Metals as Antimicrobials

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The nature of microorganisms and the efficiency of antimicrobials have witnessed a huge co-dependent change in their dynamics over the last few decades. On the other side, metals and metallic compounds have gained popularity owing to their effectiveness against various microbial strains.

metals nanoparticles antimicrobial action

1. Introduction

Several kinds of microorganisms lead to the initiation and further development of microbial infections. Such infections primarily and solely manifest in many pathological conditions with variant degrees of severity. Their pathologies precipitate numerous mild symptoms (fever, fatigue, nausea, headache) to serious symptoms (cyanosis, tissue necrosis, lymphadenopathy, respiratory effects) [1][2]. These have also evolved to be one of the major secondary factors in various diseased conditions, while in some, they ultimately cause death [3][4]. Microbial infections and their manifestations interfere at every step of medical methodologies from concluding misleading and erroneous diagnoses to resulting in deleterious surgeries as well as unsuccessful and incomplete treatments [5]. The severity of the condition worsens when there is any kind of additional or major infection. All of this has made antimicrobials a very important and fundamental part of therapeutics and pharmacology [6][7].

The last century has seen excessive use of antibiotics for various kinds of infections. They work by targeting bacterial cell components and altering necessary processes like DNA replication, cell wall synthesis, etc. [8][9][10]. However, they do have certain drawbacks that make them insufficient and problematic in various ways:

- They may affect healthy bacteria present in the body [11][12].
- Monitoring its effectiveness is difficult and challenging [13][14].
- Inconsistency in therapeutic security and the number of associated side-effects [15].

Along with these deficiencies, increasing antibiotic resistance has hinted at the clinical need for newer antimicrobials to tackle microbial growth and biofilm production effectively. Continuous mutations, irrational use of antibiotics, and the production of enzymes that inactivate the bacterial cells have contributed to this increasing resistance to the agents [16][17].

Barring antibiotics, metal compounds were largely in use and practice before the 1920s, after which antibiotics took over [18][19][20]. The potential of metals to conveniently restrict biofilm production make them the best possible alternative in present times [21][22]. Antimicrobial properties of metals have been used since ancient times for disinfecting food and water, managing plant diseases in agriculture, and in medical areas as well [23][24]. Certain metals are necessary for cell functioning and cell membrane formation but their presence in excess amounts can be lethal, whereas specific other metals like non-essential groups, such as mercury, silver, etc., are found to be microbicidal even at very low concentrations [25].

2. Metals as Antimicrobials

Metals are abundant in the earth's crust and ecosphere. The Great Oxidation Event (GOE), which took place 2.3–2.4 billion years ago, exposed bacteria to a wide range of metal ions. The earth's crust contains a variety of oxidized forms of metal compounds as a result of the atmosphere's rising oxygen level. Enzymes used metals like copper, iron, and zinc for their redox reactions. Metals are necessary for the process of life but are toxic at high intracellular concentrations, and, thus, cells need a homeostasis mechanism to keep the intracellular concentration constant. Zinc and copper share a similar pathogen-killing mechanism in eukaryotes, where oxidative stress is used to destroy the encapsulated bacterium. Metals like gold, silver, and mercury are extremely poisonous to microorganisms at low concentrations [26].

Metals were once utilized as antibacterial agents, but their industrial usage can harm the ecological system, although they do have a medical use. Infections were treated with arsenic, mercury, silver, copper, zinc, and other elements. Antimony and arsenic are employed as fungicides, rodenticides, insecticides, and to treat protozoal illnesses. While zinc salts can be used to treat diarrhea, copper salts are used to make the Bordeaux and Burgundy mixture, which is used to prevent bacterial and fungal problems in plants and to promote animal growth. Burns can be relieved with silver. Organic mercury compounds are utilized to keep eye drops in good condition. Mercury was utilized as a disinfectant and a syphilis infection treatment. In dental restorations, mercury is combined with copper, silver, and tin [27].

2.1. Metal-Based Nanoparticles as Antimicrobials

Metallic NPs of sizes ranging from 1 nm to 100 nm can be synthesized by two approaches, i.e., top-down and bottom-up. The top-down approach involves beginning with the material in bulk, which is then broken down into the size of a nanoscopic scale via ball milling or attrition etc. It is an easy method to employ, but increased accommodated impurities and non-uniform sizes of particles limit its use [28][29]. On the other hand, the bottom-up nanofabrication approach includes variant techniques such as the colloidal synthesis, the sol-gel method, the chemical vapor decomposition process, and the atomic layer deposition among others. The process, though time consuming and tedious, has the benefit of uniform-sized and uniform-shaped smaller particles bearing the least number of defects and controlled surface properties [29][30][31].

The use of metal-based nanoparticles as components in the creation of antibacterial agents has been made possible by nanotechnologies. Metal-based nanoparticles (NPs) demonstrate an effective role in locating and eliminating bacteria through a variety of mechanisms, including attraction to the surface of the bacteria, disruption of the cell wall and membrane, and induction of a toxic mechanism mediated by an increase in oxidative stress (e.g., the production of reactive oxygen species (ROS)) [32][33][34][35]. The creation of oxidative stress is a valuable and effective antibacterial method to combat MDR bacteria, given the absence of new antimicrobial medicines with unique mechanisms of action. Therefore, it is important to identify and properly characterize whether NPs might cause oxidative stress in these bacteria [36][37][38]. Metal-based NPs physically interact with bacterial cell surfaces, disrupt their membrane, and, ultimately, restrict the formation of biofilms [39]. The formation of biofilms also leads to the development of resistance against antimicrobial agents, so their hindrance ultimately restricts the modulation of resistant mutants, too [40][41][42]. The shape of metal-based NPs along with their ultra-small, compliantly controllable size, and resultant greater surface area to mass ratio all contribute to the prevention of biofilm formation [43][44][45]. The target microorganisms and their mechanisms of action for a few metal-based nanoparticles are provided in **Table 1**.

Table 1. Antimicrobial activity mechanisms of different metal-based NPs.

S. No.	Metal-Based Nanoparticles	Microorganism	Mechanism of Action	Reference
1.	Smaller silica nanoparticles	*E. coli* bacteria	Cell wall rupturing	[46]
2.	AgNPs	*K. pneumoniae*	Damage to bacterial cell wall Reactive Oxygen Species (ROS) generation	[47]
3.	CuNPs	*F. oxysporum*	Structural and functional changes in fungi cell, affects DNA and its replication, and protein synthesis	[48]
4.	AuNPs	*B. subtilis*	Bacterial membrane damage	[49]
5.	Iron nanoparticles	*P. aeruginosa*, *E. coli*, *S. aureus* and *B. subtilis*	Bacterial cell membrane rupture ultimately led to bacteria death	[50]
6.	Gallium based nanoparticles	*P. aeruginosa*	ROS-mediated bacterial cell wall damage	[51]

The targeted drug delivery approach of metal-based NPs can be achieved through either active or passive targeting. Active targeting involves the modification of surfaces of metal-based NPs and processes like magnetic targeting, receptor targeting, and other approaches such as temperature-dependent cell death patterned targeting. Passive targeting, meanwhile, is generally accomplished by improving permeation and enhanced retention at the site of infection [52].

Within a single metal-based NP, multiple drugs can be accommodated to bring an elaborative action. Different drugs that have different kinds of mechanisms will exert a joint action and will subsequently result in higher efficiency. The microbe being either resistant or a multi-drug resistant mutant will probably be successfully affected via one or the other of the variant processes [53][54].

2.2. Mechanisms Involved in Antimicrobial Activity of Metal and Metal-Based NPs

Metal and metal NPs interfere with bacteria's hemostasis in 3 major ways: disruption of the membrane, oxidative stress, and interaction with proteins and enzymes (**Figure 1**).

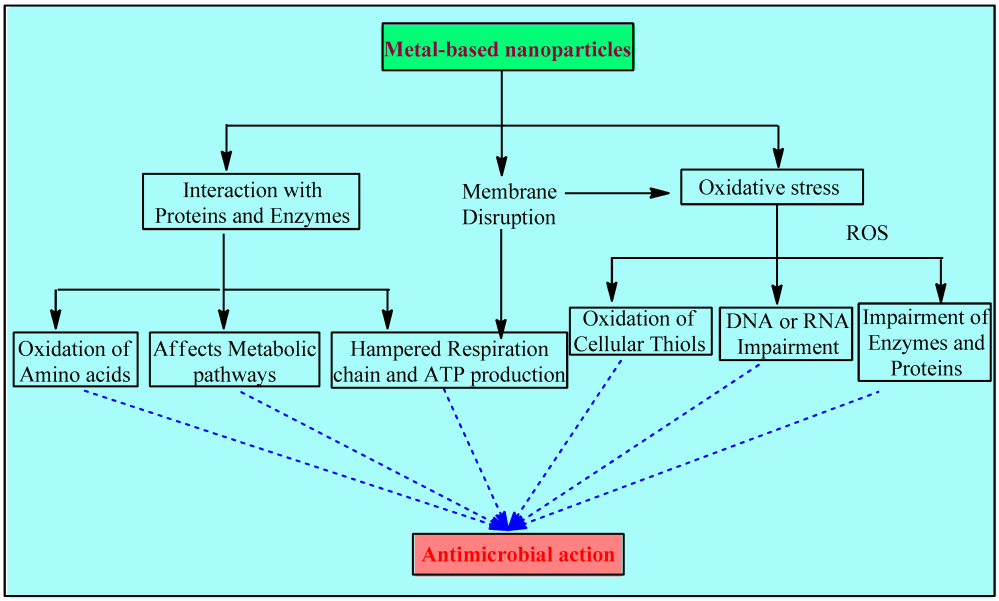

Figure 1. Mechanisms involved in the antimicrobial activity of metals and metal-based NPs.

2.2.1. Disruption of the Membrane

Associating metal nanoparticles with conducting polymers that have positive charges on their surfaces is essential for stabilizing solutions with high nanoparticle concentrations. According to the bacterial eradication mechanism, cell death is caused by electrostatic contact between the negatively charged bacteria (electronegative groups of the polysaccharides in the membrane) and the positively charged compound, such as metal and metal oxide nanoparticles with a variety of forms, roughness, and positive zeta potentials. Positively charged NPs interact with electro-negatively charged bacterial membranes, directly causing bactericidal toxicity in the membrane and targeting cell integrity The surface charge is an important factor for the antibacterial activity of the metal-based NPs. Positively charged NPs are more effective than neutral or negatively charged ones. As reported in [42], NPs with a positive charge display higher toxicity due to their electrostatic interaction with the negative charge of the bacterial cell wall. A comparative study showed that magnetic NPs with a positive charge (NP+) efficiently attracted over 90% of E. coli, while negatively charged magnetic NPs (NP−) did not show any affinities. These results suggest that NPs+ have good potential to capture bacteria via electrostatic attraction. In another study, the antibacterial efficiency of three different AgNPs that were positively, negatively, and neutrally charged were

compared, and it was found that positively charged NPs showed the highest bactericidal activity, while the negative ones showed the lowest [55][56][57].

Electron microscopic studies over *S. aureus* and *E. coli* also indicate the compromised cytoplasmic membrane's integrity due to toxic doses of certain metals such as aluminum and silver. A few agents, especially silver, impede the electron transport chain [ETC] [58][59]. Cell wall synthesis is also interrupted due to the interaction between the sulfur-containing constituents of the membrane and the silver nanomaterials. Apart from this, toxic doses of copper and cadmium have also been thought to cause lipid peroxidation [57][60][61].

All such disruptions lead to oxidative stress and, subsequently, to further damage, such as interrupted energy homeostasis, impeded respiration, and, ultimately, cell death [62].

2.2.2. Oxidative Stress

The metal-based NP system provides the benefit of controlling the particle specifications, including its shape, size, and even the charge on the surface, and it also provides the option to manage the release of metal ions [63]. The mode of their action is generally linked with the disruption of the membrane initially and the generation of ROS in large amounts gradually. The driving force of their action is associated with the controlled release of metal ions, while some research suggests that this release is through the leaching of metal complexes with amino acids of bacteria [64]. Metal ions in solution, ROS, and ROS-mediated machinery may all play a role in the toxicity of metal oxide nanoparticles. The potential of CuO NPs for toxicity may be related to problems with DNA synthesis and repair as well as an increase in the production of reactive oxygen species [65][66]. Higher antimicrobial activity of smaller metallic NPs is reported compared to larger NPs, and this is due to their larger surface area to volume ratio, which increases the production of ROS [67].

The introduction of metal-based NPs initiates intracellular ROS production, which has been confirmed by the electron paramagnetic resonance technique [38]. Such oxidation reactions are catalyzed by numerous metal ions, such as copper, iron, chromium, arsenic, etc., which upregulate genes and also cause other damage [68]. Iron brings in auto-oxidation through aerobic respiration, which leads to the production of oxygen radicals and hydrogen peroxide [69].

Moreover, the consumption of cellular anti-oxidants may also begin during this redox cycling phase of metals. Oxidative imbalance causes oxidation of cellular thiols as well, which, in turn, develops covalent bonds with sulfur. Ultimately, this results in the formation of protein disulfides and the reduction of anti-oxidant sources [67][70][71][72]. Oxidative stress led by ROS impairs the DNA or RNA, attacks enzymes and proteins, and thereby damages macromolecules [73].

2.2.3. Interaction with Proteins and Enzymes

Metallic NPs initiate an antimicrobial response by binding to cytosolic proteins. The interaction of these NPs with enzymes and DNA hampers the whole homeostasis. Since metabolic pathways are affected, the respiratory chain,

ATP production, and replication processes are impaired and ultimately inhibited [74][75].

2.3. Bio-Medical Antimicrobial Applications of Metal-Based NPs

Multi-drug resistant organisms are often resistant to commonly used antibiotics. The lack of and the great need for effective antimicrobial agents have led to the development of novel strategies to address this growing public health issue. A growing number of drug-resistant mutants and the inability to cure infective conditions completely has fueled the production of NPs, and this has now found several applications:

Dental products—Microbes tend to settle on teeth, leading to the development of plaque, thereby increasing the chance of mouth infections. NPs not only potently restrict the growth of bacteria but nano-crystallization also improves their performance and inhibits the formation of biofilms as well [76].

Coating of implantable devices—Coating of implantable devices like heart valves prevents adhesion and further growth of bacteria like *E. coli*, reducing the risk of inflammation and infections [77][78]. Devices that are commonly prone to the colonization of bacteria, such as dental implants, catheters, etc., are generally subjected to NP coatings [53][59].

Wound dressings—Several microbes like *Streptococcus*, *E. coli*, and *Staphylococcus*, among others, can cause wound infections, inflammation, and other complications that can be precipitated. To significantly prevent this, broad-spectrum antimicrobial NPs are an option [79][80].

Other than these, NPs can often be used along with bone cement and also in certain drug delivery systems [81]. It has been stated that researchers are on the verge of the ‘post-antibiotic era’ by the Centre for Disease Control and Prevention (CDC). The prediction of more deaths due to antimicrobial resistance than cancers by 2050 has also been made by many, and all of these predictions and statistics have led to the desire for newer molecule options and drug delivery methods as well as post-numerous research and studies, and the use of metal-based nanoparticles seems to be an effective lead here [82]. Indeed, the latter have been spotted to target resistance and biofilms via different mechanisms and pathways, depending on the metal and its potential.

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