in metal-based nanoparticles. Transition metals are anticipated to be optimal candidates for producing nanoparticles made from metals due to their partly filled d-orbitals, which enhance their redox activity (facilitating reduction to zerovalent atoms) and promote nanoparticle aggregation. The many synthesis techniques may be categorized into physical procedures, methods involving chemicals, and, in recent years, biological approaches [19].

Physical approaches use a top-down methodology, as shown in Figure 2, beginning with the biggest metal undergoing mechanical forces, which leads to disintegration into increasingly smaller components. This approach, however straightforward, produces nanomaterials with a somewhat broad size range, making it unsuitable for producing metal-based nanoparticles, where size is a critical determinant of function. Conversely, bottom-up techniques are synthesized via nature solvents with medical techniques centered on green synthesis methods involving various microorganisms [20].

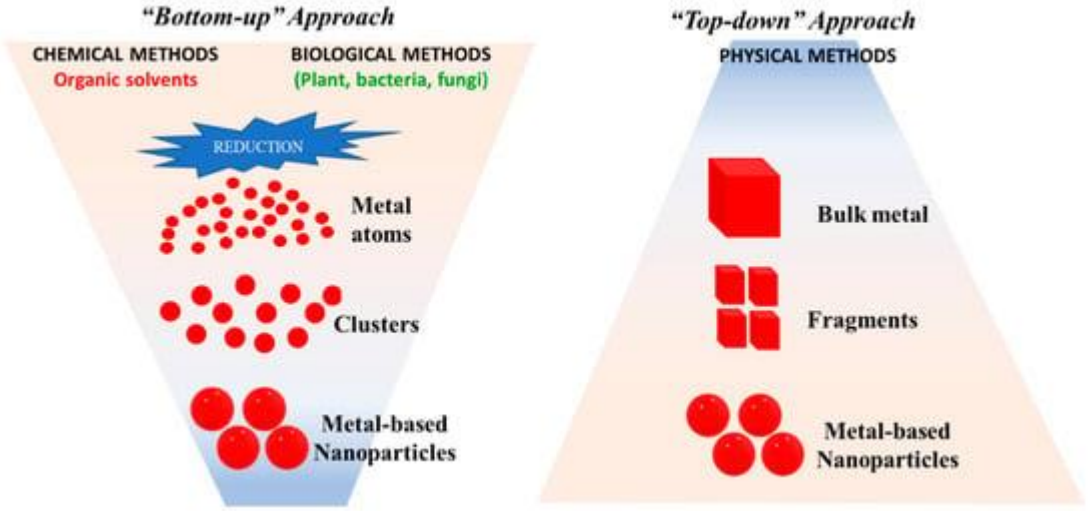

Figure 2. Various techniques are employed for the production of metal-based nanomaterials [20].

Gold nanoparticles (AuNP)

Gold nanoparticles generally vary in size from 4 to 77 nm and exhibit many morphologies, including spherical, triangular, hexagonal, and rod-like forms. Gold nanomaterials drug conjugates have higher against bacterial activity than nanomaterials or medicines alone [21].

Gold nanomaterials interact with several antimicrobial agents, such as ampicillin and vancomycin, the antimicrobial enzyme lysozyme, and other nanomaterials against microscopic activity. The unique characteristics of gold nanoparticles for functionalization provide them a potential option for biofilm treatment. Gold nanoparticles (AuNPs) might inhibit Staphylococcus aureus biofilm formation by around 97% and Acinetobacter baumannii biofilms by about 40%. Vancomycin has been conjugated to gold nanoparticles (AuNPs) for use against vancomycin-resistant enterococci (VRE). Au Van nanoparticles augmented the inhibitory effect of vancomycin against vancomycin-resistant Enterococcus (VRE) [22].

The antibacterial activity of vancomycin-bound gold nanoparticles (VBGNPs) is ascribed to their nonspecific binding to trans peptidases, substituting for terminal peptidases on the outside of bacterial cell glycopeptide precursors. The VBGNP exhibited significant antibacterial action against *E. coli*, which is often resistant to vancomycin owing to its inability to penetrate the outer membrane of Gram-negative bacteria. This indicates that AgNPs facilitate the binding of vancomycin to bacteria, irrespective of their classification as Gram-negative or Gram-positive [23]. Ampicillin-AuNPs have shown the ability to eradicate ampicillin-resistant bacteria, including *P. aeruginosa*,

Enterobacter aerogenes, and *E. coli* K 12 sub-strain DH5-alpha [24].

Silver nanoparticles (AgNP)

Silver nanoparticles have broad-spectrum antibacterial activity towards bacteria of all kinds of microscopic. Silver nanoparticles (AgNPs) often possess a size ranging from one to one hundred nanometers, involving around 20 to 15,000 Ag atoms [25]. Silver nanoparticles may be produced in many ways [25, 26]. Some research has been conducted on combining silver nanoparticles with various antibacterial. The use of able aztreonam is being illustrated to not eliminate biofilms being formed and to enhance their growth by up to 250% relative to treatment cellulose. The amalgamation of aztreonam with AgNPs decreased the growth of biofilm. The mechanism by which AgNP performs its antimicrobial activity remains unclear; nonetheless, it is strongly proposed that reactive oxygen species (ROS) inflict damage on bacterial cells, resulting in DNA and protein impairment [27], as shown in Figure 3.

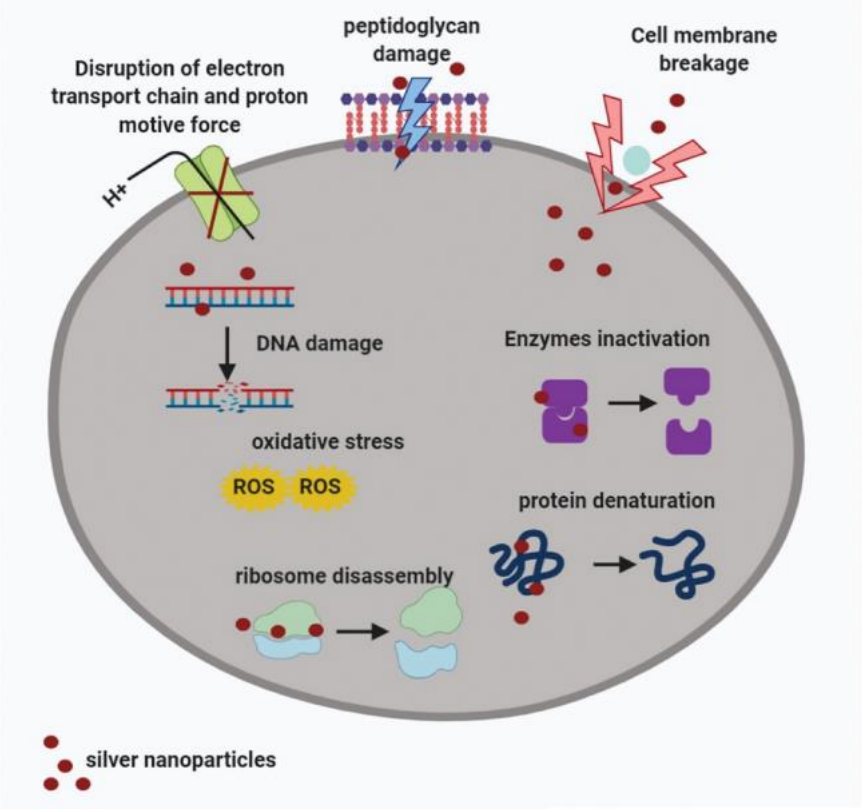

Figure 3. Proposed processes behind the antibacterial activity of silver nanoparticles. (1) AgNPs follow the microbial cell surface, resulting in membrane impairment and altered transport activity; (2) AgNPs infiltrate microbial cells, interacting with cellular organelles and biomolecules, thereby affecting cellular processes; (3) AgNPs induce an elevation of reactive oxygen species (ROS) within microbial cells, leading to cellular damage; and (4) AgNPs regulate cellular signaling pathways, ultimately triggering cell death [27].

Advantages of nanoparticles

1. Enhanced pharmaceutical solubility:

The field of nanotechnology has been employed to improve the solubility of medications with limited solubility in water. Numerous pharmaceuticals that have possible therapeutic value have been unsuccessful in research studies due to solubility challenges, poor permeability, limited bioavailability, and various other adverse biological properties [28].

2. Augmented stability:

Appropriate selection of surfactants and stabilizers may provide a physically stable alternate product

form in nanosuspensions. Nanoparticles have provided enhanced stability against coalescence. Furthermore, nanoparticles include an internal core that facilitates the incorporation of hydrophobic medicines, leading to improved stability. Research indicates that nano-formulations may enhance the stability of protein pharmaceuticals via PEGylation. Solid lipid nanoparticles are applicable for the administration of both hydrophilic and hydrophobic pharmaceuticals [29].

3. Decreased adverse effects:

Nanomedicine often exhibits enhanced specificity in the administration of pharmaceuticals to designated locations. Consequently, the adverse consequences may be mitigated. Polymers are often used to encapsulate pharmaceuticals into nanoparticles, improving the selectivity of medications to specified receptors, hence augmenting therapeutic efficacy and reducing adverse effects [30].

4. Multimodal technology for antibacterial activity:

A small particle consists of many parts exhibiting antibacterial characteristics. Lam et al. provided an example in which a nanoparticle of an antibiotic, encapsulated in an antibacterial core material (metal or metal oxide) and surrounded by a polymeric shell, exhibits antimicrobial action; this combination approach allows the small particle complex to employ three distinct antibacterial mechanisms, thereby increasing the probability of therapeutic effectiveness. Wu et al. synthesized zinc-doped copper oxide nanoparticles with substantial bactericidal effectiveness [31], as seen in Figure 4.

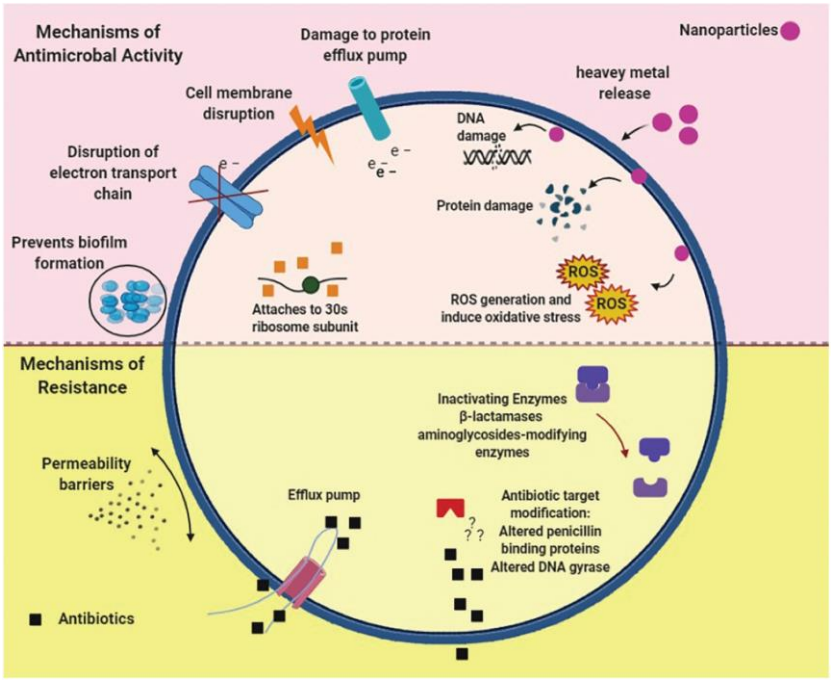

Figure 4. Various mechanisms for resistance associated with bacteria and the effects of nanomaterials [31].

The use of nanotechnology in the Management of viral illnesses

1. Imperative for Non-Antibiotic Strategies in Disease Control

Despite the transformative impact of antibacterial agents on human history through the effective treatment of numerous infectious diseases and the facilitation of major surgical procedures with a marked decrease in surgical site infections, antimicrobial resistance emerged swiftly following the introduction of these agents, rendering some previously effective treatments inaccessible [32].

The rise of widely resistant drugs and pan-drug-resistant bacteria has posed considerable treatment problems in the standard medical management of viral illnesses. The gap between the slow production of novel antibiotics and the fast change of antimicrobial resistance necessitates the exploration of unique non-classical therapy options to effectively battle illnesses with significant

AMR. Various treatment tactics have been used, including organic and synthetic substances, prebiotics, probiotics, antibiotic peptides, bacteriophages, predatory bacteria, immunotherapy, and vaccines. Nanoparticles may provide critical tools in the fight against illnesses demonstrating significant antibiotic resistance [33].

2. Essential Tenets of Nanotechnology in the Control of Infectious Illnesses

Nanomaterials may treat infectious diseases, including resistant infections returned to their tiny dimension and distinctive electrical, conductive, and chemical properties. Their characteristics and dimensions may facilitate the traversal of bacterial membranes and the targeting of certain biosynthetic and enzymatic processes. This contrasts with traditional antimicrobials, which may fail to achieve sufficient intracellular concentrations due to the scarcity of pores and the requisite transport mechanisms for cellular entry, as well as the efflux mechanisms and enzymatic inhibition employed by target cells to expel antimicrobial agents. Nanoscale particles may operate via many strategies to combat infections. They may possess intrinsic antibacterial properties or function as carriers for antibacterial. In these instances. Inorganic nanoparticles may possess intrinsic antibiotic properties and exhibit several modes of antibacterial action. These are called nanobacteriocides, while nanoparticles functioning as nanoparticle-based delivery systems for transporting conventional antibiotics are termed nanocarriers [34].

3. Nanotechnology, also known as Enhanced Medication Transport in the Treating of viral diseases

Nanomaterials may be used to treat infectious disorders by facilitating the targeted distribution of antibiotics, hence enhancing their pharmacological effects via improved absorption and increased transport to tissues and target microbial cells. This provides this by encapsulating amphotericin B inside the core of an anhydrous crystal formed from calcium and phospholipids. The resulting composition radically alters the mechanism of action of the medicine, allowing, for the initial time, consumption, which had been limited to intravenous delivery for decades. This medicine has not yet received FDA approval for clinical usage [35].

Liposomes are the primary nanomaterials used to enhance the delivery of medications for both therapeutic and cardiovascular purposes. They are appropriate for both polar and water-friendly substances. Liposomes has several advantages that make them ideal candidates for drug delivery. They are environmentally friendly and biodegradable, composed of components similar to biological cell walls. Moreover, they may be modified in several dimensions, such as as dimensions, fatty acids composition, and overall surface charge, facilitating alterations to their half-life, medicine, and drug delivery systems. Ultimately, they can merge with membranes, whether those of human cells or pathogens, facilitating the introduction of the antibiotic into the pathogen or, in the event of intracellular infection, into human cells. An instance of liposomes functioning as carrier molecules in infection therapeutics is the administration of antiretrovirals, such as zidovudine or indinavir, for HIV infection, which facilitates more effective drug delivery to lymphoid tissues compared to non-liposomal administration [36].

Dendrimers that may function as carriers of medicinal products in the management of viral illnesses. Their hyper-branched design, with a single core and dimensional divisions, improves the ability to dissolve hydrophobic medications, increasing their efficacy [37]. The administration of efavirenz using dendrimers has been investigated, resulting in improved medication transport to immune system cells [36].

4. Antimicrobial Agents Nanoparticles

Metal nanoparticles may harm pathogens by potentially inducing the formation of ROS under certain conditions, such as exposure to UV light. Metallic nanoparticles composed of Au or metal oxides have considerable antibacterial efficacy concerning pathogenic organisms, viruses, and fungi [10, 38].

AgNPs function as antibiotics through four processes: adhesion to microbial cells, Destabilization of the mitochondrial surface and modification of flexibility, leading to the formation of ROS and free radicals, which have harmful effects on the cells of bacteria, and initiation of modifications in the exchange of signals within the microbe that causes infection. Initially, AgNPs adhere to the pathogen's membrane, mostly influenced by their net charge, as part of their antibacterial action [39]. The AgNPs with a more positive net charge exhibit enhanced antimicrobial efficacy due to their superior capacity to adhere to the pathogen's membrane layer, although elevated concentrations of AgNPs can also induce a significant inhibitory effect by saturating the bacteria's layer. Upon adhering to the microorganism's cell wall, diminutive AgNPs may infiltrate the membrane, whilst bigger AgNPs may persist on the microorganism's surface. In both instances, the nanoparticles release Ag+ ions, compromising the microorganism's barrier and leaking cellular contents. This membrane instability may let even big AgNPs infiltrate the pathogen, enabling them to function intracellularly. Upon introducing the target bacterium, AgNPs and released Ag+ ions may engage with numerous components of the living thing, including proteins, DNA, and lipids, obstructing multiple essential biological activities. They may produce free radicals, ROS, and oxidative stress, which combine with carboxyl, thiol, and phosphate chains in amino acids, thus affecting their ability to function and preventing microbial proliferation. Ultimately, AgNPs exhibited enhanced penetration in microbial biofilms dependent on pH [40]. This leads to the sustained growth of AgNPs in biofilms, suppressing microbial biofilm formation and enhancing antibiotic effectiveness.

Conclusion

The use of nanotechnology in antibacterial medicine delivery signifies substantial progress in combating infectious illnesses. This study emphasizes the unique methodologies used in creating nanocarriers that improve the effectiveness, bioavailability, and targeted delivery of antibacterial drugs. Researchers use the distinctive characteristics of nanomaterials to surmount the constraints of traditional drug delivery techniques, including inadequate solubility and non-specific dispersion. Moreover, the capacity to engineer nanoparticles with tailored surface changes facilitates superior contact with bacterial cells, possibly resulting in greater therapeutic efficacy. As nanotechnology advances, future research must prioritise optimizing these systems for clinical applications, guaranteeing safety and biocompatibility, and tackling the obstacles posed by bacterial resistance. The use of nanotechnology in antibacterial medication delivery systems has the potential to transform treatment methodologies and enhance patient outcomes in the fight against bacterial illnesses.

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