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REVIEW

Revisiting the smart metallic nanomaterials: advances in nanotechnology-based antimicrobials

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Abstract
Despite significant advancements in diagnostics and treatments over the years, the problem of antimicrobial drug resistance remains a pressing issue in public health. The reduced effectiveness of existing antimicrobial drugs has prompted efforts to seek alternative treatments for microbial pathogens or develop new drug candidates. Interestingly, nanomaterials are currently gaining global attention as a possible next-generation antibiotics. Nanotechnology holds significant importance, particularly when addressing infections caused by multi-drug-resistant organisms. Alternatively, these biomaterials can also be combined with antibiotics and other potent biomaterials, providing excellent synergistic effects. Over the past two decades, nanoparticles have gained significant attention among research communities. Despite the complexity of some of their synthesis strategies and chemistry, unrelenting efforts have been recorded in synthesizing potent and highly effective nanomaterials using different approaches. With the ongoing advancements in nanotechnology, integrating it into medical procedures presents novel approaches for improving the standard of patient healthcare. Although the field of nanotechnology offers promises, much remains to be learned to overcome the several inherent issues limiting their full translation to clinics. Here, we comprehensively discussed nanotechnology-based materials, focusing exclusively on metallic nanomaterials and highlighting the advances in their synthesis, chemistry, and mechanisms of action against bacterial pathogens. Importantly, we delve into the current challenges and prospects associated with the technology.

Keywords Nanotechnology · Nanoparticles · Metallic nanoparticles · Nanoparticles synthesis · Antimicrobial resistance · bacteria

Introduction

Managing infectious diseases due to bacterial pathogens presents a multitude of challenges that require strategic solutions. The primary impediment to effective treatment and management of infectious diseases is the absence of safe and efficacious drugs. This deficiency lies at the heart of our inability to combat these diseases effectively. In certain instances, the ineffectiveness of drugs can be attributed to pathogen resistance, necessitating costlier treatment

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regimens for a cure. Furthermore, these challenges are exacerbated in Low and Middle-Income Countries (LMIC). Low patient adherence to prescribed therapies and the need for continuous patient monitoring pose significant hurdles to achieving successful infectious disease treatment. Overcoming these obstacles requires a concerted effort at both the scientific and policy levels.

The field of nanotechnology has tremendous potential to transform the identification and management of a broad range of illnesses (Mba and Nweze 2021, 2022; Aderibigbe 2017; Wang et al. 2021; Al-Awsi et al. 2023). Nanotechnology and nanobiotechnology are relatively recent innovations that involve designing and creating structures at atomic, molecular, or macromolecular levels by efficiently manipulating or modifying the fundamental structures of materials. Nanoparticles range between 1 and 100 nm in dimension (Yetisgin et al. 2020; Joudeh et al., 2022). Extensive research efforts spanning several decades have resulted in the development of nanosystems, including FDA-approved chemotherapeutics, anesthetics, imaging agents, and nutritional supplements, among others. Unsurprisingly, nanotechnology has undergone rigorous evaluation for enhancing the treatment of infectious diseases due to bacterial pathogens (Al-Awsi et al. 2023).

Nanomaterials possessing physicochemical attributes that influence biological processes can be synthesized from diverse materials (Joudeh et al., 2022; Kirtane et al. 2021). These nanomaterials exhibit numerous distinctive features and capabilities due to their unique structural characteristics, including their favorable size, heightened solubility, improved capacity to traverse cellular barriers, and heightened reactivity (Hajipour et al., 2023). Furthermore, the activity of nanoparticles depends on their composition, size, and shape. Over the years, nanoparticles have received considerable attention due to their wide application in different fields and as an antimicrobial agent (Stark et al. 2015; Rai and Ferreira 2021; Dadfar et al. 2019; Najahi-Missaoui et al. 2020). The advent of nanotechnology has ignited fresh optimism in addressing contemporary human challenges. Over recent decades, nanotechnology has emerged as a significant factor impacting various industries, leading to a rapid proliferation of nanomaterial applications across multiple domains. The pharmaceutical and medical sectors, in particular, have witnessed substantial benefits from nanotechnology, giving rise to a range of novel products in the market (Stark et al. 2015; Mazayen et al. 2022).

One of the remarkable advantages of nanotechnology lies in its precise targeting capabilities, which offer substantial benefits for advancing medical science and refining the treatment of infectious diseases. This potential is particularly significant in the context of diseases like malaria, traditionally treated with chemotherapy drugs associated with adverse side effects, dosing inconsistencies, and the emergence of drug resistance (Qasim et al. 2014; Kirtane et al. 2021a). Nanoparticles (NPs) are now being considered a promising alternative to antimicrobial agents, primarily because of their significant therapeutic potential against microbial cells. The use of combinatorial therapy, which involves combining NPs with antibiotics, substantially diminishes the required antibiotic dosage. This approach mitigates the toxicity associated with various antibiotics and curbs the development of antibiotic resistance. Embracing combinatorial therapy could pave the way for NPs to complement existing antimicrobial treatments, thereby contributing to the fight against microbial resistance. Despite the potential NPs are promising materials against superbugs, there is still much to be discovered about their activities.

This review offers an overview of several facets, including the synthesis of metallic nanoparticles and the application of metallic nanomaterials in medicine, especially in preventing drug-resistant bacterial pathogens. Finally, we discuss the challenges of translating these technologies from the laboratory to clinical practice.

Increasing resistance to antimicrobial agents and the need for alternative treatment approach

The era of groundbreaking antibiotic discoveries began with Sir Alexander Fleming's momentous finding in 1928 when he uncovered penicillin from the *Penicillium rubens* mold. This discovery marked the zenith of antibiotic exploration and persisted until the mid-1950s. The period spanning from the 1940s to the 1960s is often referred to as the "Golden Age," during which the majority of antibiotics still used today were identified. Regrettably, the momentum in antibiotic discovery has waned since that time, coinciding with the emergence of multidrug-resistant pathogens. Bacterial resistance to antibiotics has been evident almost since the dawn of the antibiotic era. Even prior to the therapeutic use of penicillin in 1940, the first penicillin-resistant *Staphylococcus* strain had already been documented. Despite the introduction of new antibiotics, instances of methicillin-resistant *Staphylococcus* strains were recorded. As efforts were being made to combat antimicrobial resistance (AMR), more resilient strains continued to emerge. These included vancomycin-resistant strains of coagulase-negative *Staphylococci* (CoNS), vancomycin-resistant *Enterococcus* (VRE), and vancomycin-resistant *Staphylococcus aureus* (VRSA) (Zaman et al. 2017; Suay-García and Pérez-Gracia 2019; Salam et al. 2023). As if this wasn't enough, resistance to β-lactam antibiotics (cephalosporins) developed and introduced in 1945 to tackle penicillin-resistant strains

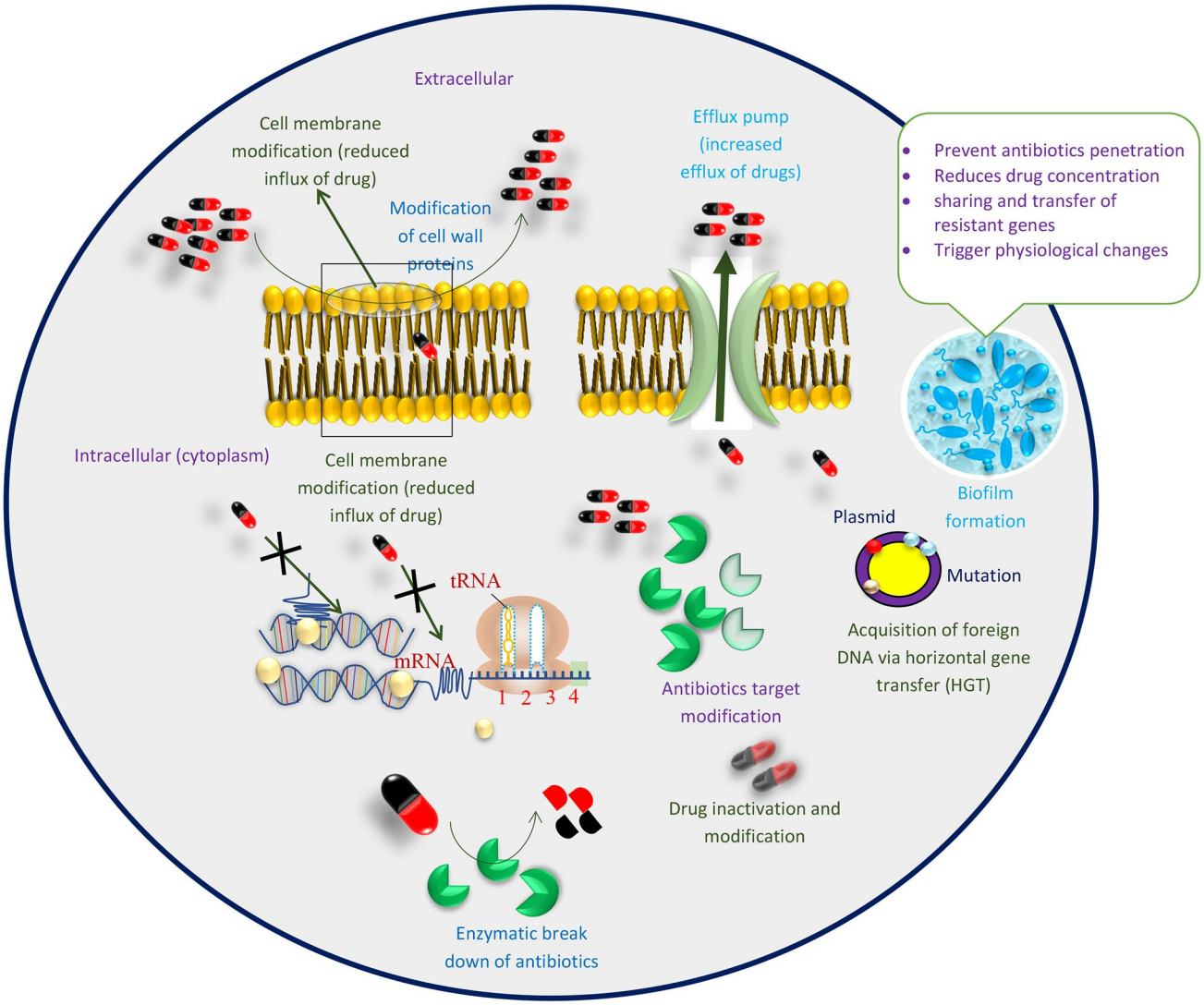

Fig. 1 Mechanism of microbial resistance to antibiotics

was reported. Subsequently, resistance to many other antibiotics was reported, including tetracycline, fluoroquinolone, and carbapenems, especially among enterobacterales. While the pharmaceutical industries introduced two new antibiotic classes between 1960 and 1980, the pace of discovery has declined.

Currently, bacterial superbugs are rampant, threatening therapeutic efforts. These superbugs are microorganisms that have developed resistance to multiple or all antimicrobial agents typically used to combat them. Moreover, these pathogens use different mechanisms to evade antimicrobial attack (Figure 1). Currently, infections caused by superbugs often present a significant challenge in terms of treatment, with limited or sometimes even nonexistent therapeutic options (Salam et al. 2023). The emergence of multidrug-resistant bacteria can be attributed to prolonged and widespread antibiotic usage in treating infections caused by these organisms. In healthcare, superbugs are a significant concern, especially in hospital-acquired or healthcare-associated infections (Mancuso et al. 2023). Infections due to multidrug-resistant pathogens increase morbidity and mortality rates, leading to elevated treatment costs and extended hospital stays (Chinemerem et al., 2022). This underscores the urgent need for research and development of alternative treatments and prevention strategies to combat the growing threat posed by superbugs.

Antibiotic resistance is one of the top three global public health challenges recognized by the World Health Organization (WHO) in the 21st century. The ESKAPE group, which comprises Enterococcus, Staphylococcus, Klebsiella, Actinobacter, Pseudomonas, and Enterobacter, represents the most pressing concern, given their association with elevated mortality rates (Chinemerem et al., 2022; Mancuso et al. 2023). These superbugs also pose substantial global

health challenges and are encountered frequently in clinical settings. The proliferation of multidrug-resistant bacteria and other resilient pathogens has significantly constrained the available therapeutic and preventive measures. How microbes adapt to antimicrobial attacks is a significant example of evolution in action. Despite significant progress in diagnoses and therapeutics, microbial infections still cause approximately 3 million deaths annually in developing nations (Antimicrobial Resistance Collaborators 2022). Developed countries are not immune to this problem either. As a result, AMR has become a pressing global public health concern within the field of medicine. In the United States alone, the economic impact of multidrug-resistant (MDR) microbes is estimated at around $20 billion annually (Dadgostar 2019). The challenge of resistance often leaves healthcare providers with limited options for effectively treating infected patients.

Therefore, these challenges underscore the demand for alternative treatments against microbial pathogens. The ineffectiveness of the majority of antibiotics prompts the quest for improved therapeutic choices. Nanoparticles present a promising alternative for addressing many bacterial infections, particularly those caused by multi-drug resistant strains. Furthermore, the potential synergistic benefits of combining nanoparticles with antibiotics will be explored in detail within this review.

Synthesis of nanoparticles

Generally, two methods are used in synthesizing nanoparticles: top-down and bottom-up approaches (Paramasivam et al. 2021). (Fig. 2). The top-down approach involves the disincorporation of bulk materials producing nanoparticles. The bottom-up approach involves assembling single atoms and molecules to produce nano-sized particles (Bayda et al., 2019; Kumar et al. 2017). The top-down method uses the physical method, while the bottom-up approach involves both chemical and biological methods. The synthesized nanomaterial can be characterized using different approaches (Table 1).

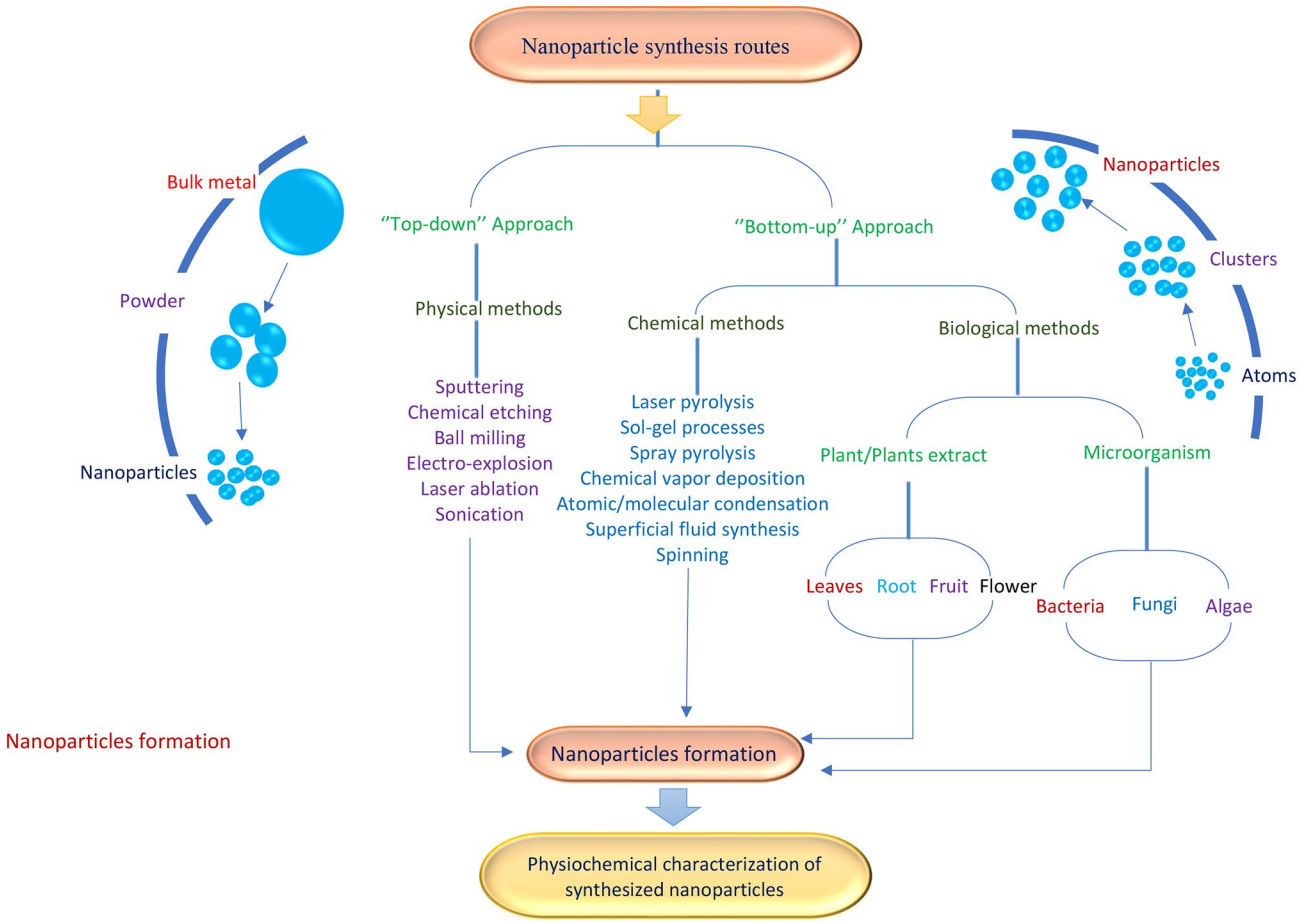

Fig. 2 Flow chat for nanoparticles synthesis and characterization FTRI = Fourier transform infrared, TEM = Transmission electron microscopy, SEM = Scanning electron microscopy, XRD = X-ray diffraction

Table 1 different approaches for characterizing nanoparticles and their features

S/No	Characterization methods	Properties
1	UV-Visible spectroscopy	Determination of nanoparticle formation
2	Fourier transform infrared (FTIR)	Morphological characterization
3	Scanning electron microscopy (SEM)	It is based on the electron scanning principle It offers the vital information about the nanomaterial at the nanoscale level. Can be used to detect the morphology of nanomaterials and their dispersion in the bulk or matrix
4	Transmission electron microscopy (TEM)	Controlled by the electron transmittance principle. it provides information on the bulk material can be used to study the diverse morphologies of the AuNPs
5	X-ray diffraction (XRD)	Important for the evaluation and calculation of crystalline nanoparticle size and for nanoparticle confirmation. It is one of the most useful characterization techniques. It provides information on nanomaterials structural features It gives insight into the crystallinity and phase of nanoparticles. It provides an idea about the size of the nanoparticle Difficult in the correct measurement of the structure of nanomaterial, especially for smaller nanoparticles with a size of < 100 atoms. Furthermore, nanoparticles characterized by greater amorphous attributes and a variety of inter-atomic distances may influence the diffractogram. Consequently, it is imperative to make a valid assessment by comparing the diffractograms of bimetallic nanoparticles to those of their respective monometallic counterparts and their physical blends to acquire dependable data. Used to determine the atomic structure of nanomaterials Important in both qualitative and quantitative analysis.
6	Energy dispersive X-ray (EDX)	EDX when fixed with field emission scanning electron miscopy (FE-SEM) or TEM device is used to study the elemental composition with a rough idea of percentage weight. It gives support to SEM and other methods for the confirmation of the elements in synthesized nanomaterial
7	XPS	Most sensitive technique It works on the basic spectroscopic principles Important in determining the actual elemental ratio and actual nature of bonding of the elements in the nanoparticles. It is a surface-sensitive technique Can be used in in-depth profiling investigations to understand the overall composition and the compositional alterations with depth.
8	Atomic force microscopy (AFM)	Used to determine the size, shape, and surface area of synthesized nanoparticles.
9	Surface-enhanced Raman spectroscopy (SERS) FT-IR	Used to study vibrational features – this feature is due to the SPR in the semiconductor system It is the most developed characterization method
10	Brunauer–Emmett–Teller (BET) theorem.	it is the best method to ascertain the surface area of nanomaterials. it operates on the adsorption and desorption principle and BET theorem. Its large surface area makes it possible for this method to be used for different applications
11	Ultraviolet–visible (UV–Vis), photoluminescence (PL) and the null ellipsometer	Used in determining nanomaterials optical properties Used to understand the optical properties of the photoactive materials Offers extra information and insight about the absorption or emission capacity of nanomaterials.

Table 1 (continued)

S/No	Characterization methods	Properties
12	UV/vis- diffuse reflectance spectrometer (DRS) Extra infromation	Used in determining the optical transmittance, absorption, and reflectance. Used specifically to determine the bandgaps (important to determine the photoactivity and conductance of materials) of nanoparticles and other nanomaterials. Used to visualize the absorption shift in case of doping, formation of composite or heterostructure of nanomaterials a) Various techniques can be employed to gauge the dimensions of nanoparticles, including TEM, SEM, XRD, AFM, and dynamic light scattering (DLS). TEM, SEM, XRD, and AFM provide insights into particle size, while for exceedingly minute dimensions, the zeta potential size analyzer/DLS can be employed to assess nanoparticle size. b) Comprehending the composition and bonding characteristics of nanomaterials necessitates a keen focus on their structural attributes. Common methods for scrutinizing these structural features include XRD, BET, EDX, XPS, IR, Raman spectroscopy, and Zeta size analyzers. c) In the realm of photocatalytic applications, the optical properties of nanomaterials assume great significance. The Beer-Lambert law and fundamental principles of light, as elucidated by Swinehart in 1962, offer insights into nanoparticle properties such as absorption, reflectance, luminescence, and phosphorescence. d) For a foundational understanding of nanomaterials' practical applications, a thorough grasp of absorption and reflection values proves highly pertinent.

Major limitations and disadvantages of the physical method include agglomeration, greater power consumption, long duration of synthesis, complex equipment/machinery needed, and high operating cost (Table 2). Physical and chemical methods are labor-intensive. They are also very hazardous. In addition, physical and chemical methods are associated with toxicity and high-energy requirements. Therefore, biological synthesis (green synthesis) is currently the most promising nanoparticle production method (Shah et al. 2015; Bahrulolum et al. 2021). Any modification during the synthesis of nanoparticles can significantly alter the size. The structure and stability, in addition to the assembling patterns of the nanoparticles, can also be affected. All these parameters greatly influence the antimicrobial potential of nanoparticles.

Chemical synthesis

Chemical synthesis utilizes several synthesis conditions with diverse time, temperature, and reactant concentrations. Alterations of these conditions greatly affect the size and spatial attributes of the resulting nanoparticle. The chemical method of synthesizing nanoparticles is characterized by low yield, capital intensive, toxicity, and non-eco-friendly conditions.

The methods used in chemical synthesis are made to occur during the liquid phase, and the general technique involves (a) dissolving the metal salts in aqueous solutions, (b) disintegration into positively and negatively charged ions, and (c) nanotization (neutral particle formation). Several chemical processes are used in the reduction of metal ions to nanoparticles. Modifying the reducing and capping agents is very crucial to synthesizing nanoparticles with specific attributes such as size, shape, and dispersion rate (Singh et al. 2018a; Ying et al. 2022; Javed et al. 2020, 2022). Stabilizing agents are employed to prevent the aggregation of nanoparticles. Nonetheless, for the safety and efficacy of this procedure, the following factors should be taken into account: (a) the choice of substances with relatively low levels of toxicity, (b) the utilization of environmentally benign reducing agents, and (c) the selection of an appropriate solvent medium.

The chemical synthesis of nanoparticles employs various chemical reductants. The synthesis process achieves stabilization through electrostatic or steric repulsion mechanisms. Consequently, these methods entail the use of substantial quantities of chemicals that pose risks to both human health and the immediate environment. The pursuit of a straightforward, non-toxic, and eco-friendly approach to producing nanoparticles remains a compelling area of exploration.

Table 2 different methods of nanoparticle synthesis

Synthesis methods	General remark
Physical synthesis	Agglomeration – this is because this method does not make use of capping agents Greater power consumed Long duration of synthesis Complex equipment/machinery needed High operating cost The physical method does not involve the use of chemicals which frequently release toxic material hazardous to human health and the immediate environment. • Evaporation-condensation approach • Laser ablation approach
Chemical synthesis	Utilize several chemical processes in reducing the metal ions to Nps chemical reductants: N-dimethylformamide (DMF), Citrate-used in the Turkevich method, Ethylene glycol ($C_2H_6O_6$), Glucose, Sodium borohydride-used in the BSS method, Hydrazine (N_2H_4), Dextrose, Hydrazine hydrate, Ascorbate Capping and surfactant agents: Chitosan, Cellulose, Oleylamine gluconic acid, Polymers (polymethacrylic acid, PMAA), Poly N-vinyl-2-pyrrolidone (PVP), Poymethylmethancrylate (PMMA), Polyethlene glycol (PEG). low yield capital intensive toxicity noneco-friendly
Green/biological synthesis	intracellularly or extracellularly synthesized from microorganisms or higher plants. Bacteria is mostly used in Nps synthesis. This is due to their ease of culturing, extracellular production, relatively mild experimental conditions (temperature, pressure, pH), short generation time, and easy downstream processing. Have more advantages and thus have gained an upper hand over the physical and chemical method Energy Efficient Higher stability, Higher solubility and yield Low-cost production Environmental friendly Important in the pharmaceutical industry Diverse biomedical application.

Green/biological/biogenic synthesis

Considering the toxicity and high-energy requirement associated with the physical and chemical approaches, biological synthesis (green synthesis) is currently the most promising nanoparticle production method (Bahrulolum et al. 2021; Abbasi et al. 2023). The biological method has more advantages and has gained an upper hand over chemical and physical methods (Table 2). Nanoparticle biosynthesis is classified as a bottom-up approach (Fig. 2). Nanoparticles can either be intracellularly or extracellularly synthesized from microorganisms or higher plants (Ghosh et al. 2021; Kapoor et al. 2021; Bahrulolum et al. 2021). Metals like silver (Ag), aluminum (Al), palladium (Pd), zinc (Zn), iron (Fe), copper (Cu), titanium (Ti), and gold (Au) have frequently been used in nanoparticle synthesis. However, to date, nanoparticle synthesis is mostly focused on AgNps. Green synthesis that utilizes microorganisms and plant extracts is currently a valuable process for nanoparticle synthesis.

The use of plants in the formulation of nanoparticles

This entails the production of nanoparticles using plant materials or biomass. This method of synthesis uses non-toxic chemical solvents like biological extracts. It also makes use of microwave-assisted synthesis. The size of nanoparticles synthesized using this method depends on certain properties such as oxidation, dissolution, electron transfer, adsorption/desorption, redox cycles, Fenton reactions, and surface pH (Hano and Abbasi et al., 2021). Green synthesis exhibits more favorable characteristics, including enhanced stability, increased solubility, and greater yield. It is less laborious and more cost-effective (Habeeb et al., 2022; Mustapha et al. 2022). Phytochemicals are abundant in several plant extracts. They have the potential to reduce metallic ions, leading to nanoparticle formation (Fig. 3).

Over the years, there has been a growing interest in nanoparticle synthesis using plant extract because of its efficiency. This is because the extract can serve as both the reducing and capping agents. Several researchers have investigated the green synthesis of AgNps using plant extracts (Carson et al. 2020; Mohanta et al. 2022; Erenler et al. 2023; Ahmad et al. 2022; Nawabjohn et al. 2022) (Table 1).

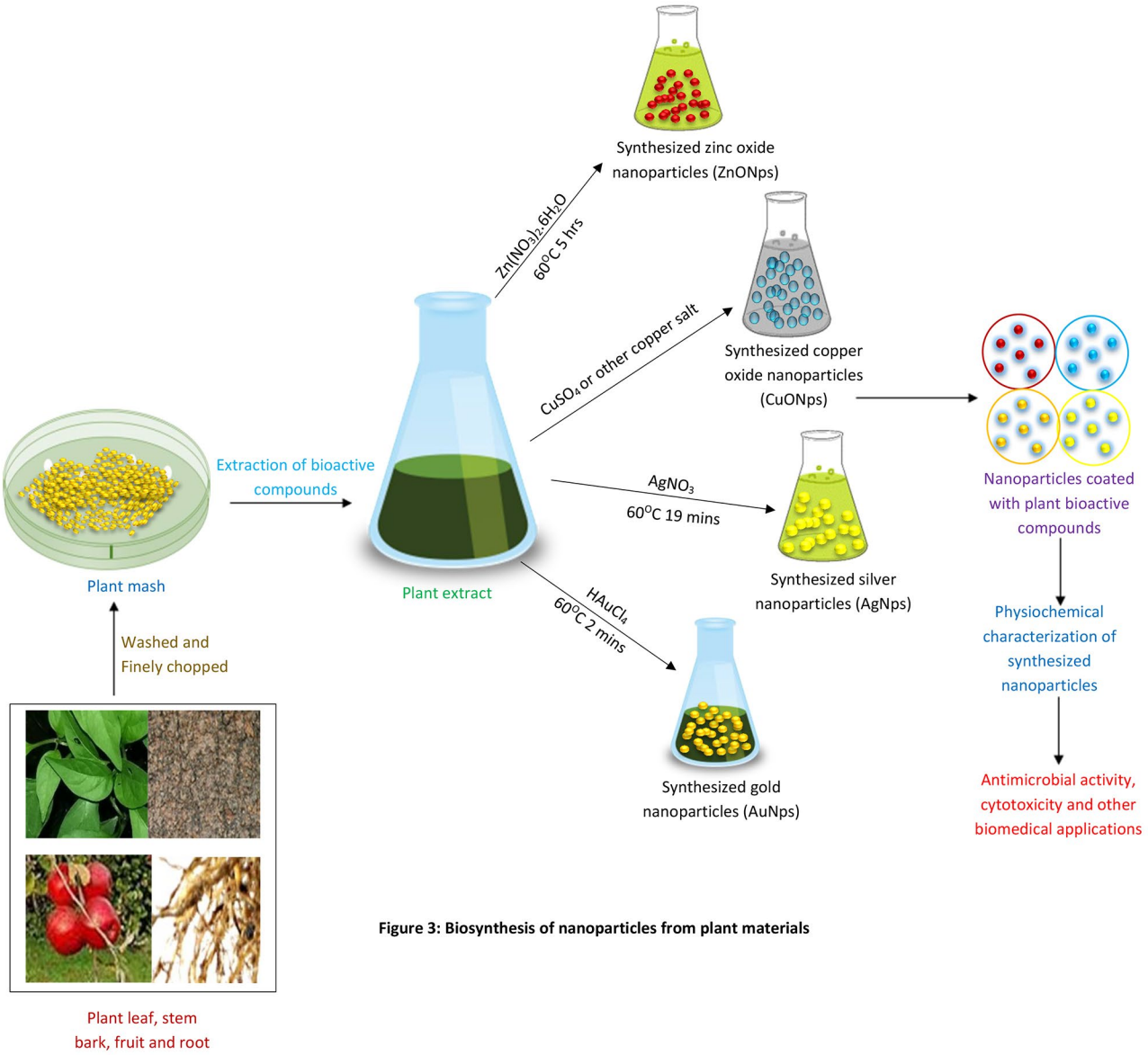

Figure 3: Biosynthesis of nanoparticles from plant materials

Fig. 3 Biosynthesis of nanoparticles from plant materials

Use of microbes in the formulation of nanoparticles

Over the past two decades, microbial biosynthesis of nanoparticles has gained attention. This synthesis can take place in the cytoplasm or the periplasmic space. Not minding the complexity of the process and conditions limiting the use of microbes in the synthesis of nanoparticles, some successes have been recorded. In 1989, Simkiss and Wilbur stated that most unicellular organisms (e.g., bacteria) can synthesize intracellular and extracellular inorganic particles (Dasaratrao et al., 2008). When these organisms are immobilized by enzymes produced by live cells, reduction of metal ions occurs, followed by nanotization, leading to the production of nanoparticles. Metal ion interaction with cell components such as organelles, DNA, membranes, and proteins also facilitates several catalytic processes leading to nanoparticle formation (Hano and Abbasi 2021; Singh et al. 2018a).

The microbe is first cultured using microbes on a suitable broth medium during nanoparticle synthesis. It is then incubated on a rotary shaker at an appropriate specific temperature and revolutions per minute (rpm) for a specific number of days. Bacteria are mostly used in nanoparticle synthesis due to the ease of culturing, extracellular enzyme production, relatively mild experimental conditions (temperature, pressure, pH), short generation time, and easy downstream processing (Singh et al. 2018a; Busi et al., 2019; Pandit et al., 2022). Thus, via processes involving enzymatic oxidation,

reduction, adsorption, and chelation, bacteria enhance nucleation and growth, leading to nanoparticle generation. The prokaryote architecture is well-suited for nanoparticle transport and extracellular precipitation (Zou et al. 2021).

During the biosynthesis of AgNps using fungi, the particles are produced underneath the fungal cell wall surface. The Ag^+ ions are trapped on the fungal cell surface. This is followed by intracellular reduction of the ions forming Ag nuclei. Subsequently, nanoparticles are formed in the cytoplasmic spaces (Costa Silva et al. 2017; Guilger-Casagrande 2019; Elamawi et al. 2018). For bacteria, the intracellular reduction of nitrate (source of nitrogen) to nitrite by nitrate reductase (NADH-dependent nitrate reductases) is exploited in Ag^+ ions bio-reduction and subsequent production of AgNps. The NADH-dependent reductases (electron carriers) form NAD^+. Ag^+ ions obtain the electron and are reduced to AgNps (elemental form). The resulting AgNps are stabilized via intracellular capping agents (Sunkar and Nachiyar 2012; Esmail et al. 2022). Several studies have used microbes in the synthesis of metal nanoparticles (Table 1). Nanoparticle biosynthesis using microbes can either be intracellular or extracellular (Fig. 4).

During the intracellular synthesis, microbe proliferation continues even after metal nanoparticle biosynthesis. According to Faramarzi and Sadighi, these microbes have mechanisms protecting the toxicity of the heavy metal residues (Iravani et al. 2014; Asif et al. 2022). The defensive mechanism reduces ions to harmless metallic salts and metallic nanoparticles. These mechanisms are (a) secretion of metal ions across the permeable membrane, (b) enzymatic oxidation/reduction (c) nanoparticle accumulation outside the plasma membrane, (d) binding to peptides (inhibit DNA destruction and damage to cell cycle due to the toxic nature of the metals) (e) efflux pump system (f) precipitation of nanoparticles (this can be in the form of sulfides, carbonates, or phosphates). Nanoparticles synthesized using microbes are usually very efficient, clean, and with no significant cytotoxicity. Overall, the synthesis of nanomaterials using microorganisms is categorized as ''green chemistry''. More insight into the molecular mechanism of nanoparticle formation will reveal more in terms of its biomedical application and clinical diagnostic, targeted drug delivery, and as an agent against drug-resistant pathogens.

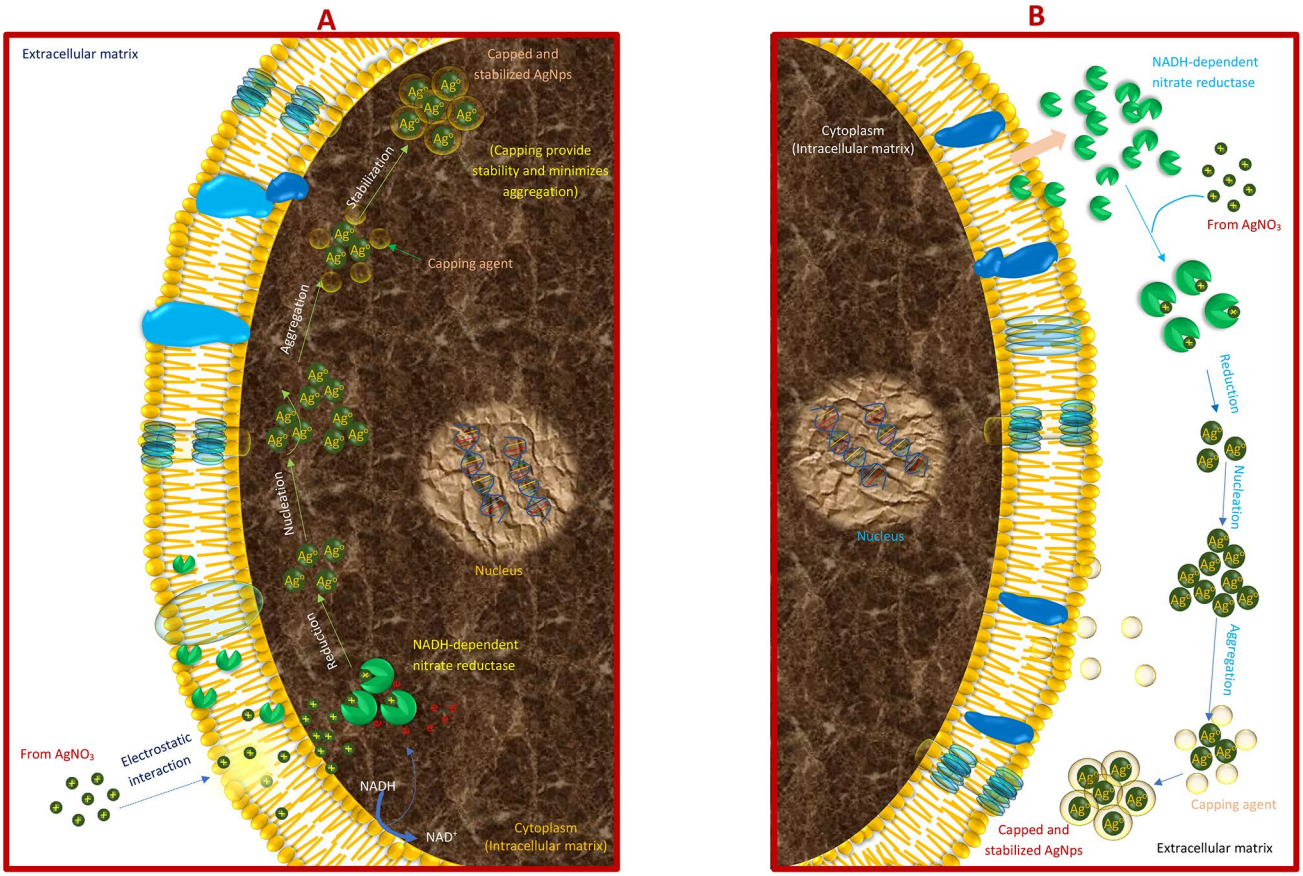

Fig. 4 Mechanisms of nanoparticle synthesis by microbes

Major metallic nanoparticles and their mechanisms of antimicrobial activity

Silver nanoparticles (AgNps)

Researchers have mostly focused on AgNps. This is broadly due to their superior biological, chemical, and physiological properties. Their well-structured shape, size, composition, and crystalline nature make them extremely relevant (Gahlawat and Choudhury 2019). They are used in biomedical device coating, imaging probes, drug-delivery carriers, and as agents against pathogenic microbes (Burdusel et al., 2018). They have also been found useful in diagnostic and optoelectronic platforms in addition to other clinical and pharmaceutical applications (Burdusel et al., 2018; Lee and Jun 2019; Takac et al., 2023).

Silver nanoparticles (AgNps) are currently regarded as next-gen antibiotics due to their exceptional efficacy in killing microorganisms. At present, AgNps stands at the forefront among all the commercialized nanomaterials. It accounts for greater than 50% of consumed nanoparticle products. The instability of silver materials is one limitation compared to other nanoparticles, such as AuNps. They can be oxidized in an oxygen-containing fluid (Adamczyk et al. 2016). However, their size can be adjusted depending on the intended use (Iravani et al. 2014). Their physical, chemical, and optical properties can be optimized for various applications. Thus, during their synthesis, the size, surface features, morphology, composition of the particle, dissolution, and ionization rate, in addition to the nature of the reducing and capping agents, must be taken into consideration. Over the years, research on employing them as antimicrobial agents has surged due to their lower toxicity compared to alternative nanoparticles.

The initial stage in the cytotoxic action of AgNps typically involves the attachment and penetration of these nanoparticles onto the surface of microbial membranes (Mba and Nweze 2021). This process is controlled by the electrostatic interaction between the microbial cell membrane and the nanoparticles (as depicted in Fig. 5). This adherence leads to an increase in membrane permeability or alterations in the lipid bilayer. AgNps dissociate into Ag^+ ions after attachment to the host cell. More Ag^+ ions are released when Ag^+ attaches to the cell wall (Mba and Nweze 2021). AgNps antimicrobial potential is based on the released Ag^+. The ions interact with peptidoglycan. This interaction triggers several morphological alterations (cell membrane detachment and shrinking of cytoplasm). The membrane permeability and the pits formed by the interaction between Ag^+ ion, sugar, and amino acid disrupt transport processes. The Na^+/K^+ ATPase pump is also affected. Leakage of intracellular material to the extracellular space leads to cell function inhibition and cell disintegration, which all combine to cause cell death. Signal transduction pathways are also disrupted, leading to apoptosis (Fig. 5).

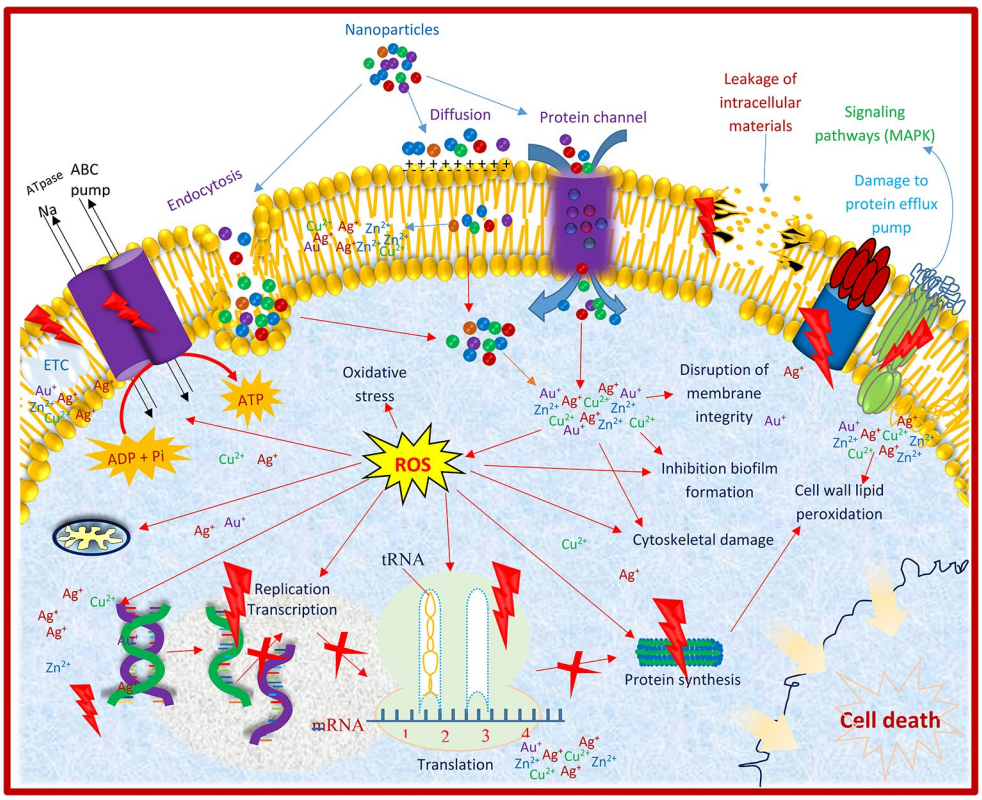

Fig. 5 Mechanisms of antimicrobial activity of nanoparticles

Within cells, AgNps induce the formation of reactive oxygen species (ROS) and free radicals, including singlet oxygen, hydrogen peroxide (H_2O_2), hydroxyl radical (OH), superoxide anion (O^{2-}), and hypochlorous acid (HOCl). This, in turn, results in intracellular damage to micro-organelles. When these ROS and radicals come into contact with bacteria, they create pores in the cell wall, ultimately causing cell death (More et al. 2023). Consequently, damage to internal components is primarily caused by the release of Ag^+ ions, which triggers the generation of ROS and subsequently induces oxidative stress.

In an aqueous solution containing dissolved oxygen, the surface of AgNps undergoes oxidation, releasing Ag^+ ions. AgNps can also interact with protein thiol groups (sulfur-containing proteins), which mediate enzymatic activity. This interaction results in microbial cell damage due to the inhibition of enzymatic activity. Furthermore, Ag^+ ions and AgNps can interact with DNA (phosphorus-containing compounds), leading to protein inactivation and eventual cell demise. Notably, sulfur, chlorine, thiols, and oxygen play crucial roles in influencing the release of Ag^+ ions (Qing et al. 2018).

It is important to note that critical factors like surface area, charge, concentration, ion released, and colloidal state can greatly affect AgNps' cytotoxic potential. The rate at which this Ag^+ ion is released depends on the shape, size, colloidal state, and capping agent of the AgNps. Anisotropic AgNps (small-size AgNps) with larger surface areas exhibit superior (faster and more efficient) ion release rates than bigger-size AgNps with small surface areas (Mba and Nweze 2021; Yonathan et al. 2022). Therefore, size is a very important factor when considering its use as an antimicrobial agent (Mba and Nweze 2021, 2022). AgNps of small size can easily infiltrate the bacterial cell wall, leading to alterations in structural integrity and membrane architecture. This results in an increase in membrane permeability and eventual cell apoptosis. It's worth noting that the type of bacterial species can influence the effectiveness of AgNps, whether gram-positive or gram-negative, due to variations in cell wall composition, thickness, and arrangement (Dakal et al. 2016; Bruna et al. 2021; More et al. 2023). For instance, *E. coli* is more susceptible to Ag^+ than *Staphylococcus aureus*, primarily because of differences in the peptidoglycan structure within their membranes.

According to the research by Hamouda and colleagues (Mikhailova 2020), the antimicrobial action of AgNps, in addition to generating ROS, is closely linked to damage inflicted on the cell wall and plasma membrane (as outlined in Table 1). This damage results in protein inactivation and lipid peroxidation within the membrane, ultimately leading to structural membrane integrity disruption, disarray among transport proteins, and potassium leakage. Overall, the mechanism of action of AgNPs against microbes is categorized into two: oxidative and non-oxidative (Fig. 5).

Gold nanoparticles (AuNps)

AuNps is among the most widely researched nanoparticles. AuNps can be synthesized from the whole plant or using several compounds acting as reducing agents. Just like other nanoparticles, the nature of reducing agents utilized during their fabrication influences their size and shape. AuNps exhibit good antimicrobial activity (Zhan et al., 2022; Shamaila et al. 2016). AuNps come in various forms, such as triangles, spheres, hexagons, and even rods (Mba and Nweze 2021; Tripathi et al. 2019). Triangular AuNps, as observed in prior research by Smitha and Gopchandran, demonstrate robust antibacterial effects against multiple bacterial strains in contrast to their spherical counterparts (Smitha and Gopchandran 2013). Its overall synthesis method is based on chloroauric acid ($HAuCl_4$). This is followed by agglomeration using a stabilizing agent. In general, the method involves three major procedures: nucleation, growth, and coagulation. Seed-mediated growth techniques are indispensable when the uniformity of the AuNps (with desired shapes and sizes) is of utmost importance.

The synthetic versatility of AuNps, which enables the alterations of the size, shape, and surface properties, is a crucial advantage of AuNps. Their coating can be changed to regulate their stability, solubility, and their environmental interaction. Thus, they are materials of extreme interest to researchers in the medical field due to their diverse important features. Temperature, pH, surface stabilizer, and reducing abilities affect the final size of the synthesized AuNps. Normally, bulk metallic gold (Au) is almost non-reactive. However, when it is reduced to the size of a nanoparticle, it begins to exhibit several biological characteristics (Ielo et al. 2021). Several researchers have published studies that reported the biosynthesis of AuNps using microbes and plant extracts (Table 1). The broad use of AuNps is mostly due to their possession of dielectric and electrical conductivity function, in addition to their inert property to oxidation compared to other nanoparticles. They possess surface plasmon resonance (SPR). They can also be altered or modified using several coating agents with diverse functions, especially in biology and medicine.

Gold nanoparticles (AuNps) attach to the cell membrane through electrostatic interactions and disrupt the integrity of the membrane (Rattanata et al. 2016; Joshi et al. 2020). This disruption can lead to the release of intracellular components as the AuNps create openings in the membrane. Additionally, AuNps have the ability to bind to DNA, thereby inhibiting DNA replication and transcription. They can also aggregate with microbial biofilms. Furthermore,

interactions between AuNps induce the generation of reactive oxygen species (ROS), which play a crucial role in causing cell death. AuNps also affect the membrane potential and reduce the activity of ATP synthase, thereby impacting various metabolic processes. Similar to silver nanoparticles (AgNps), AuNps can disrupt the structure and integrity of the cell membrane (Rattanata et al. 2016). AuNps hinder the binding of ribosomal RNA (rRNA) to its subunits, thereby preventing the translation process (Lee et al. 2022). These nanoparticles can also interact with nucleotides containing sulfur or phosphorus. Furthermore, they can target the thiol group of several enzymes, such as NADH dehydrogenase, disrupting the electron transport chain (ETC) and leading to oxidative stress. The effectiveness of their antimicrobial action depends on their concentration and average size.

When combined with antibiotics, AuNps typically exhibit potent antibacterial activity. A study conducted by Brown et al. (2012) demonstrated that the integration of ampicillin with AuNps significantly enhanced its effectiveness against bacteria resistant to ampicillin, including *P. aeruginosa, E. coli, Enterobacter aerogenes*, and MRSA. The AuNp-ampicillin (AMP) complex disrupts and inhibits the transmembrane pump responsible for drug efflux, and it also effectively neutralizes the high levels of β-lactamase expressed by the bacteria. Recent studies on AuNps and their antimicrobial potential are summarized in Table 1.

Copper/copper oxide nanoparticles (CuNps/CuONps)

CuNp is a nanomaterial that has broad applications in transport, cosmetics, power, agriculture, the pharmaceutical industry, and, most importantly, as an antimicrobial agent (Crisan et al. 2022). Unlike other nanoparticles, synthesizing CuNp poses a serious challenge. This is because of the ease with which they are oxidized when in an aqueous medium. However, available data indicates that it can synthesized under inert conditions from copper salts (Khan et al. 2016). CuNp biosynthesis is relatively new. Research is currently ongoing to improve the process. Its disadvantages include low potency, high toxicity, and high exposure. In addition, it's hazardous to humans and the environment. CuO has wide applications and has gained more attention in the last decade. It is inexpensive and has a longer shelf life compared to other organic antibacterial agents. It can be used as a drug delivery agent in addition to other biomedical applications. High-temperature superconductivity, electron correlation effects, and spin dynamics are some of its unique properties. These properties usually increase when it is converted to a nanoparticle. CuONps have unusual crystal morphologies in addition to several unique properties. Asemani and Anarjan biosynthesized CuONps using *Juglans regia* leaf extract and further assessed its antimicrobial properties. The result showed that CuONps exhibit good antibacterial activity against *E. coli*. (Flores-Rabago et al., 2023). Other reports on the antimicrobial activity of CuONps are summarised in Table 1.

The mechanism of antimicrobial activity of copper nanoparticles is yet to be properly elucidated. However, it is believed that when CuNp attaches or adheres to microbial cells, it releases Cu^{2+} ions, which damage the membrane, leading to cell death. This is made possible via the electrostatic attraction between the nanoparticle and the cell (Ma et al., 2022). The Cu^{2+} ion has the capability to penetrate the lipid bilayer and enter the cell. Once inside, it initiates the generation of reactive oxygen species (ROS). This results in observable lipid peroxidation and protein oxidation processes (Chatterjee et al. 2014; Ma et al., 2022). The antimicrobial properties of copper are attributed to its ability to switch between the + 1 and + 2 oxidation states.

During the process of differentiating Cu from other trace metals, hydroxyl radicals are produced. Hydroxyl radicals attach to the DNA molecules, causing disorder of the helical structure and subsequent damage to nucleic acids and proteins. There is also the inactivation of the enzymes and cell surface proteins essential for the movement of materials across the cell membrane. These processes affect membrane integrity as well as membrane lipids. A recent study revealed that CuONps can engage with amino acids, significantly affecting their bacterial activity (Badetti et al. 2019). Other studies on copper oxide nanoparticles are summarized in Table 1.

Zinc oxide nanoparticles (ZnONps)

ZnO is a multifunctional semiconductor utilized in the formulation of products such as paints, batteries, plastics, and anti-bacterial agents. Its chemical stability, high electronic conductivity, and nontoxicity make it a valuable compound. The ZnONps can be synthesized using microbes and several parts of plants. ZnONps have antibacterial potential (Mohd et al., 2019; Murali et al. 2023). It also has applications in photodegradation, drug delivery (Noman et al. 2021; Chopra 2022), and use in anticancer therapy (Anjum et al. 2021; Bisht and Rayamajhi 2016). Previously, it was noted that the surface coating of ZnONps could be a barrier to their interactions with biological fluids. However, Pranjali et al. discovered that PEGylated ZnONps exhibit a strong affinity for and interaction with peritoneal dialysis (PD) fluid, lactic acid, and citric acid, resulting in particle agglomeration.

Furthermore, both ZnONps and PEG-coated ZnONps dispersed in biological fluids demonstrated a significant reduction in their ability to inhibit bacterial growth. This investigation highlighted that the composition of peritoneal dialysis fluid can counteract the effectiveness of ZnONps

(Pranjali et al. 2019). Consequently, it is evident that surface coating does not entirely eliminate the possibility of nanoparticles binding and interacting with biological fluids.

When ZnONps come into contact with microbial cells, they release Zn^{2+} ions. These ions disrupt the cell membrane and cause harm to the cell by interacting with various intracellular components (Lallo da Silva et al. 2019). Additionally, Zn^{2+} induces the generation of reactive oxygen species (ROS), which are known to be detrimental to cell survival (Ng et al. 2017; Mendes et al. 2022). Studies have demonstrated that ZnONps and their composites can also influence the expression of numerous genes. Recently, Nejabatdoust et al. reported that ZnONPs, when conjugated with thiosemicarbazide and functionalized with glutamic acid, can modify the expression of efflux pump genes in multi-drug-resistant *S. aureus* (Nejabatdoust et al. 2019). Further insight into their antimicrobial potential is provided in Table 1.

Titanium dioxide nanoparticles (TiO_2Nps

TiO_2 is a promising semiconductor oxide material with high catalytic ability. In addition, TiO_2 has high stability, is non-toxic, and has good gas-sensitive characteristics with a di-electricity feature. TiO_2Nps can be synthesized using the already discussed synthesis techniques (Aravind et al. 2021). During the synthesis, several reducing and stabilizing agents are used to produce TiO_2Nps with various morphologies (Verma et al. 2022; Saka et al. 2022). TiO_2Nps have several uses and applications: medical diagnostics, biosensors, solar cells, and catalysts.

TiO_2Np generates reactive oxygen species (ROS), which play a pivotal role in causing damage to the cell membrane and disrupting oxidative phosphorylation processes (Manke et al. 2013; Samrot et al., 2023). Furthermore, TiO_2Np interferes with signaling pathways, diminishes the co-enzyme-independent respiratory network, and hampers the uptake and transportation of essential elements like iron (Fe) and phosphorus (P). Additionally, it reduces the biosynthesis and breakdown of the heme group. It's important to note that the activity of TiO_2Np is influenced by light exposure, as it is photo-dependent. The generation of free radicals has also been documented as a result of TiO_2Np exposure (Kubacka et al. 2014). Moreover, there is evidence suggesting that TiO_2Np can cause damage to peptidoglycan, lipopolysaccharide, and the phospholipid bilayer in bacterial cells (Parra-ortiz and Malmsten et al., 2022).

Magnesium oxide nanoparticles (MgONps)

MgO, an important inorganic oxide, is used in the medical field to treat various ailments: antacids for heartburn, sore stomach, bone regeneration, and tumor treatment. Just like other nanoparticles, several methods are available for its synthesis. However, its biosynthesis has not been widely exploited. One advantage of MgONp over ZnO and TiO_2 nanoparticles is its ability to degrade and metabolize them in the body. Mg^{2+} and OH^- (byproduct of their degradation) can be easily removed from the biological system by a fully functioning renal system - this removes the concern regarding their accumulation in the body. Thus, MgONps are non-toxic in nature and odorless. It has high purity, high melting point, and hardness (Lin et al. 2020).

The mechanism underlying the antimicrobial effectiveness of magnesium oxide nanoparticles (MgONps) involves the generation of reactive oxygen species (ROS) (Lin et al. 2020; Nguyen et al. 2018). The attachment of MgONps to the cell surface damages the integrity of the cell membrane, consequently releasing intracellular components (Rotti et al. 2023). MgONps achieve their antimicrobial activity through a combination of processes, including the production of Mg^{2+} ions, interaction with the cell membrane, and alterations in pH (Nguyen et al. 2018). Research conducted by Nguyen et al. indicated that MgONps can reduce the ability of *S. epidermidis* to form biofilms and cause membrane damage in *E. coli*, leading to cell apoptosis. The authors proposed that the production of ROS, changes in Ca^{2+} concentrations, and quorum sensing mechanisms are contributing factors to the antimicrobial action of MgONps. In a recent study, MgONps and MnONps were synthesized using an extract from *Matricaria chamomilla L*. The results revealed that these nanoparticles enter the cells and disrupt the cell membrane, releasing intracellular cytoplasmic contents (Roy et al. 2013; Ogungemi et al. 2019; Farani et al. 2023).

Utilizing MgO nanoparticles in conjunction with other materials such as Ag, Zn, chitosan, graphene, and similar substances can enhance the stability and antibacterial characteristics of the composite. A study has shown that CS-ZnO nanocomposite films are more effective in inhibiting bacterial growth (Li and Zhuang 2020). Furthermore, incorporating MgO nanoparticles into the chitosan matrix results in improved antibacterial, bioactivity, and strength properties (Guler and Bogci 2020). Numerous investigations have explored the attributes and potential applications of MgO composites. For instance, Yamamoto et al. (2010) conducted a study on the impact of $CaCO_3$-MgO nanocomposites in plaque removal, thereby enhancing oral hygiene. The result showed the effectiveness of nanocomposite in eliminating plaque due to bacterial pathogens.

In a noteworthy experiment, Zhu et al. (2016) synthesized Ag – MgO nanocomposites by incorporating Ag nanoparticles onto MgO nanoparticles, creating an exceptional antibacterial agent against *E. coli.* Antibacterial assessments

revealed that this composite exhibited greater antibacterial activity when compared to pure Mg and standalone Ag nanoparticles, indicating a synergistic effect between Ag and MgO. Tests detecting reactive oxygen species (ROS) production demonstrated an increase in ROS generation and enhanced antibacterial activity. Other recent findings on MgONps are summarized in Table 1.

Calcium oxide nanoparticles (CaONps)

CaO, an exceptionally vital industrial compound, is used as a toxic waste remediation agent and catalyst and has several important applications due to its electrical, chemical, and optical characteristics. CaONp is safe in humans and animals and has found application as a drug delivery agent due to its biocompatibility and as an antimicrobial agent. A study conducted by Roy et al. (2013) investigated microwave-exposed calcium oxide nanoparticles' (CaO-NPs) antimicrobial properties against gram-negative and gram-positive bacteria, along with pathogenic yeast. The research revealed that the minimum inhibitory concentration (MIC) of CaO-NPs fell within the 2–8 mM range for all the tested strains. This bioactive nanoparticle also demonstrated the ability to hinder the formation of biofilms, suggesting its potential as an inexpensive and non-toxic antimicrobial agent for the development of skincare products.

Among metal-based nanoparticles, CaO-NPs exhibit significant potential as an economical and readily accessible industrial compound that can effectively combat biofilms (Roy et al. 2013). Additionally, research by Maringgal et al. in 2020 showed that CaO-NPs possess antifungal properties, while Flores-Rábago et al. (2023), reported their antibacterial activity. These CaO-NPs can disrupt biofilms and interfere with genes controlling quorum-sensing, destabilizing biofilm integrity (Lahiri et al. 2021b).

Several theories have been proposed regarding the interaction between the cell wall and the surface of CaO-NPs, which is positively charged (Asikin-Mijan et al. 2015). However, the primary mechanism through which CaO-NPs break down bacterial cell walls involves the induction of oxidative stress, generating a substantial amount of ROS (Kumari et al. 2023). CaO-NPs exhibit antibacterial activity due to the presence of superoxide (•O − 2) and HO•2, as well as H_2O_2 free radicals (Sajjad et al. 2023). These free radicals damage the bacterial cell membrane. There is also the disruption of the polyunsaturated polyunsaturated phospholipids (Roy et al. 2013). Due to the oxidative stress induced by CaO-NPs, the microbial cell's antioxidant system becomes imbalanced, ultimately leading to bacterial cell death (Manke et al. 2013; Kumari et al. 2023).

Another potential mechanism involves binding CaO-NPs to the bacterial cell wall through interactions, with consequent damage to the cell membrane (Hetta et al. 2023). The antibacterial tests conducted on CaO-NPs against *Bacillus* bacteria further confirm their ability to inhibit the formation of biofilm in various bacterial strains (Jagadeesh et al., 2020). Also, the effective penetration of CaO-NPs through the extracellular matrix enables them to disrupt bacterial growth (Lahiri et al. 2021b).

Iron/iron oxide nanoparticles (Fe/Fe_2O_3/Fe_3O_4Nps)

Iron nanoparticles are also promising nanoparticles with good therapeutic and antimicrobial activity (Mohanraj et al. 2014; Rueda-Gensini et al. 2020; Mulens-Arias et al. 2020). Their mechanism of action is similar to those of other nanoparticles. They trigger the rupturing of the cell. A recent investigation demonstrated that Fe_3O_4Nps diminish the flow of H^+ ions across bacterial membranes. These nanoparticles specifically hinder metabolism linked to ATP. Furthermore, the study observed a reduction in membranes associated with hydrogen (H_2) production (Gudkov et al. 2021). Several researchers have investigated the antimicrobial activity of biosynthesized FeNps and Fe_2O_3Nps (Arakha et al. 2015; Uchechukwu et al. 2021; Gudkov et al. 2021; Armijo et al. 2020).

Cytotoxicity and limitations of metallic nanoparticles

Nanoparticles instigate distinctive biological impacts at the cellular level by influencing processes across cell membranes and basic cellular functions. The major explanatory factors in cytotoxicity are oxidative stress and inflammation, which have garnered significant attention. Oxidative stress is marked by excessive reactive oxygen species (ROS) generation, leading to alterations. Conversely, inflammation, though protective, can have detrimental effects if uncontrolled. ROS can trigger and enlist inflammatory cells, fostering inflammatory responses, which can subsequently intensify ROS production. Conversely, an overabundance of ROS can prompt mitochondrial dysfunction and disrupt the equilibrium of the redox system (Xiong et al., 2022). In the cytotoxic effect, metallic nanoparticles influence several signaling pathways. For instance, ZnO nanoparticles can trigger neurotoxicity by activating several pathways, including extracellular signal-regulated kinase and other signaling pathways (Attia et al. 2018; Abd Elmonem et al. 2023). Moreover, Cu nanoparticles have been show to activate similar pathways (Mou et al. 2020; Feng et al. 2023; Sajjad et al. 2023).

Furthermore, numerous investigations have indicated that the toxicity triggered by metallic nanoparticles is linked

to factors such as the size of particles, specific surface area, crystal structure, exposure method, and chemical constituents, among others (Mba et al., 2021; Abbasi et al. 2023). Appropriately modifying the size and shape of metallic nanoparticles may alleviate cytotoxicity to a certain degree (Xiong et al. 2022; Długosz et al. 2020). Additionally, adverse interactions between nanoparticles and proteins may stem from improper surface functionalization, free energy, curvature, and larger particle size and shape, impacting protein folding processes and compromising structural integrity. Consequently, extensive and methodical experiments are necessary to elucidate metallic nanoparticles' harmful effects comprehensively. Furthermore, each parameter of this nanomaterial must be individually screened to confirm the influence of each element. Developing a model establishing the relationship between the characteristics of metallic nanoparticles and substances within the organism can provide a scientific foundation for a thorough and precise assessment of the cytotoxicity associated with this biomaterial. Additionally, employing structure-based computational molecular modeling is vital for comprehending and forecasting the interaction between nanomaterials and biological systems. Moreover, surface structural modification can serve as a viable strategy to overcome cytotoxicity.

Besides the bio-effect levels, the regulation of molecular pathways can be influenced by surface chemistry, particularly in the context of surface decorations with varying charges, hydrophobic characteristics, and combinations thereof. It has been suggested in some quarters that modifying polyethylene glycol (PEG), employing ligands with varying charges and hydrophobicities, and employing combinatorial surface decoration can fine-tune various bioeffects related to cytotoxicity. The incorporation of PEG decoration on nanoparticles has been shown to alleviate these cytotoxicity-related effects (Suk et al. 2016; Abbasi et al. 2023; Yusuf et al. 2023).

It is increasingly evident that nanoparticles can revolutionize public health by enhancing existing treatments or bringing novel biomaterials to the limelight. Research on the potential cytotoxicity and compatibility with the human body for various nanoparticle combinations is required to facilitate their integration into clinics. The resistance mechanisms of microorganisms to metallic nanoparticles have yet to be adequately explored thus far and necessitate thorough investigation. In the upcoming years, nanomaterials are poised to transform the realm of technology due to their distinct properties. Nevertheless, a critical focus of nanotechnology study should be directed toward mitigating their harmful impact on human cells while enhancing their biodistribution, availability, and stability in the human body. The interaction of nanoparticles with biological fluids represents a critical domain that warrants further exploration. Subsequent research endeavors should investigate undesired non-target interactions. This kind of interaction can involve nanoparticles and other biomaterials, like antibiotics.

The fundamental mechanism governing the actions of nanoparticles has yet to be comprehensively elucidated. The absence of a unique approach for nanoparticle investigation, coupled with the intricacies of bacterial membranes, poses challenges in understanding their mechanism of action against microbes. Also, besides in vitro investigation, in vivo studies are also needed to properly elucidate the therapeutic potentials of nanoparticles and their utility in biological systems. Furthermore, nanoparticles appear to prompt the simultaneous selection and expression of genes conferring antibiotic resistance (Niño-Martínez et al. 2019; Chakraborty et al. 2022; Mba et al., 2021; McNeilly et al. 2021). In an exploration conducted by Wang et al. (2018), microbial cells were exposed to ZnONps at sub-lethal concentrations. This exposure initiated the transfer of genes. The exposure induces an elevation in membrane permeability, thereby enhancing the frequency of horizontal gene transfer (HGT). Moreover, the adverse effects (toxicity) of TiO_2 nanoparticles were shown to arise from the electrostatic interactions between bacteria (*E. coli*) and the nanoparticles. These interactions result in the absorption of the nanoparticles onto the surface of the cell (Pagnout et al. 2012).

Conclusion and perspectives

The field of nanotechnology has experienced rapid growth, finding diverse applications across various domains. Obviously, the emergence of nanotechnology heralds a new era in antibacterial treatments. Several metallic nanomaterials have shown antibacterial activity as shown in many reports (Table 3). While the applications of nanoparticles in various medical fields cannot be questioned, various challenges and issues remain to be addressed before nanomaterials are fully integrated into medicine (Geng et al. 2023). First, a notable gap exists in our understanding of the risks associated with prolonged NP usage, demanding further investigation. The toxicity and efficacy of nanomaterials require in-depth exploration, and an intriguing emerging frontier lies in the development of personalized healthcare. This endeavor should be founded on the principles and mechanisms of nanodevices and nanorobots, effectively preparing us for the near future. Therefore, nanotechnology's precision targeting capabilities constitute a significant advantage in advancing medical science and improving the treatment of infectious diseases. This technology bears particular relevance in the context of treating different non-infectious and infectious diseases associated with drug-resistant pathogens.

Table 3 Antimicrobial activities of metallic nanoparticles

AgNps	Plant extracts of Phoenix dactylifera, Ferula asafetida and Acacia nilotica	Spherical 67.8 ± 0.3-155.7 ± 1.5 nm	S. aureus, P. aeruginosa, E.coli	Significant antibacterial activity. IZD: 10-32 mm Cytotoxicity: tested using Lovo cells. IC 50 : 35.15–56.73 µg/mL	Mohammed et al. 2018
AgNps	Commercial	Spherical 5-20 nm	Multidrug resistant *P. aeruginosa*	Bactericidal effect on *P. aeruginosa* with MIC and MBC of 1.406–5.625 µg/ml and 2.813–5.625 µg/ml respectively. Mechanism: disruption of cell morphology and structure. Disequilibrium of oxidation and antioxidation process. Prevent the elimination of the excessive ROS by the cell.	Liao et al. 2019
AgNps	Olive leaf extracts (OLEs) Rosemary leaf extracts (RLEs)	Spherical 45 ± 2 nm for OLE 38 ± 3 nm for RLE	*E. coli*, *S. enterica*, *S. aureus*	Strong antibacterial activity. *E.coli* and *S. aureus*: MIC of 9.38 and 4.69 µl/ml for OLE-AgNps and RLE-AgNps respectively. *Salmonella enterica*: 18.75 µl/ml for both OLE-AgNps and RLE-AgNps	AbuDalo et al. 2019
AgNps	Honey (*Ziziphus spina-christi* and *Acacia gerrardii*)	Spherical 50-98 nm	Methicillin-resistant bacteria, *S. aureus*, *E. coli*, *P. aeruginosa*	IZD: 20.8 ± 1.2–15.6 ± 0.8 mm Cytotoxicity: Lovo and HepG2 ca. cells. Cytotoxicity was detected in a dose dependent manner. LC50: 12.8–19 µg/ml	AlBrahim & Mohammed 2020
AgNps	Biosynthesized using endophytic bacterium *pantoea ananatis*	Spherical 8.06-91.32 nm	Multidrug resistant bacteria *S. aureus ATCC 11,632, B. cereus ATCC 10,876, E. coli ATCC 10,145, P. aeruginosa ATCC 10,145*, Multi-drug resistant (MDR) *Streptoccus pneumonia (ATCC 700,677), E. faecium ATCC 700,221, S. aureus ATCC 33,592, E. coli NCTC 13,351*	Significant antimicrobial activity at 6 µg/disc concentration against *B. cereus* ATCC 10,876. Showed promising antibacterial efficiency at 10 µg/disk concentration against MDR strains.	Monowar et al. 2018
AgNps	*Aspergillus flavus* and *Penicillium crustosum*	Spherical to oval shape AgNps by A. flavus: 5-10 nm. AgNps by *P. crustosum*: 30-40 nm	*E. coli*, *S. aureus*	MIC of *A. flavus* AgNps was 0.42 and 0.41 µg/ml towards *S. aureus* and *E. coli*, while the MIC of *P. crustosum* AgNps was 0.86 µg/ml and 0.65 µg/ml respectively	El-Sayed and Ali 2018
AgNps	*Phenerochaete chrysoporium (MTCC-787)*	Spherical and oval shape 34-90 nm	*P. aeruginosa*, *K. pneumonia*, *S. aureus*, *S. epidermidis*	Significant activity was shown at a high dose Cytotoxicity: non-toxic at 12.5 µg/ml toward fibroblast cells	Saravanan et al. 2018
AgNps	Leaf sap extract from *Aloe arborescens*	38 ± 2 nm	*P. aeruginosa*, *S. aureus*	Good antibacterial activity Mechanism: damage cell membrane and increases the percentage of dead cells	Kumar et al. 2018
AgNps	Biosynthesized using Lysimachia foenum-graecum hance extract	Spherical 10-20 nm	*E. coli, S. aureus*	Strong antibacterial activity especially against *S. aureus.* IZD of 19.08 ± 0.67 mm	Chartarrayawadee et al. 2020
AgNps	Synthesized using *Pseudomonas* strains	Spherical 20-70 nm	*S. epidermidis*, *Streptococcus agalactic*, *K. pneumonia*, *P. aeruginosa*, *P. mirabilis*, *Citrobacter koseri, A. baumanii*, *Serratia marcescens*	For the gram-negative bacteria, the larger IZD was against *E. coli* (19.0 mm). Smallest was against *P. aeruginosa* and *S.* marcescens (14 mm). In gram-positive, the highest IZD (15 mm) was formed against *S. aureus*	John et al. 2020

Table 3 (continued)

AgNps	Plant extracts of Phoenix dactylifera, Ferula asafetida and Acacia nilotica	Spherical 67.8 ± 0.3-155.7 ± 1.5 nm	S. aureus, P. aeruginosa, E.coli	Significant antibacterial activity. IZD: 10-32 mm Cytotoxicity: tested using Lovo cells. IC 50 : 35.15–56.73 µg/mL	Mohammed et al. 2018
AgNps	Extract of parsley, corn silk, and gum Arabic (*P. crispum, S. maydis*, gummy excudate of Acacia Senegal	Spherical 16-13.35 nm, 5.28-9.39 nm, 6.56–21.47	*Staphylococcus saprophyticus, E. coli, Enterococcus faecalis, Psedomonas aeruginosa*	Showed significant activity against pathogens. All the extracts showed different antimicrobial activity against all the pathogens. AgNps prepared by the combination of the different extracts had the highest IZD (18-19 mm) against *P. aeruginosa*	Helmy et al. 2020
AgNps	*Cinnamomum tamala* leaf extract	Spherical and irregular 16 nm and 9 nm at 25°C and 60°C respectively	*B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa*	Strong antibacterial activity. IZD: 9 and 10 mm, 8 and 10 mm, 12 and 13 mm, 10 and 12 mm	Al Mashud et al. 2022
AgNps	Aqueous root extract of *Arnebia hispidissimia*	Sphere, rod, triangle, hexagon and polygon 10-75 nm (TEM) 20-200 nm (FE.SEM)	*E. coli*, *S. aureus*, *E. faecalis*, *K. pneumonia*	Showed dose-dependent strong antimicrobial activity Cytotoxicity: dose-dependent cytotoxicity against HeLa (cervical cancer, IC50 = 4.4 µg/ml) cells. Non-toxic towards normal L20 B cells (non-malignant mouse cell line)	Nahar et al. 2020
AgNps	Leaf extract from *melia azedarah*	Spherical 14-20 nm	*B. cereus*, *E. coli*	Antibacterial activity: 33 mm, 37 mm Cytotoxicity: analysed at 1000 µg/ml using human chang liver cells (CCL-13). AgNps treated cells had a viability of 92–94% for up to 72 h. insignificant cytotoxic effect was observed	Chinnasamy et al. 2019
AgNps	*Impatiens balsamina* and *Lantana Camara* fresh leaves	- < 24 nm	*S. aureus* and *E. coli*	AgNps inhibited the growth of the two organisms. The best activity was shown by AgNps synthesized from *L. camara*	Aritonang et al. 2019
AgNps	Green synthesis using green quercetin as a reducing agent	Spherical 8.4 ± 0.3 nm and 20.0 ± 0.4 nm	*Streptococcus sp. and E. coli*	AgNps with a diameter of 8 nm exhibit MIC value of 1.0 µg/mL against all the pathogens. Those with 20 nm diameter had a MIC value of 2.5 µg/mL	El-Sayed and Ali 2018
AgNps	Biosynthesized from *Bacillus subtilis* strain	Spherical 80 ± 0.18 nm	*Acinetobacter baumannii, P. aeruginosa*, MRSA and *E. coli*	Good antimicrobial activity with IZD of 6 ± 0.12 mm, 5 ± 0.12 mm, 4 ± 0.09 mm and 6 ± 0.12 mm	Tariq et al. 2020
AgNps MnO_2Nps	Synthesized using *Cussonia zuluensis* strey plant species	Spherical 7.43 nm	*E. coli, E. faecalis*, and other Gram-positive and Gram-negative	AgNps showed better activity than MnO_2Nps and was more effective against *E. coli* and *E. faecalis*	Mahlangeni et al. 2020
AuNps	*Lignosus rhinocerotis* sclerotial extract (LRE) and chitosan (CS)	Mostly spherical but triangular, pentagonal, irregular and rod shapes also observed. 80.3 ± 23.4–125.3 ± 41.5 nm and 49.5 ± 6.7–82.4 ± 41.5 nm	*E. coli*, *P. aeruginosa*, *S. aureus* and *Bacillus* sp.	Cs-AuNps medidated by LRE displayed effective antibacterial activity. Better activity against gram-negative bacteria. The addition of LRE as a reducing agent resulted in higher antibacterial activity.	Katas et al. 2019
AuNps	Biosynthesized using endophytic fungi *fusarium solani* from plant roots of *Chonemorpha fragrans*	Needle and flower like structure 40-45 nm		Strong antibacterial activity. Cytotoxicity: exhibited dose-dependent cytotoxic effects. IC50 value was 0.8 ± 0.5 µg/ml on MCF-7 cell line and was found to be 1.3 ± 0.5 µg/ml on HeLa cell lines.	Clarance et al. 2020

Table 3 (continued)

AgNps	Plant extracts of Phoenix dactylifera, Ferula asafetida and Acacia nilotica	Spherical 67.8 ± 0.3-155.7 ± 1.5 nm	S. aureus, P. aeruginosa, E.coli	Significant antibacterial activity. IZD: 10-32 mm Cytotoxicity: tested using Lovo cells. IC 50 : 35.15–56.73 µg/mL	Mohammed et al. 2018
ZnONps	Chemical synthesis	Oval to rod shape ~ 15–100 nm	*S. aureus* NCIM 2654, *Proteus vulgaris* NCIM 2613	Different degree of antimicrobial and antibiofilm activity inversely proportional to the nanoparticles. ZnONps with least size ~ 15 nm showed strong antibacterial and antibiofilm activity MIC range: 10–20 µg/ml	Mahamuni et al. 2018
ZnONPS	Culture of *Chlorella vulgaris*	Rod-like shape Length and width of 150 nm and 21 nm respectively	*S. aureus*, *E. faecalis*, *P. aeruginosa* and *E. coli*	Showed antimicrobial activity, and 250 µg/ml was the most effective concentration	Taghizadeh et al. 2020
ZnO quantum dots	*Eclipta alba* plant extract	Spherical ~ 6 nm	*E. coli*	IZD of 15.69 mm	Singh et al. 2018
ZnONps	Solochemical process	Nanorods 90.1-100 nm	*S. aureus*, *S. typhimurium*, *B. cereus* and *P. aeruginosa*	MIC and MBC = 0.05 mg/ml and 0.5 mg/ml for *S. aureus* and *S. typhimurium* respectively	Katas et al. 2019
ZnONps	Sonochemically synthesized	Hexagonal 41 nm	*S. aureus*, *E. coli* and *K. pneumoniae*	MIC and MBC: 20 µl/ml and 30 µl/ml, 5 µl/ml and 5 µl/ml and < 1 µl/ml and 10 µl/ml	Hozyen et al. 2019
ZnONps	Aqueous *Tabernaemontana divaricate* green leaf extract	Hexagonal wurtzite 20-50 nm	*E. coli*, *Salmonella paratyphi*, *S. aureus*	Showed higher activity against *S. aureus* and *E. coli*	Raja et al. 2018
ZnONps	Biogenic reduction of applied Cucurbita seed extract	Rod, rectangular and hexagonal shape 45-65 nm	*E. coli*, *Bacillus pumilus* and *Salmonella typhi*	Strong antimicrobial activity Cytotoxicity: good toxicity on *E. coli* AB1157	Chennimalai et al. 2019
AgNps	*Cinnamomum zylinicum* bark extracts	Spherical 10-78.9 nm	*Acinetobacter baumanni, Klebsiella pneumonia, Pseudomonas aeruginosa, S. aureus*	IZD and MIC: 22 mm/5.7 ± 0.48 µg/ml, 24 mm/2.8 ± 0.3 µg/ml, 24 mm/3.1 ± 0.01 µg/ml, 25 mm/4.8 ± 0.2 µg/ml. Incorporation of the AgNps with antibiotics showed amazing antimicrobial effects. AgNps + gentamycin showed the highest effect against *S. aureus, K. pneumonia, P. aeruginosa*, and *A. baumanni*	Almalah et al. 2019
AgNps	Commercially obtained	-	*E. coli* AH5α (non-pathogenic), *Salmonella enterica serovar Typhimurium* ATCC SC 14,018 (pathogenic), *S. aureus* (pathogenic), *B. subtilis* (non-pathogenic)	MIC ranges from 10–12 µg/ml AgNps exhibit synergistic effects with antibiotics Mechanism: sublethal concentration of AgNps (6–7 µg/ml) altered the bacterial membrane potential and caused structural damage leading to an increase in cell membrane permeability and subsequent cell death	Vazquez-Muñoz et al. 2019
ZnONps TiO_2Nps	Commercial	- -	*E. coli, S. enteritidis, Listeria monocytogenes, and S. aureus*	The highest susceptibility was observed for *L. monoctytogenes* (0.025 ml/µg) to TiO2 and lowest susceptibility was noted in the reaction of ZnONps with *S. enteritidis* (0.0033 ml/µg). the process of cell death followed first-degree kinetics and the survival ratio of bacteria decreased by an increase in treatment time	Alizadeh-Sani et al. 2020
ZnONps	Aloe vera plant extract	Rod-shape 18–618 µm	*E. coli*	IZD: 1.325mm^2	Rasli et al. 2020
ZnONps	Commercial	- < 50 nm	*S. typhimurium*	MIC and MBC = 0.313 mg/ml and > 5 mg/ml respectively	Akbar et al. 2019
CuONps	Tulsi leaves (*O. sanctum*)- extracted eugenol (4-allyl-2-methoxyphenol)	Flower shape 50 nm	*P. vulgaris, P. fluorescens, S. aureus* and *E. coli*	For *E. coli*, 27 ± 2 mm at the concentration of 100µgmL^{-1}. At a concentration of 25µgmL^{-1}, they exhibit weak activity against all the organisms	Siddiqui et al. 2020

Table 3 (continued)

AgNps	Plant extracts of Phoenix dactylifera, Ferula asafetida and Acacia nilotica	Spherical 67.8 ± 0.3-155.7 ± 1.5 nm	S. aureus, P. aeruginosa, E.coli	Significant antibacterial activity. IZD: 10-32 mm Cytotoxicity: tested using Lovo cells. IC 50 : 35.15–56.73 µg/mL	Mohammed et al. 2018
CuONps	*Bauhinia tomentosa* leaf extract	Spherical 22-40 nm	*E. coli*, *P. aeruginosa*	IZD of 22 mm and 17 mm	Sharmila et al. 2018
TiO_2Nps	Synthesized via a combination of electrospinning and atomic layer deposition approach	Spherical 16.8 nm	Multidrug resistant *E. coli* and *S. aureus*	Antimicrobial activity greater than commercial TiO_2Nps. Hollow TiO_2 nanospheres present potential antimicrobial activity when irradiated with UV light	de Dicastillo et al. 2019
MgONps	*Manihot esculenta (crantz)* leaf extract	Hexagonal 36.7 nm	Gram-positive and gram-negative	Good antibacterial activity	Essien et al., 2020
MgONps	Leaf extract of *Rhizophora lamarckii*	Nanohexagonal and spherical 20-50 nm	*S. aureus*, *S. pneumonia*, *S. typhi*, *E. coli*	Strong antimicrobial activity at low concentrations. IZD was dose-dependent	Prasanth et al. 2019
MgONps	Green synthesis using orange fruit waste	Spherical < 10 nm	*E. coli*, *P. aeruginosa*	Biocompatible and good antimicrobial activity.	Munjal et al. 2017
MgONps	Chemical synthesis	27 nm	*Bacillus sp. E. coli*	6µgmL^{-1} of dose sufficiently killed *Bacillus* sp. while 7.5µgmL^{-1} killed *E.coli*	Maji et al. 2020
MgONps	*Penicillium chrysogenum*	7–40 nm	*S. aureus*, *B. subtilis*, *P. aeruginosa*, *E. coli*, and *C. albicans*	Good antimicrobial activity	Fouda et al. 2021

As mentioned, green synthesis methods offer a safe approach to producing non-toxic NPs with added benefits. Green synthesis has already found its footing in multiple fields, leveraging natural alternatives. A particularly compelling arena is nanomedicine, encompassing research into diagnostics and therapeutic interventions, including cancer treatment and drug delivery. To fully harness the potential of NPs in this context, there is a critical need for NPs of uniform size, consistent properties, biocompatibility for drug loading, and precise release targeting only the affected cells. While NPs have undeniably advanced diagnosis and therapy, their potential should extend into other areas that have been overlooked. They could find applications in addressing parasitic infections and enhancing cancer therapy responses. However, fundamental research must focus on identifying key NP markers that enable precise targeting of diseased tissues without disrupting normal cellular functions.

The integration and advancement of nanotechnology in the field of medicine offer the potential for simplified treatment regimens requiring lower dosing frequency and reduced maintenance. Injectable nanocarriers capable of prolonged drug transport and controlled release hold revolutionary promise, especially in addressing healthcare challenges. These drug delivery systems may involve the utilization of nanocarriers, which modulate drug release via inert vehicles like lipids or polymers or by facilitating gradual drug breakdown within poorly soluble mediums such as nano-drug crystals. A notable breakthrough in this realm is the development of long-acting injectable nanoparticles serving as antiretrovirals, which significantly reduce the dosing frequency for HIV patients and represent one of the most advanced nanotechnology treatments for this virus. As this field progresses, incorporating nanotechnology into medical practices offers innovative strategies to enhance the overall quality of health care.

Furthermore, various photodynamic nanomaterials have demonstrated potent bactericidal effects against common drug-resistant pathogens, especially enterobacterial, inhibiting initial bacterial colonization and biofilm formation (Wang et al. 2018; Sun et al. 2019; Zhang et al. 2023; Pairhajibagher et al., 2022; Pietrowska et al. 2022; Buchovec et al. 2022; Yuan et al. 2020, Han et al. 2020; Vogeling et al., 2019; Pourhajibagher et al. 2018). Nonetheless, employing a solitary antibacterial treatment faces a range of complex hurdles, encompassing intricate technological procedures, pharmacological factors, the toxicological effects on nearby and remote tissues, and economic efficiency. Therefore, nanomaterials should adhere to consistent standards, including minimal toxicity to the human body, customizability to meet the specific requirements of various scenarios and conditions, high specificity, and effective penetration of targeted sites. Moreover, integration into

intelligent therapeutic multimodal platforms like hydrogels, which are capable of enhancing their efficiency, will help promote their therapeutic values. The engineering and production of these materials should also be cost-effective and scalable for mass production.

Comparing the antimicrobial efficacy of different nanomaterials and facilitating their adaptation for clinical use is complex. It is important to note that limited studies have addressed the biocompatibility of nanomaterials and their stability within biological tissues. Safety concerns arise from potential interactions between nanoagents and other biological components. Consequently, rigorous in vivo testing and methods to enhance biocompatibility (e.g., through biosynthesis and optimization of antibacterial effectiveness) require further exploration. Nevertheless, the complex synthesis procedures and high production costs associated with most nanoproducts currently hinder large-scale manufacturing. Additionally, the transition of nanoproducts into clinical applications is challenging, especially in the absence of adequate support.

Future research is expected to prioritize biosafety considerations, encompassing the interactions of nanomaterials with the immune system, long-term safety assessments, the evaluation of potential degradation byproducts, and the consequences of unintended diffusion of nanomaterials. Systematic investigations into the antibacterial mechanisms of metallic nanomaterials, assisted by *in silico* prediction models, may provide insights into their effectiveness against various bacterial pathogens. Furthermore, well-structured studies are essential to critically examine the pharmacological aspects, including dynamics, kinetics, and toxicology, in order to provide comprehensive profiles of metallic nanoparticles. These aspects will encompass administration routes, biodistribution, nanoparticle metabolism, excretion (clearance), off-target effects, cytotoxicity, and interactions with the commensal microbiota.

In conclusion, the field of nanotechnology represents a promising avenue for curtailing the spread of superbugs. Nanotechnology must transition from laboratory-scale production of synthesized nanomaterials to large-scale manufacturing for widespread clinical therapeutic device implementation. Given their potential for deep tissue penetration and synergistic bactericidal effects, addressing the limitations of metallic nanoparticles and other nanomaterials is paramount. Strategies may include functionalizing these nanomaterials for specific bacteria and exploring multimodal synergistic therapies to minimize side effects and maintain cost efficiency. Achieving success in these therapies' design, characterization, and clinical implementation will necessitate a collaborative multidisciplinary approach. This collaboration is very critical to fully design an effective nanomaterial, understand their exact mechanisms of action, and, most importantly, fully translate this technology to clinical application.

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Declarations

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