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The Role of Biosynthesized Metallic and Metal Oxide Nanoparticles in Combating Anti-Microbial Drug Resilient Pathogens

Gemechis Waktole[1*], Bayissa Chala[2]

[1]College of Natural and Computational Sciences, Department of Biotechnology, Dambi Dollo University, Dambi Dollo, Ethiopia
[2]School of Applied Natural Sciences, Department of Applied Biology, Adama Science and Technology University, Adama, Ethiopia
Email: *gamewa2010@gmail.com

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Abstract

Because of their high efficiency, antibiotics have long been the primary treatment for infections, but the rise of drug-resistant pathogens has become a therapeutic concern. Nanoparticles, as novel biomaterials, are currently gaining global attention to combat them. Drug-resistant diseases may need the use of nanoparticles as a viable therapeutic option. By altering target locations and enzymes, decreasing cell permeability, inactivating enzymes, and increasing efflux by overexpressing efflux pumps, they can bypass conventional resistance mechanisms. Therefore, understanding how metal and metal oxide nanoparticles affect microorganisms that are resistant to antimicrobial drugs is the main objective of this review. Accordingly, the uses of metal and metal oxide nanoparticles in the fight against drug-resistant diseases appear promising. However, their mechanism of action, dose, and possible long-term effects require special attention and future research. Furthermore, repeated use of silver nanoparticles may cause gram-negative microorganisms to acquire resistance, necessitating additional study.

Keywords

Nanoparticle, Drug Resistance, Metal Oxide, Metals, Pathogens

1. Introduction

Following the discovery of penicillin in 1928, many additional antibiotics were discovered and commercialized. Antimicrobial components and therapy, on the other hand, have marked a watershed moment in medicine, saving millions of lives. The rise in morbidity and mortality associated with microbial infections has been related to the evolution of multidrug-resistant microorganisms. Anti-

microbial resistance has become serious in recent years, posing a major public health hazard worldwide. The absence of novel and effective antimicrobials is linked to the rise in multidrug resistance. Although antibiotic resistance exists naturally, it has been rapidly spreading in recent decades due to incorrect antibiotic use [1]. This has led to global initiatives to identify novel and more effective antimicrobial agents in addition to discovering novel and effective drug delivery and targeting methods.

Antibiotics have long been the preferred strategy for treating infections due to their high efficacy, but the emergence of multidrug-resistant bacteria has become a major clinical issue. Super bacteria, which evolved as a result of antibiotic overuse, are currently gaining attention due to their resistance to practically all antibiotics [2]. Even though developing new antibiotics is costly and time-consuming [3], several studies have found that routinely used antibiotics are the primary cause of crucial multidrug-resistant pathogens [4]. Recently, multidrug-resistant pathogenic strains have appeared where most of the available antibiotics are not effective against these pathogens. Due to increasing microbial resistance to standard frontline antibiotics, studies on the antimicrobial activity of nanoparticles have improved [5].

Nanotechnology is an attractive area in current biomedical applications and is recognized as the usage of nanoscale (1 - 100 nm) materials. Due to their properties, these materials can provide enhanced physicochemical and biological properties. Considerable attention has been given to nanomaterials due to their wide application in agriculture, pharmaceuticals, consumer products, transportation, energy, cosmetics, and, more importantly, antimicrobial agents. Metals and their oxide nanoparticles are naturally sourced materials that have been used against infectious pathogens since ancient times because of their therapeutic and blocking effects [2]. Metals have been employed as antibacterial agents for thousands of years, with the oldest mention of copper salts as an astringent dating back to 1500 BC [6]. Metals and their oxide nanoparticles appear to hold the most promise of all nanoparticles and have piqued the curiosity of numerous researchers. Nanoparticles, as novel biomaterials, are currently attracting global attention as a way to fully achieve this feat. Drug-resistant illnesses may require the use of nanoparticles as a feasible therapeutic alternative [7]. The goal of this review is to learn more about the effects of metal and metal oxide nanoparticles on antimicrobial drug-resistant pathogens.

2. Overview of Metallic and Metal Oxide Nanoparticles

Nanotechnology is used in creating antibacterial, antifungal, antiplasmodial, anti-inflammatory, anticancer, antiviral, antidiabetic, and antioxidant drugs in medicine. Microbes are less likely to develop resistance to nanoparticles (NPs), which implies they might be utilized to tackle the growing problem of antibiotic resistance, according to researchers [8] [9] [10]. They have antimicrobial action that can overcome common resistance mechanisms, such as enzyme inactivation, decreased cell permeability, alteration of target sites/enzymes, and en-

hanced efflux through overexpression of efflux pumps, to escape antibacterial activity [11]. The use of nanoparticles could be a viable technique for treating infections caused by multidrug-resistant organisms (MDROs) [12].

Metallic nanoparticles have piqued the interest of scientists for over a century, and they are now widely used in biomedical research [13]. Nanotechnology employing nanoparticles has been the subject of extensive research in recent years. Nanoparticles such as copper, gold, and silver as well as zinc oxide, magnesium oxide, and titanium dioxide have been employed and modified for diagnostic and therapeutic purposes over the years. They are also efficient against sensitive and multidrug-resistant bacterial strains as nanobactericides and nanocarriers [14]. The electrical, optical, physical, chemical and thermal properties of NPs influence the production and utility of metal-derived materials. Some of these properties are important for medical applications, whereas others offer opportunities for industrial and environmental applications.

NPs can be made in a variety of ways. The technique of synthesis determines the size, chemical composition, and form of these NPs. They might be biological or inorganic. Organic NPs, such as polymeric NPs, lipid-based nanocarriers, liposomes, carbon-based nanomaterials, and solid lipid NPs, are biodegradable, but inorganic NPs are made of inorganic materials such as metals and metal oxides such as silver oxide and zinc oxide [15]. However, controlling the size and form of monodispersed NPs with greater stability during synthesis is a major problem. Interestingly, various parameters, including NP size, shape, and content, influence the interaction between NPs and living cells/tissues [16]. They can be made in a variety of ways, including top-down and bottom-up approaches. The numerous methods for synthesizing NPs and their applications are depicted schematically in **Figure 1**.

2.1. Silver Nanoparticles

Among all nanoparticles, silver nanoparticles (AgNPs) are the most studied and commonly employed. They are currently regarded as next-generation antibiotics due to their excellent efficiency in suppressing bacteria [17]. It is the most frequently used inorganic NP, accounting for more than 25% of all consumer items [18]. AgNPs are active antibacterial agents and can suppress the growth of antibiotic-resistant organisms at very low concentrations. It binds to membrane proteins and bacterial DNA that contain phosphorus and sulfur complexes that attract AgNPs. It also has antibacterial and bactericidal capabilities that are effective against Gram-positive and Gram-negative bacteria as well as methicillin-resistant strains [19]. The use of silver nanoparticles as antiseptics has resurfaced due to challenges and demands, which may be related to their broad-spectrum activity and lower potential to promote microbial resistance than antibiotics. AgNPs have also the following advantages: they can be synthesized using a variety of methods, can be used as biosensor materials, have optical properties, can improve wound healing, and can be used in the medical industry because of their antibacterial, antifungal, antiviral, anti-inflammatory, and osteoinductive properties [20].

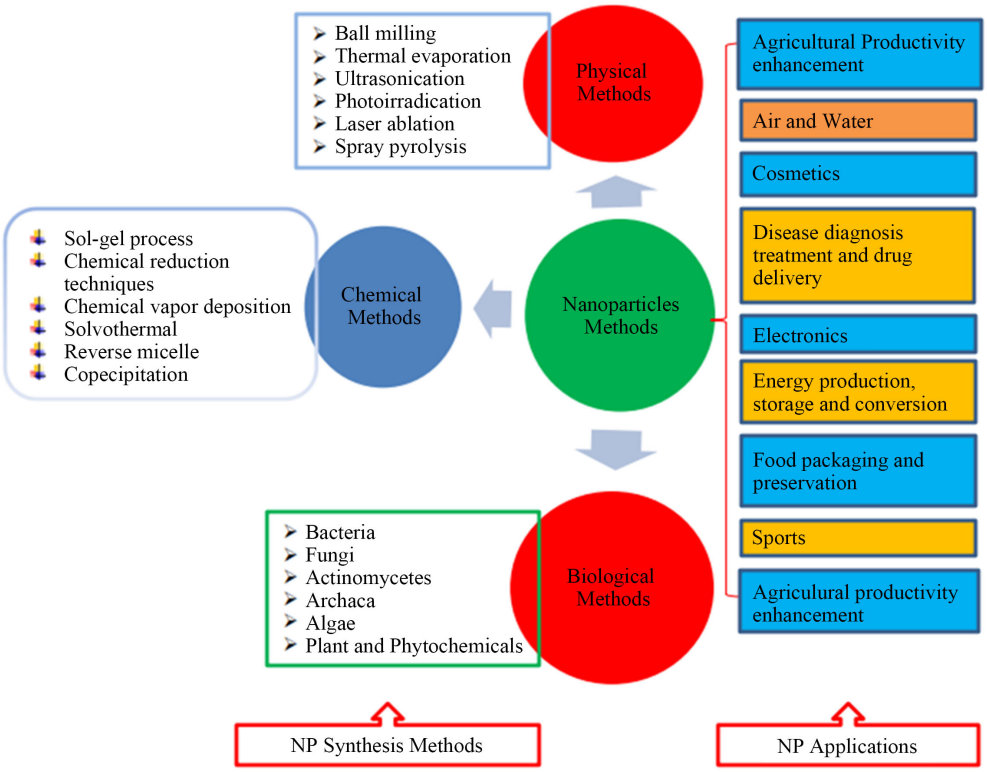

Figure 1. A schematic illustration of several nanoparticle fabrications and application methods.

The exact antibacterial actions of silver nanoparticles are unknown; nanoparticles can continuously emit silver ions, which could be the process of germ-killing. Silver ions can stick to the cell wall and cytoplasmic membrane due to electrostatic attraction and affinity for sulfur proteins. The attached ions can increase the permeability of the cytoplasmic membrane, causing the bacterial envelope to be disrupted. Respiratory enzymes can be disabled once free silver ions are taken into cells, resulting in reactive oxygen species but no adenosine triphosphate synthesis [21]. Cell membrane rupture and deoxyribonucleic acid (DNA) alteration can be triggered by reactive oxygen species. Because sulfur and phosphorus are key components of DNA, the interaction of silver ions with these elements can create issues with DNA replication, cell reproduction, and even microorganism death. Furthermore, silver ions can prevent protein production by denaturing ribosomes in the cytoplasm [21]. Silver nanoparticles can not only release silver ions but can also kill germs directly. After anchoring to the cell surface, silver nanoparticles can aggregate in pits that form on the cell wall [22].

Despite being regarded as next-generation antibiotics, research has shown that gram-negative microbes might become more resistant to silver nanoparticles after repeated exposure. The formation of the sticky protein flagellin by the flagellum protein causes the nanoparticles to combine, which causes resistance. Only phenotypic alteration required to modify the colloidal equilibrium of the nanoparticles and, as a result, remove their antibacterial activities is this resistance.

AgNP may be stabilized as an alternative to polymers or surfactants to get past the resistance mechanism. However, the generation of flagellin is considerably reduced when pomegranate rind extract is used [23].

2.2. Gold Nanoparticles

Because of their long history of medicinal applications, gold nanoparticles are the most important metal nanoparticles. Gold NPs come in a variety of sizes ranging from 2 to 100 nm, although particle sizes between 20 and 50 nm indicated the best cellular uptake. 40 - 50 nm particles have been found to cause specific cell toxicity. During their synthesis and functionalization with different groups, the size can be controlled. The thiol/gold ratio determines the size of the conjugated nanoparticles [24]. The particle size will be small when the amount of thiol is large. Gold nanoparticles can be employed in a variety of applications, including odor elimination and the removal of hazardous carbon monoxide from rooms, emission management, water purification, power cells, and important medicinal applications. These particles can enter tissues and assault immune cells, such as lymphoid tissues, due to their small size, making them potentially beneficial in immunotherapy [25]. Gold NPs have the following advantages: they have unique physical and chemical features that improve drug effectiveness, drug loading, biocompatibility, easy access to the targeted region with blood flow, are noncytotoxic to normal cells, and may be produced using a variety of processes [26].

2.3. Copper Nanoparticles

Copper nanoparticles have been shown to be highly effective antimicrobial agents. They are therefore of tremendous interest to scientists due to their unique biological, chemical, and physical properties, as well as their antibacterial capabilities and inexpensive cost of synthesis [27]. The synthesis methods are chosen to define the properties of CuONPs, which are critical for their applications in a variety of fields, the most common of which is biomedical research. The size of the nanoparticles, which can be modified during synthesis, is the most essential property since it allows for customized modeling of their optical, catalytic, electrical, and biological capabilities [28].

They manifest differently depending on the various properties. CuO nanoparticles can be used for a variety of purposes, all of which are influenced by their size, surface characteristics, optical, and magnetic properties, with the synthesis technique playing a significant role in controlling all of them, as well as their biological features. Doping materials in semiconductors, such as chemical sensors, antimicrobial agents, catalysts for various cross-coupling reactions, anticancer formulations, and coating materials, are only a few of these uses. It has potential biomedical applications in the future in disease detection, in addition to antibacterial drugs, and could have prospective applications in a variety of other fields, such as the diagnosis of diseases [29].

2.4. Zink Oxide Nanoparticles

Various synthetic methods have been used to generate a variety of ZnO nanostructures, including nanoparticles, nanowires, nanorods, nanotubes, nanobelts, and other complicated morphologies, due to their wide range of applications [30]. Zinc oxide has strong antibacterial capabilities. Rings, propellers, belts, and wires are just some of the morphologies that ZnONPs can take on [31]. Zinc oxide nanoparticles are inorganic metal oxides that can be used safely as medications, package preservatives, and antibacterial agents. It easily diffuses into food materials, killing germs and preventing illness in humans [32].

Zink oxide, like other nanoparticles, has a wide range of applications. Because biomolecules are extremely sensitive to pH and temperature in solution, metal oxide semiconducting nanoparticles are in high demand for applications in biological sensing, biological labeling, drug and gene delivery, and nanomedicines [33]. ZnO nanoparticles, in particular, can provide a superior solution for numerous biological applications due to their ease of production, ecologically friendly nature, and nontoxic synthesis technique. The essential requirements for biological applications are the water solubility and biocompatibility of ZnO nanoparticles.

Although the mechanisms of action responsible for the antimicrobial activity of ZnONPs are still unknown, some proposed mechanisms include the destruction of cell integrity caused by direct contact between ZnONPs and cell walls, the formation of reactive oxygen species (ROS), and the release of antimicrobial ions, primarily Zn^{2+} ions. Nonetheless, because the molecular composition of dissolved zinc is affected by media elements, the mechanism of ZnONP toxicity is most likely media-dependent. Zinc oxide nanoparticles are known to be antibacterial and hinder the growth of germs by penetrating the cell membrane. Lipids, carbohydrates, proteins, and DNA are all damaged by oxidative stress. The most crucial factor that leads to changes in the cell membrane is lipid peroxidation.

2.5. Magnesium Oxide NPs

By nature, magnesium oxide contains periclase minerals and has antibacterial qualities. Gram-positive and gram-negative bacteria are both susceptible to MgO's antibacterial effects [34]. The mechanism of action of MgONPs is by damaging the cell membrane, causing the loss of intracellular contents and the death of bacterial cells. Additionally, the generation of reactive oxygen species has been attributed to the surface alkalinity of MgONPs. Because of their structure, surface characteristics, and stability, MgONPs with an average size of 20 nm has considerable potential as antibacterial agents in food safety applications [35].

2.6. Titanium Dioxide NPs

Titanium dioxide (TiO_2) has fascinated many scientists and has provided a

wealth of information on its properties and uses [36]. Recently, researchers have focused on modified TiO_2 nanoparticles because of their unique physical and chemical properties. As a result of increased attention, TiO_2 nanoparticles are being used more effectively in a variety of areas, including therapeutic and medical applications [37]. The antibacterial properties of TiO_2 are determined by its crystal structure, shape, and size [38]. The formation of reactive oxygen species (ROS) is considered a particularly important process for TiO_2 nanoparticles. ROS then causes DNA damage at specific sites [39].

3. Burden of Antimicrobial Drug Resilient Pathogens

Antibiotics have dramatically changed the fate of mankind as well as the treatment of infectious diseases. In contrast, antibiotic-resistant infections pose a significant global public health threat due to increased prevalence and limited treatment options. These infections are primarily associated with extended hospital stays, increased incidence of treatment complications, and extended treatment periods, thus increasing the cost to patients. Antimicrobial resistance (AMR) is the ability of bacteria, viruses, fungi, and parasites to circumvent the efficacy of drugs that were once sensitive [40]. Antibacterial resistance is increasing rapidly around the world. This growing concern about the public health burden of AMR raises conceptual and technical challenges and has driven medicine to advance and save the lives of millions of people. Estimates of the disease burden specific to drug resistance are not currently available, but drug resistance is believed to contribute significantly to the burden of infectious diseases. Even between July 2017 and November 2021, the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), or both authorized twelve novel antibacterial agents [41].

Resistance arises from malaria, HIV, tuberculosis and other bacterial infectious diseases, which together make up a significant portion of the disease burden in developing countries [42]. The global problem of antibiotic resistance is especially acute in developing countries, where the burden of infectious diseases is high and cost constraints prevent the widespread use of newer and more expensive drugs. Gastrointestinal, respiratory, sexual, and nosocomial infections are the leading causes of illness and death in developing countries, and the treatment of all these illnesses is severely affected by the emergence and rapid spread of drug resistance [43].

AMR has a widespread impact on the treatment of infectious diseases. This limitation of treatment options often results in the need to rely on broad-spectrum antibiotics, some of which may be less effective or safer than narrow-spectrum antibiotics. Tolerance also affects empirical treatment. When clinicians choose antibiotics to treat infections without microbiological consequences, they may underestimate the risks associated with certain infections or the use of inappropriate antibiotics. For example, meta-analysis results show that patients with bacteremia caused by resistant *Enterobacteriaceae* are five times more likely to be delayed in receiving effective treatment than patients infected with suscepti-

ble strains [44]. This can compromise the long-term efficacy of antibiotics, delay access to effective treatments, increase treatment failure rates with associated complications, and ultimately lead to higher mortality rates. Research studies have consistently shown a longer stay, increased need for surgery, and increased mortality from infections caused by resistant Gram-positive and Gram-negative bacteria [45]. In 2019, six pathogens were each more causative of over 250,000 AMR-related deaths: *Escherichia coli*, *Staphylococcus aureus*, *K. pneumonia*, *S. pneumonia*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, order of death. Together, these 6 pathogens accounted for 929,000 (95% UI 660,000 - 1,270,000) 1.27 million deaths from AMR (0.911 to 1.71) of the 4.95 million deaths and 3.57 million (2.62 - 4.78) (3.62 - 6.57) deaths associated with AMR worldwide in 2019 [46]. Consequently, the present clinical pipeline for novel antimicrobial treatments, according to the World Health Organization, is insufficient to combat AMR. As a result, researchers calculated that there were 4.95 million fatalities worldwide in 2019 (95 percent UI 3.62 to 6.57), in which AMR was likely a contributing factor [47].

4. Effects of Different Metallic and Metal Oxide Nanoparticles against Pathogens

Infectious diseases continue to be one of the world's top causes of morbidity and mortality. Pathogen resistance to antibiotics has recently become increasingly common, posing critical health risks. Pathogens resistant to antibiotics have emerged as a serious public health problem, spurring a rush of studies to improve current antimicrobial therapies. Metal and metal oxide nanoparticles are a class of materials that have been studied for their antibacterial properties [48].

Therefore, the antibiotic resistance crisis is one of the most pressing issues in global public health. The lack of new antimicrobials is associated with the rise in antibiotic-resistant pathogens. This has triggered initiatives worldwide to develop novel and more effective antimicrobial compounds as well as to develop novel delivery and targeting strategies. Antimicrobial resistance has evolved in a variety of methods among bacteria. Enzyme inactivation, reduced cell permeability, target protection, target overproduction, changed target site/enzyme, and enhanced efflux due to efflux pump overexpression are just a few examples [11]. Nanoparticles have several features that make them favorable vectors for drugs to combat disease-causing pathogens. These include their enhancement of drug solubility and stability; [49] their ease of synthesis; [50] their biocompatibility with target agents; and their modulated release, which can be controlled by stimuli, such as light, pH and heat [51].

4.1. Antimicrobial Effects of Different Metallic and Metal Oxide Nanoparticles

The application of NPs provides a potential strategy to manage infections caused by MDROs [12]. In this respect, they have shown therapeutic promise owing to their unique physical and chemical attributes [52]. NPs exhibiting antibacterial

activities can target multiple biomolecules and have the potential to reduce or eliminate the evolution of MDROs [53]. However, the translation of NPs to clinical use requires not only appropriate methods for the synthesis of NPs but also a thorough understanding of the physicochemical particularities, *in vitro* and *in vivo* effects, biodistribution, pharmacokinetics, and pharmacodynamics of NPs [54].

Nanoparticles possess antimicrobial activity that can overcome common resistance mechanisms, including enzyme inactivation, decreased cell permeability, modification of target sites/enzymes, and increased efflux through overexpression of efflux pumps, to escape the antibacterial activity of antimicrobial agents. Moreover, they conjugated with antibiotics show synergistic effects against bacteria, prohibit biofilm formation and have been utilized to combat multidrug resistant organisms [3]. The antimicrobial effects of selected metals and their oxide nanoparticles are reviewed as follows.

Silver NPs have shown good antibacterial properties due to the release of Ag^+ ions, which likely interact with thiol and phosphate groups in proteins and DNA of the pathogens. This interaction disrupts the cell wall integrity, impairing essential enzymes, inactivating pathogens' DNA and RNA, or binding subcellular components [55]. Another study found that silver nanoparticles have high antibacterial activity against *Escherichia coli*, with a minimum inhibitory concentration of 128 mol/L, but no activity against *S. aureus*. This high antibacterial activity is also maintained against two multidrug-resistant *E. coli* strains [56].

Burduniuc *et al.* [57] demonstrated the high antifungal activity of silver nanoparticles in vitro against 100 different clinical isolates belonging to 19 species and 5 genera. They suggest further investigation *in vivo* and proper standardization, stabilization, and toxicology to make them applicable as antimicrobials/antifungals. The authors demonstrate that silver nanoparticles have relatively uniform antifungal activity against all tested fungal isolates at relatively close concentrations. Mussin and his colleagues demonstrated broad-spectrum antimicrobial properties with the fungicidal action of AgNPs and their accumulation in affected areas with a sustained release profile, which added to the great antifungal activity of ketoconazole (KTZ) against Malassezia infections and other superficial mycoses, allowed us to obtain a gel based on carbopol formulated with AgNP–KTZ with the potential to improve the topical therapy of superficial malasseziosis, reduce the number of applications and prevent recurrence [58].

Jeremiah *et al.* [59], evaluated the antiviral effect of AgNPs. They evaluated a surplus of AgNPs of different sizes and concentrations and observed that particles with diameters of approximately 10 nm were effective in inhibiting extracellular SARS-CoV-2 at concentrations ranging between 1 and 10 ppm, while a cytotoxic effect was observed at concentrations of 20 ppm and above. A luciferase-based pseudovirus entry assay revealed that AgNPs potently inhibited viral entry steps by disrupting viral integrity. These results indicate that AgNPs are highly potent microbicides against SARS-CoV-2. Finally, they suggest that it should be used with caution due to its cytotoxic effects and its potential to de-

range environmental ecosystems when improperly disposed of.

Nguyen *et al.* [60], compared the efficacy of MgONP against nine prevalent pathogenic microorganisms, including two gram-negative bacteria, three gram-positive bacteria with drug-resistant strains, and four yeasts with drug-resistant strains. The MIC of MgONP varied from 0.5 mg/mL to 1.2 mg/mL, and the minimal lethal concentration (MLC) of MgONP at 90% killing varied from 0.7 mg/mL to 1.4 mg/mL against different pathogenic bacteria and yeasts. The most potent concentrations (MPCs) of MgONPs were 1.4 and/or 1.6 mg/mL, depending on the type of bacteria and yeasts tested. As the concentration of MgONPs increased, the adhesion of bacteria and yeasts decreased. Moreover, *S. epidermidis* biofilms were disrupted at 1.6 mg/mL MgONPs. *E. coli* and some yeasts showed membrane damage after being cultured with ≥0.5 mg/mL MgONPs. Overall, MgONPs killed both planktonic bacteria and disrupted nascent biofilms, suggesting new antimicrobial mechanisms of MgONPs. The production of reactive oxygen species (ROS), Ca^{2+} ion concentrations, and quorum sensing likely contribute to the action mechanisms of MgONPs against planktonic bacteria, but transient alkaline pH of 7 to 10 or increased Mg^{2+} ion concentrations from 1 to 50 mM showed no inhibitory or killing effects on bacteria such as S. epidermidis. They suggest further studies to determine if specific concentrations of MgONPs at MIC, MLC, or MPC levels can be integrated into medical devices to evoke desired antimicrobial responses without harming host cells.

MgONPs have been examined for their antibacterial efficacy and mode of action against *Campylobacter jejuni*, *E. coli*, and *Salmonella enteritidis strains*. The study found that following exposure to MgONPs, the permeability of the bacterial membrane was disrupted, resulting in the presence of hydrogen peroxide, which caused cell death. Studies of *P. aeruginosa* and *S. aureus* versus MgONPs revealed that *S. aureus* had a larger inhibitory zone than *P. aeruginosa*. The authors speculate that the bactericidal effect of MgONPs is related to the binding of surface oxygen to bacteria. MgONP-modified glass-ionomer cement (GIC) demonstrated effective antibacterial and antibiofilm action against two cariogenic microorganisms, according to Noori and Kareem, and could be considered for further research as a biocompatible antibacterial dental restorative cement [61].

Additionally, MgONPs were tested against the gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* (500 and 1000 g/ml) and the gram-positive bacterium *Staphylococcus aureus* (1000 g/ml) by Pugazhendhi *et al.* [62], Ultrasound-induced lipid peroxidation in liposome membranes was increased by MgONPs. The mechanism of action in this situation could be connected to the existence of surface flaws or a lack of oxygen in the NP, which causes lipid peroxidation and the generation of reactive oxygen species. The permeability of the bacterial membrane was decreased following exposure to MgONPs, the presence of hydrogen peroxide was detected, and finally, cell death occurred.

Usman *et al.* [63] evaluated the antibacterial and antifungal activities of Cu-chitosan nanoparticles on several microorganisms, including methicil-

lin-resistant *S. aureus*, *B. subtilis*, *P. aeruginosa*, *Salmonella choleraesuis*, and *C. albicans*, and indicated the high potential of these nanoparticles as antimicrobial agents. However, the rapid oxidation of Cu nanoparticles upon exposure to air limits their application. Additionally, the antibacterial activity of CuO nanoparticles against *Klebsiella pneumoniae*, *P. aeruginosa*, *Salmonella paratyphi and Shigella* strains was evaluated by Mahapatra *et al.* [64], who reported the potential antibacterial activity of nanoparticles against the mentioned bacterial strains. They also believe that bacterial cell membrane crossing ability and then damaging the vital enzymes bacteria of the nanoparticles might be the main factor for bacterial death.

Additionally, other researchers also investigated and reported the antibacterial activities of CuO nanoparticles against two gram-positive bacteria (*S. aureus and B. subtilis*) and two gram-negative bacteria (*Pseudomonas aeruginosa and E. coli*). Accordingly, they concluded that CuO nanoparticles exhibited inhibitory effects against both groups of the mentioned bacterial strains, and the bactericidal activity of these nanoparticles depended on their size, stability, and concentration added to the growth medium [65]. CuONPs showed excellent antimicrobial activity against various bacterial strains (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Enterococcus faecalis*, *Shigella flexneri*, *Salmonella typhimurium*, *Proteus vulgaris*, *and Staphylococcus aureus*). Moreover, *E. coli* and *E. faecalis* exhibited the highest sensitivity to CuONPs, while *K. pneumonia* was the least sensitive [24]. Another study revealed that VeA-CuO NPs were synergistic in their influence versus bacterial strains, *S. aureus*, *E. coli*, *P. aeruginosa*, and *E. aerogenes*. The uppermost zone of inhibition of 15 mm was observed for *E. aerogenes*. The bioactive compounds capped around the CuO NPs served an effective role in disrupting the cell wall of bacterial strains [66].

ZnO nanoparticles showed bactericidal effects on gram-positive and gram-negative bacteria as well as spores that are resistant to high temperature and high pressure [67]. The improved antibacterial activity of ZnO nanoparticles compared to its microparticles was related to the surface area enhancement in the nanoparticles. Janaki *et al.* [68] investigated the antibacterial activity of ZnO nanoparticles with various particle sizes. Their results demonstrated that the bactericidal efficacy of ZnO nanoparticles increased with decreasing particle size. A comparative investigation of the antimicrobial activity of ZnO, CuO, and Fe_2O_3 nanoparticles against gram-negative (*E. coli and P. aeruginosa*) and gram-positive (*S. aureus* and *B. subtilis*) bacteria was reported by Azam & Oves [65]. According to their results, the most bactericidal activity was reported for the ZnO nanoparticles, while Fe_2O_3 nanoparticles exhibited the least antibacterial effect. Meron and her colleagues synthesized ZnO nanoparticles using *Lippia adoensis* leaf extract and obtained promising results against both Gram-positive and Gram-negative bacterial strains with maximum inhibition zones of 14 mm and 12 mm, respectively, using the uncalcinated form of the synthesized ZnO nanoparticles [69].

Jesline *et al.* [70], evaluated the effect of TiO_2 nanoparticles with different an-

tibiotics against methicillin-resistant *S. aureus* (MRSA). They reported that TiO_2 nanoparticles improved the antimicrobial effect of beta lactums, cephalosporins, aminoglycosides, glycopeptides, macrolides, lincosamides, and tetracycline against MRSA. In another experiment, the antimicrobial resistance of MRSA against various antibiotics decreased in the presence of TiO_2 nanoparticles. Carré *et al.* [71], considered that antibacterial photocatalytic activity was accompanied by lipid peroxidation that enhanced membrane fluidity and disrupted cell integrity. However, the use of TiO_2 nanoparticles under UV light is restricted because of genetic damage in human cells and tissues.

Ansari and his colleagues presented an innovative and creative sustainable technique for the fabrication of titanium (TiO_2) using *Acorus calamus* leaf extract as a new biogenic source, as well as a capping and reducing agent. The antimicrobial efficacy of the prepared nanoparticles was investigated using the disc diffusion technique. Furthermore, biosynthesized TiO_2 showed excellent antimicrobial activity against selected gram-positive staining (*B. subtilis*, *S. aureus*) against gram-negative (*P. aeruginosa*, *E. coli*) pathogenic bacteria in comparison to bare TiO_2 [72].

The antibacterial property of gold (AuNPs) has recently been a major research topic, making them good candidates for antibiotic complementation. The antibacterial activity of AuNPs is mediated by the development of holes in the bacterial cell wall, resulting in cell death due to the loss of cell contents. Furthermore, AuNPs can inhibit multidrug-resistant pathogens by attaching to bacterial DNA and blocking the uncoiling of DNA during transcription by binding to bacterial DNA. The antibacterial activity of PG-AuNPs was found to be strong against gram-negative bacteria and moderate against gram-positive bacteria. Based on the results, it was concluded that AuNPs could be used to combat antibiotic drug resistance. In addition, in vitro and in vivo toxicity studies of AuNPs should be conducted [73].

An antimicrobial strategy using self-therapeutic AuNPs to combat multidrug-resistant bacteria was reported by Li and his colleagues. Cationic and hydrophobic functionalized AuNPs effectively suppressed the growth of 11 clinical MDR isolates, including both Gram-negative and Gram-positive bacteria. The NP ligand structure-activity relationship revealed that surface chemistry played an important role in AuNP antimicrobial properties, providing a design element for the prediction and rational design of new antibiotic NPs. Because of their effective antibacterial action on MDR bacteria, excellent biocompatibility, and gradual development of resistance, cationic hydrophobic nanoparticles are a promising long-term method for treating multidrug-resistant bacteria, a major healthcare concern [74].

4.2. Anti-Parasitic Effects of Different Metallic and Metal Oxide Nanoparticles

In vitro and *in vivo*, Adeyemi and his colleagues examined the anti-parasite potential of nanoparticles. They tested numerous nanoparticles (NPs) for antipara-

sitic activity against several *Trypanosoma* species as well as *Toxoplasma gondii* [75]. Biogenic production of metallic NPs such as silver, gold, copper, and zinc using different biological materials has antimalarial potential against diverse *Plasmodium* species. Anselmo *et al.* [76], reviewed that the Mosquitocidal activity of metallic NPs has been described at different stages of the insect's life cycle with increased pesticide efficacy compared to plant-based preparations. Thus, the half-lethal concentration, LC50, of synthesized AgNPs estimated for eggs, larvae, pupae, and adults is between 1 and 40 $mg{\cdot}ml^{-1}$, which is a much lower value than that observed for the corresponding plant extracts. AgNPs have been mainly applied as larvicides but are also active as ovicides, adulticides, and pupicides. It is important to note that they do not show toxicity for nontarget organisms. Other effects of AgNPs are to reduce mosquito longevity and fecundity as well as to act as a lure and kill approach. This has been observed for AgNPs synthesized from a plant that provides capping with metabolites that are attractive to a kind of mosquito.

Glc-NCs are glucose-based ultrasmall gold nanoparticles that bind to the cysteine-rich areas of *Plasmodium falciparum* surface proteins. Glc-NCs bind selectively to extracellular and intraerythrocytic phases of *P. falciparum*, according to microscopy. As shown with ciprofloxacin, a weakly soluble antibiotic with low antimalarial action, Glc-NCs can be employed as drug delivery agents. Ciprofloxacin conjugated to Glc-NCs is more water-soluble and powerful than the free drug. Malaria prevention and therapy could benefit from *glyco*-gold nanoparticles that target parasite cysteine-rich domains [77].

There is a wide range of metallic nanoparticles that are being used for anti-leishmanial activity, providing minimal toxicity and high efficacy [78]. Zinc oxide nanoparticles (ZnONPs) are massively produced and used. A study was conducted in which ZnONPs were employed in varying concentrations (0.18, 0.37, 0.75, and 1.5 μg/mL) against the amastigote form of Leishmania, *L. donovani*, in *in vitro* culture. The results were analyzed by colorimetric assay, which suggested that ZnONPs exerted a cytotoxic effect on the amastigote cells, causing hindrance in their proliferation and suppression of the activity of *L. donovani*. The study suggests that ZnONPs could be a cost-effective means against anti-leishmanial drug development [79], prepared ZnONPs from *Verbena officinalis* and *Verbena tenuisecta* plant leaf extracts. The results suggest that *V. officinalis* had a higher phenolic content. Both plant ZnONPs were tested for anti-leishmanial activity, whereas the *V. officinalis* ZnONPs had better activity due to the greater phenolic content and smaller size compared to *V. tenuisecta*-mediated ZnONPs [80].

5. Limitations of Metallic and Oxide NPs

Metal and metal oxide NPs have innumerable applications in addition to acting as antimicrobials in end uses as varied as medical diagnostics, therapeutics, sensors, cosmetics, solar cells, and coatings. Despite the high benefits and frequent

use of these particles, there are still concerns about their potential risks and side effects. Some particles have boosted toxicology in this area, owing to the importance of trying to minimize the potential risks of these drugs and materials on human cells and tissues, as well as the environment [81].

In contrast, concerns with the usage of NPs include local and systemic toxic consequences, as well as negative effects on beneficial microbes in humans. Hemolysis and interference with blood coagulation pathways can be caused by both NPs and their hazardous breakdown products. Although the specific mechanism of toxic consequences is unknown, it has been established that the larger the NP is, the higher the chance of negative health effects [3]. Furthermore, it has been shown that NPs exert antibacterial activity by releasing heavy metals, which cause oxidative stress in humans and can cause a variety of physiological, biochemical, and behavioral dysfunctions. To better understand the harmful consequences of metallic NPs, more research is needed. As a result, the therapeutic use of NPs still faces numerous hurdles.

Among the metallic NPs, the toxicity of AgNPs has been extensively studied. Although most studies have been conducted *in vitro*, it has been shown to be more toxic to cell lines [82]. It is well known that AgNPs can accumulate in the human body and various organs, especially the brain, due to their ability to cross the blood–brain barrier. AgNP was also identified in the lungs, spleen, kidneys, liver, and brain of exposed rats. In mammalian cell lines, zinc-based nanomaterials have been shown to produce toxicity and membrane damage, as well as enhance oxidative stress [83]. TiO_2 is hazardous to DNA damage, genotoxicity, pneumonia, and other diseases and hence has a negative impact on nanomorphology. In addition, many NPs are coated with a flexible hydrophilic polymer, usually containing polyethylene glycol, allowing these particles to circulate longer. Oxidative damage to CuONPs and DNA damage induced by ZnONPs or TiO_2NPs limit their use [51]. Intravenously administered NPs can accumulate in the colon. The effects of NP on biological systems are not fully understood. Therefore, the harmful effects and limitations of NP need to be carefully studied [84].

6. Conclusion and Future Perspectives

The ability of metallic and oxide nanoparticles to inhibit pathogenic strains, as well as their mechanisms of action, is, in contrast, less understood. Both nanoparticles seem promising in the fight against drug-resistant diseases because of their distinctive properties and low cost of *in vitro* synthesis. As a result, they can lessen the activation of bacterial resistance and boost the effectiveness of antimicrobial therapy. Since both efflux pumps and enzymes must be deactivated simultaneously, ROS production, permeability changes, protein and DNA breakdown, and cell wall and membrane damage follow. However, gram-negative microbes may develop a resistance to silver nanoparticles after repeated treatment, which may call for further research. Additionally, their mode of action, dose, and long-term effects demand additional consideration and research.

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Authors' Contributions

Gemechis Waktole designed the study, retrieved the data, analyzed the data and wrote the manuscript. Bayissa Chala supervised and edited the manuscript. Both authors reviewed and approved the manuscript for publication.

Availability of Data and Materials

No data set is generated.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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