REVIEW ARTICLE

Green Synthesis of Nanoparticles for Combatting Antibiotic-Resistant Bacterial Infections: A Comprehensive Review

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ABSTRACT

Innovative strategies are required to address this worldwide dilemma since the rise of antibiotic-resistant bacterial illnesses presents a serious danger to public health. The environmentally benign and sustainable process of green synthesis of nanoparticles has drawn interest as a means of creating antibacterial nanomaterials. This thorough analysis looks at the most recent developments in creating nanoparticles that fight bacterial illnesses resistant to antibiotics by using green production processes. In order to create nanoparticles with increased antimicrobial activity, the study highlights the efficacy of many green synthesis techniques, including the use of plant extracts, microbial sources, and other natural materials. The study also looks at these green-synthesized nanoparticles' methods of action against bacteria that are resistant to antibiotics and their therapeutic uses. Through the synthesis of nanoparticles utilizing environmentally friendly methods, this study seeks to combat antibiotic resistance by offering a comprehensive overview of the existing research landscape and encouraging the development of innovative solutions.

Keywords: Antibiotic-resistant bacterial diseases, Metallic nanoparticles, Green production, Resistance, Bactericidal medications**.**

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INTRODUCTION

The emergence of bacterial resistance to traditional medicines has made antibiotic-resistant bacterial illnesses a serious problem. As a result, developing novel and effective bactericidal medicines is critical for therapeutic success. Metallic nanoparticles (NPs) were shown to be interesting alternatives to antibiotics. The challenging issue of treating resistant illnesses has arisen as a result of bacteria developing antibiotic resistance. The development of drug-resistant bacteria, a global issue, is increasing the possibility of mortality and morbidity among those with the infection and adversely impacting the medical condition of an extensive spectrum of patients, including those being given cancer treatment, recently having surgery, receiving an organ transplant, or being admitted to the intensive care unit.[1] In a 2017 report released by the WHO Global Antimicrobial Surveillance System, antibiotic resistance was recognized as an international concern. Antibiotic-resistant diseases are expected to be expensive to treat, costing an estimated US$50,000 per person-year and US$20 billion to society.[2] Apart from these naturally existing particles, the idea of producing new particles has been recognized for decades, and the number and diversity of ways to do so are growing every year. Extracellular polymeric substances (EPS) produced by bacterial cells have the potential to function as a barrier against both host immune responses and some conventional antimicrobial therapies. In addition, biofilms show multiple changed phenotypes contributing to resistance to many routinely used antibiotics. Slow growth rates, persister cell presence, and chemical and geographical heterogeneities are some of these changed phenotypes.[3,4]

In the past ten years, there has been a lot of focus on coming up with new techniques and strategies for producing nanomaterials like metal nanoparticles, carbon nanotubes (CNTs), graphene, quantum dots (QDs), and their mixtures. These developments have significantly enhanced the field of nanoscience and technology.[5] Green nanotechnology is a young branch of science and technology that aims to provide sustainable and ecologically friendly methods of producing nanoparticles (NPs). This technique employs natural materials, such as plants, as reducing and encapsulating agents to create NPs. The utilization of plants as "eco-friendly nano-factories" is gaining attention in pharmacy and medicine owing to their biocompatibility and stability. Green production of metallic NPs, especially silver NPs, is a viable alternative to

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chemically manufactured NPs. Biogenic NPs, generated in living creatures, including plants, are enclosed by capping layers that offer an active surface for interaction with biological components. These capping layers may be changed to enhance the effectiveness and distribution of NPs. Biogenic NPs have a greater antibacterial impact than chemically generated NPs, notably against multidrug-resistant pathogens. Utilizing plant-based nanoparticles in agriculture represents a promising advancement towards the nano-revolution in the agricultural industry. The use of green nanotechnology for synthesizing metallic nanoparticles is more advantageous than chemical synthesis. This is due to the simplicity, cost-effectiveness, and environmentally friendly nature of the synthesized NPs. These factors indicate the superiority of plant-based NPs over chemically manufactured NPs.[6-9]

Importance of Combating Antibiotic-Resistant Bacterial Infections

The increasing rise of antibiotic-resistant bacterial illnesses poses a substantial danger to world health and well-being. Antibiotic abuse and misuse have led to the emergence of resistance, which makes treating common infections more challenging.[10,11]

Here are some reasons why it's critical to fight bacterial illnesses that are resistant to antibiotics:

Healthcare burden

Extended hospital stays, more complex diseases, and the need for stronger, more costly medications are all consequences of antibiotic-resistant infections.[12]

Limited therapy options

Due to the potential need for second and third-line therapies, treating resistant infections can be challenging or even impossible. In some circumstances, there may be no treatment choices available, which can lead to organ failure and protracted care and recovery.[13]

Impact on medical progress

The use of antibiotics to combat infections is essential to many medical advances, including cancer treatment, organ transplants, and joint replacements. Antibiotic resistance would have a substantial influence on these treatments and might result in a lowering of healthcare standards.

Financial implications

The widespread increase of antibiotic resistance is a severe problem that is eroding the efficacy of traditional medicines against common bacterial infections.[14] This can lead to increased healthcare expenditures, lost productivity, and a severe economic burden on countries and their citizens.

Fighting bacterial diseases resistant to antibiotics is crucial, and it cannot be emphasized enough. The fast evolution of resistance presents enormous implications to global health, healthcare systems, and economic stability. Urgent effort is necessary to solve this dilemma and create effective solutions to combat antibiotic-resistant bacterial infections.

Causes of resistance

There are many different factors that contribute to antibiotic resistance, such as naturally occurring (biological) reasons, selection pressure, mutation, gene transfer, social pressures, improper usage, insufficient diagnosis, and excessive and improper use of antibiotics. Bacteria and fungi may evolve resistance *via* mutation, gene transfer, and selection pressure. The abuse of antimicrobials, even when administered responsibly, produces a selection pressure for resistant microbes.

Mutation

One of the main processes by which bacteria become resistant to antibiotics is mutation. Mutations may happen on their own as a result of mistakes made during synthesizing DNA. In some situations, such as resistance to fusidic acid, rifampicin, oxazolidinones, and fluoroquinolones, mutational resistance predominates. Certain antibiotics may cause bacteria to mutate more often. Antibiotic-resistant bacteria may develop resistance *via* mutations, and these germs can withstand antibiotic treatment and proliferate due to natural selection.[15-17] Figure 1 shows the mutation leading to antibiotic resistance. E.g., when one antitubercular medication is used, also termed vertical transmission of resistance.

Gene Transfer

One important route *via* which antibiotic resistance genes propagate among bacteria is horizontal gene transfer or HGT. Resistance spreads quickly as a result of the ability of bacteria to exchange genetic resources, including genes that confer resistance to antibiotics.[18] Transformation, transduction, and conjugation are a few examples of the mechanisms that may lead to HGT.[19] Little circular DNA fragments called plasmids are essential to this gene transfer process because they make it easier for bacteria to share resistance genes.

Through this process, bacteria might pick up new characteristics from other bacteria in their surroundings, such as antibiotic resistance. Three main HGT techniques exist:

Conjugation

In bacterial genetics, conjugation is the process by which genetic material is passed from one bacterium to another. During direct contact between the two bacteria, a structure known as a pilus is used by the donor cell to transfer DNA to the recipient cell in this kind of horizontal gene transfer. The receiving cell may become an F donor during conjugation, donating DNA to additional cells and producing its own pilus. This is possible if the F factor (fertility factor) is transmitted. Since conjugation is the primary method by which most resistance genes on mobile genetic components propagate across bacteria, it plays a crucial role in the transmission of antibiotic-resistance genes. One possible tactic to stop the spread of antibiotic resistance is to inhibit conjugation.[20]

Transduction

During specialized pathways, bacteriophages can only take up certain regions of the host's DNA; whereas during generalized

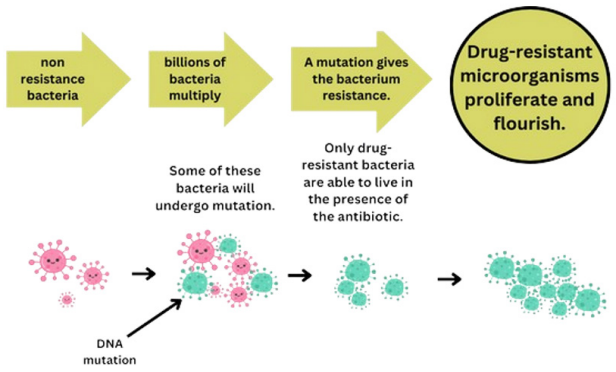

Figure 1: Mutation leading to antibiotic resistance

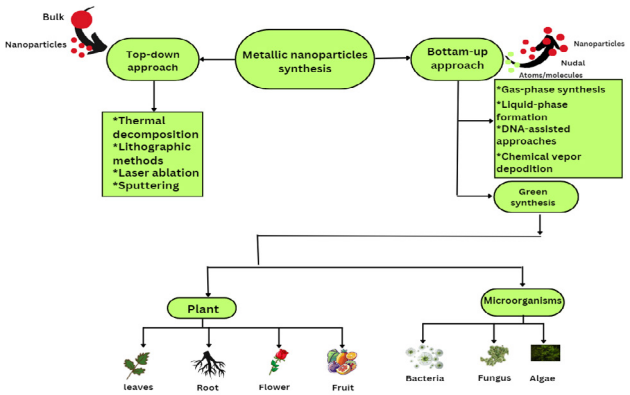

Figure 2: Various synthetic techniques available for creating metal nanoparticles.

transduction, they may take up any portion of the host's genome. This procedure is DNase resistant and does not need direct physical contact between the donor and recipient cells. Molecular scientists often use transduction as a technique to permanently insert an alien gene into a host cell.[21]

Transformation

Bacterial transformation is used in DNA cloning, a process that involves introducing a plasmid containing a desired gene into bacteria by transformation. The presence of certain markers, such as antibiotic resistance genes carried by the plasmid, may subsequently be used to select for the altered bacteria. The transformed bacteria may be selected because only the bacteria that have incorporated the plasmid will proliferate when exposed to the matching antibiotic. The synthesis of vital proteins for medicine, the examination of gene function, as well as the creation of genetically modified creatures are just a few of the practical uses for this procedure.[22]

Methods of Various Synthetic Techniques Available for Creating Metal Nanoparticles

Numerous investigations have used physical and chemical synthesis approaches to make nanoparticles since NPs have been the focus of intense investigation due to their extraordinary capabilities that are regulated by their structural morphology.[23] Metallic nanoparticles are microscopic particles of metal that possess a broad range of uses in numerous industries, which include biotechnology, engineering, and materials science. They are often constructed of a shell covering a metal core made up of organic or inorganic materials, and their qualities are altered by modifying their shape, composition, size, structure, assembly, and optical properties.[24] Metallic nanoparticles, which typically have sizes between 10 and 500 nm, are particularly interesting in the field of biotechnology because of their potential uses in noninvasive imaging drug delivery systems and their capacity to interact with biomolecules on cell surfaces.[25] The literature has examined two main principles of synthesis, namely bottom-up and top-down techniques, to produce nanomaterials with certain sizes, shapes, and functions (Figure 2).

Top-down method

The two main synthetic approaches for creating Bottom-up and top-down methods are used to create metal nanoparticles. The bottom-up technique integrates individual atoms and molecules into larger structures, while the top-down method separates large-scale components into tiny particles of nano-dimensions utilizing different physical and chemical techniques.[26]

The top-down technique is utilized for the reduction in size of current technological gadgets, whereas the bottom-up approach is used for developing even more complicated molecular devices on an atomic layout. Both top-down and bottom-up techniques can perform the synthesis of metallic nanoparticles.[27] The former works with the reduction in size of current technological gadgets, whereas the latter performs an opposite role, which is creation of even more sophisticated molecular devices on an atomic arrangement.[28]

Bottom-up

In bottom-up approaches, individual atoms and molecules are integrated into larger structures to form metal nanoparticles. Some typical bottom-up synthesis methods some common Bottom-up methods are gas-phase synthesis, liquid phase formation, DNA-assisted approach, and green synthesis. Various synthetic techniques available for creating metal nanoparticles is illustrated in Figure 2.

To manufacture NPs, two classic approaches are frequently utilized. Both approaches possess different synthesis principles but provide NPs that possess the requisite characteristics. Nanoparticles are created utilizing a variety of techniques that can be classed as a bottom-up or top-down method.[29]

These bottom-up approaches offer advantages like as excellent control over particle dimensions, composition and ability to create intricate nanostructures. However, they can be more time-consuming and demand more exact control over the synthesis conditions compared to top-down techniques.

Chemical method

Using a variety of chemical reducing agents with a stabilizing agent present, metal ions are reduced from their ionic salts to create metal nanoparticles. Common chemical techniques include the Turkevich method (citrate reduction), which reduces metal ions in a citrate solution, and the creation of metal nanoparticles using reducing chemicals such as sodium citrate.[26] These technologies are often employed to obtain particles with the necessary qualities and are possibly

damaging to the environment. However, they are typically costly and potentially damaging to the natural world and living things.[30]

Green-synthesis

Biological components are used in green synthesis as a one-pot or one-step bio-reduction technique that is environmentally benign. This runs counter to the use of very toxic and radioactive reductants in traditional physical as well as chemical synthesis processes.[5] Research on the utilization of plant extracts and microbes in the synthesis of metal nanoparticles is now underway. However, additional investigation is required to gain a comprehensive understanding of the biological synthesis process and its possible practical uses.[31]

Implementing environmentally friendly nanotechnology is the most effective technique to mitigate the negative consequences associated with the production of nanomaterials, as it minimizes the likelihood of encountering challenges present in alternative methods.[32] Compared to wet chemical nanoparticles, green nanoparticles showed much less cytotoxicity and phytotoxicity, indicating that they may be safer to utilize in melanoma therapy studies.

Biosynthesis, sometimes referred to as "greener synthesis," offers a useful, economical, low-risk, and environmentally benign method of creating NPs. The bottom-up method of NP synthesis is called biological synthesis. It takes living creatures like viruses, bacteria, fungi, algae, and plants to make nanoparticles using biological processes. Making ensuring that the bacteria, viruses, or fungus that were employed to make the nanoparticles don't pose any hazards is crucial. In particular, when people come into contact with them, they shouldn't be a threat to them.[33,34]

Plant-based nanoparticles

External factors have a significant influence on plant secondary metabolism, resulting in the production of natural products in various parts of the plant, like leaves, stems, shoots, flowers, bark, seeds, and roots. External cues can greatly speed up this process. Green synthesis involves using plant extracts or plant components to produce nanoparticles in an environmentally friendly way. The end product is identified as a plant-based nanoparticle.[35] This approach entails utilizing phytoconstituents obtained from plants to manipulate the properties of nanoparticles, including their form, biological activity, dimensions, crystallinity, surface charge, and surface coating.[36] The characteristics of nanoparticles may be examined using a variety of methods, including as dynamic light scattering, microscopy with scanning electrons, X-ray diffraction (XRD), transmission electron microscopy (TEM), and the Fourier transform of infrared spectroscopy (FTIR).[37] Plant-based nanoparticles are increasingly recognized as a kind of nanomedicine and are thought to be superior to manufactured nanoparticles.[38] Numerous industries, including biomedical science, sensors, imaging, the field of biotechnology technology, food packaging, treatment of water, medicine, beauty products, fabric engineering, and dye degradation, may benefit from the use of these materials.[39] Combinations of biomolecules, including alkaloids, phenolics, polysaccharides, proteins, vitamins, amino acids, and/or terpenes, may be used to reduce and stabilize Ag ions and generate AgNPs in an easy and economical way.[40] AgNPs, or silver nanoparticles, have been extensively studied as plant-derived nanoparticles, mainly due to their strong antibacterial and antifungal characteristics. The different biogenic metallic nanoparticles having antimicrobial properties showed in Table 1.

Notably, nanoparticles (NPs) generated by plants have a greater diversity in their morphology and dimensions in comparison to those produced by other animals.[47] The AgNPs, which were synthesized by a green synthesis process, demonstrated antibacterial and antifungal activities that were directly proportional to their concentration. Conversely, AgNPs sourced from fungi exhibited enhanced antifungal characteristics against superficial mycoses, particularly *Malassezia furfur* (= *Pityrosporum ovale*) and *Candida albicans*.[48] The plant *Dioscorea bulbifera*, which is a member of the Dioscoreaceae family, was used to extract an extract that was used to lower silver ions in water (Ag+). The resultant AgNPs showed strong antibacterial qualities against both gram-positive and gram-negative germs. This kind of plant exhibits substantial therapeutic qualities as a consequence of its particular phytochemistry.[49]

Due to their uncomplicated production, easy surface functionalization, and special qualities – such as their low toxicity and extremely biocompatible nature – AuNPs, or gold nanoparticles, have garnered a lot of interest.[50] During the production of gold nanoparticles, a number of chemical elements inside biogenic complexes serve as reducing agents, which causes gold metal ions' decrease as well as the subsequent creation of nanoparticles.[51] Figure 3 shows the suggested synthetic technique for producing gold nanoparticles by plants. Furthermore, these nanoparticles could be hazardous in the context of biological applications.[52]

In order to create AuNPs, which may be used as biomedicines to fight bacteria that are resistant to medications, a number of researchers are experimenting with employing plant extracts. *Memecylon umbellatum* nanoparticles were suggested for use as chemical sensors by Arunachalam *et al*. (2013).[53]

Due to their ability to quickly adhere to charge-negative bacterial surface cells and induce rupture of the cell wall & ensuing cell demise, positively charged FeNPs show extraordinary antimicrobial activity against microorganisms classified as bacteria that are gram-positive and bacteria that are gram-negative. Using the extract from leaves of *Eichhornia crassipes* (Pontederiaceae), rod-shaped FeNPs were bioproduced, and at aqueous FeNPs at 100 mg/mL, they showed excellent inhibiting action against *P. fluorescens* and *S. aureus*. FeNPs were also shown to inhibit *S. aureus, P. aeruginosa* and.[54] K, B. *subtilis, E. coli,* and e*pidermidis*. The lowest inhibitory dosage for the first two bacteria was 7.8 mg/l, making them the most sensitive .[55] FeNP *Couroupita*

Table 1: different biogenic metallic nanoparticles having antimicrobial properties

Microorganism	*NPs*	*Part*	*Antibiotic*	*References*
Listeria B. cereus, S. aureus, E. coli, S. typhimurium, and *monocytogenes*	AgNPs	Fight harmful germs and viruses, and break through *E. coli*'s outer membrane.	Kanamycin, rifampicin	[41]
Gram-negative bacteria: *Salmonella typhi, Klebsiella pneumoniae*, and *Escherichia coli Bacillus subtilis* and *Staphylococcus epidermidis* are examples of gram (+) bacteria; *Aspergillus fumigatus, A. clavatus, A. niger*, and *Candida albicans* are examples of fungi.	Synthesis mediated by plants	round nanoparticles with antimicrobial properties	n.c.	[42]
Strain BL-21 of *E. coli*	AgNPs	Tuber	n.c.	[43]
E. coli	CuONPs	Leaf extract	n.c.	[44]
Shigella sonnei, Citrobacter amalonaticus, Salmonella typhi, and E. coli	AgNPs	Leaves extract	Ciprofloxacin	[45]
S. aureus, *Streptococcus pyogenes*	AuNPs	Aqueous leaves extracts	n.c.	[46]

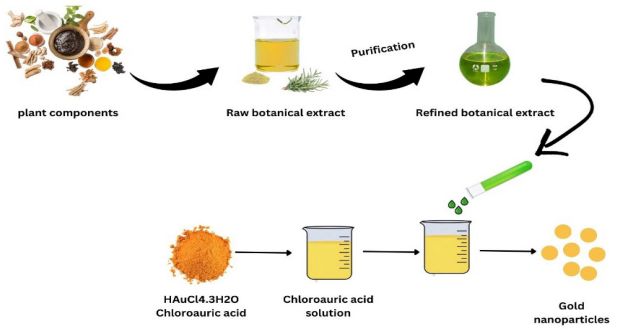

Figure 3: Synthetic technique for the manufacture of nanoparticles of gold by plants.

guianensis fruit extract was shown to have more antimicrobial activity in relation to gram-positive and gram-negative bacteria, including *S. typhi* MTCC 3917, *E. coli* MTCC 2939 and *K. pneumoniae* MTCC 530.[56] With a little suppression of *S. dysenteriae*, this novel antibacterial drug was shown to be very suitable for K, *S. aureus, S. typhi*, and *S. enterica, S. pneumoniae*. Additionally, it was confirmed that *E. coli* and *S. aureus* strains were successfully suppressed by hematite (α-Fe2O3) nanoparticles that were made using leaf extract from *Anacardium occidentale* (Anacardiaceae). The procedure of bioreduction initiated *via* the *Cynometra ramiflora* leaf extract (Fabaceae) resulted in spherical and crystalline FeNPs with significant bactericidal potential against *S. epidermidis*.[57]

Lately, there has been a great deal of curiosity around in zinc oxide nanoparticles, or ZnONPs, because of their many potential uses in biological medicine, beauty products, electronics, and optics. Too far, a large synthesis has been the subject of several published studies. and use of nanoparticles of zinc oxide (ZnONPs) by plants, microbes, and other species. Numerous studies have garnered interest because to their affordability, safety, and ease of synthesis. Plant materials such as leaves, flowers, roots, and seeds may all be used to make ZnONPs. These nanoparticles are notable because of their enormous a Their broad range of semiconducting properties may be attributed to their high exciton binding energy of 60 meV and band gap of 3.37 eV.[58-60]

Antimicrobial Activity of Various Metallic NPs

After extensive research, metal-based It has been shown that nanoparticles exhibit broad-spectrum antimicrobial action due to their non-specific bacterial toxicity mechanisms, which prevent the particles from binding to a specific bacterial cell receptor.[61] The antibacterial action of these nanoparticles is contingent upon and proportional to the release of ions; other processes, such as the production of oxygen species that are reactive, cation release, damage to biomolecules, ATP depletion, and membrane contact, have also been proposed.[62] The usage of metallic nanoparticles, like copper, zinc oxide, gold, silver, and copper oxide, has demonstrated promising antibacterial activity against diverse diseases.

Antimicrobial action of AgNPs

Silver nanoparticles' (AgNPs') capacity to combat microorganisms has been extensively studied. AgNPs indicate efficacy against a range of pathogenic and infectious microorganisms, including bacteria that are resistant to several drugs.[63] Despite being widely used in the medical field, antibiotics might cause germs to become resistant to them over time. This might be the result of the self-defense mechanism of the bacterium, which could lead to gene mutation. This makes it possible to create enzymes that render antibiotics inactive.[64] Thus, antibiotic resistance in microbes has grown to be a significant issue. Among the other NPs, silver has the strongest antibacterial properties. Ag NPs serve as nanocarriers as well for medications and treatments that boost the efficacy of antibiotics against bacteria that have become resistant to them.[65-67] Therefore, using green materials as reducing agents – such as plant, microbial, and algae extracts – offers several benefits (Figure 4). Typically, metallic salt solutions are mixed with biological extracts.[68]

Some of the most dangerous, drug-resistant bacterial strains are included in Table 2, along with the relevant antibiotics to which they have become resistant.

Table: 2 Bacterial strain and corresponding antibiotics with resistance

Bacterial strain	*Corresponding antibiotics with resistance*
Staphylococcus aureus resistant to methicillin (MRSA)	Methicillin, penicillin, amoxicillin
Enterococcus vancomycin-resistant (VRE)	Vancomycin, teicoplanin, daptomycin
Mycobacterium tuberculosis with multiple drug resistance (MDR-TB)	Isoniazid, rifampin, ethambutol, pyrazinamide
Enterobacterales that produce carbapenemase (CPE)	Carbapenems, fluoroquinolones, aminoglycosides
Group A *Streptococcus* resistant to erythromycin (GAS)	Erythromycin
Resistant to clindamycin Group B *Streptococcus* (GBS)	Clindamycin
Acinetobacter resistant to carbapenems	Carbapenems, fluoroquinolones, aminoglycosides
Staphylococcus aureus resistant to vancomycin (VRSA)	Vancomycin, teicoplanin, daptomycin
Resistance to fluoroquinolones in campylobacter	Fluoroquinolones

The Antibacterial effect of Agnps can be linked to numerous mechanisms

- *Production of oxygen species that react (ROS)*

Reactive oxygen compounds (ROS) that have a tendency to injure and interfere with bacteria's metabolic processes are produced, roughly speaking, by AgNPs.[69]

- *Ag+ ions are released*

AgNPs may produce Ag+ ions, which may combine with the sulfhydryl groups of various proteins and enzymes to disrupt the respiratory chain and destroy the bacterial cell wall.[69]

- *Binding with the cell walls of bacteria*

When AgNPs adhere to bacterial cell walls, the permeability of the membrane is disrupted, allowing cell contents to seep out.[69]

- *Relationship between thiol groups*

AgNPs can interfere with the respiratory chain and damage the cell of bacteria wall by interacting containing various enzymes' thiol groups and proteins.[69] It has been demonstrated that AgNPs are efficient against fungi, viruses, and both gram-positive and gram-negative bacteria.[70] Because of these nanoparticles' promising effectiveness against a range of germs, including both gram-positive and gram-negative bacteria, they may eventually replace conventional antibiotics. Ag NPs' size and shape affect their antibacterial action. Ag NPs' surface area rises with decreasing size, according to Pal *et al*. (2007), which enhances their molecular binding affinity. Furthermore, the antibacterial effect of Ag NP with a triangular form was shown to be substantially greater than that of Ag NP with a spherical or rod-shaped shape.[71]

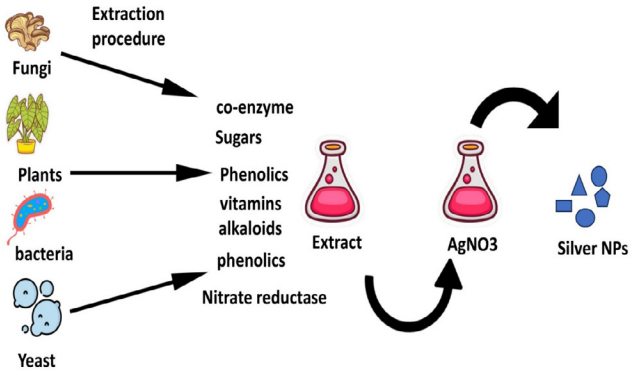

Figure 4: Schematic illustration of the technique for green manufacturing of silver nanoparticles employing diverse biological entities.

It has been shown that Ag nanoparticles are potent against gram-negative bacteria than gram-positive bacteria. This is due to the positively charged silver's binding to the surrounding negatively polarized lipopolysaccharides. On the other hand, Bacteria that are gram-positive include coated with a thick coating cross-linked by embedding proteins, comprising linear polysaccharides and peptidoglycans. This layer gives the cell rigidity and inhibits NPs from sticking to its surface. Ag NP may enter cells *via* the holes in the cell wall that are created upon binding with gram-negative bacteria, silver ions.[72]

Function of Fe NPs as an antimicrobial

Iron nanoparticles' antimicrobial properties (Fe NPs) have been investigated with varying degrees of success. Fe NPs have been discovered to exhibit antibacterial qualities in some investigations, but to have little to no influence on the growth of bacteria in other studies. According to one study, Fe2O3 NPs were less effective than ZnO and CuO NPs at inhibiting the development of *Escherichia coli*.[4] According to a different study, Fe NPs showed a stronger bacteriostatic impact than Fe3O4 NPs against *Pseudomonas aeruginosa*. On the other hand, unlike NPs denoted as Fe, Ag, or $FeSO_4$. There was no bactericidal effect reported by Lee *et al*. Fe_3O_4 NPs against *E. coli.*

Numerous investigations on iron nanoparticles' antibacterial properties have been carried out (Fe NPs). The results of numerous investigations have shed light on Fe NPs' possible antibacterial qualities. Both free iron ions and nanoparticles based on iron oxides (IONPs) have demonstrated the antibacterial qualities of Fe NPs.[73] According to reports, Fe^{3+} at specific doses suppressed the growth of *E. coli,* whereas Fe_3O_4 NPs showed a more prominent bacteriostatic effect on *P. aeruginosa*.[74]

FeNPs' green manufacturing method, which is economical, environmentally benign, and yields stable nanoparticles made from metals that don't need hazardous chemicals, has been linked to their antibacterial efficacy.[75] Moreover, iron oxide nanoparticles' ability to modify the nanoparticle-bacteria interface, where they have demonstrated antimicrobial action at comparatively high concentrations, has been related to their antimicrobial activity. The results of these investigations

indicate that Fe NPs have the potential to have antibacterial activities, especially when they come from biogenic sources. To completely comprehend the processes and possible uses of Fe NPs in antibacterial activities, more study is necessary.[76]

Zinc oxide nanoparticles' bactericidal characteristics

Significant antibacterial activity of zinc oxide nanoparticles (ZnO NPs) against a variety of bacterial infections has been shown. Numerous theories have been put forth to account for their bactericidal effects. ROS generation, cellular integrity loss upon ZnO material contact, internalization of ZnO NPs, and Zn^{2+} ion release are a few of these. ZnO NPs' antibacterial activities are thought to be primarily mediated via the generation of ROS and the release of Zn^{2+} ions. While the release of Zn^{2+} ions can contact with the cell membrane of the bacterium and impair biological activities, the production of ROS has the potential to cause harm to bacterial cells. Furthermore, ZnO NPs' smaller size has been associated with higher antibacterial action; these nanoparticles have the ability to penetrate bacterial cells and harm lipids, proteins, and DNA.[77]

Additional knowledge on ZnO NPs' antimicrobial activity has been obtained through scientific investigations. Mendes *et al*.'s paper from Scientific Reports in 2022, for instance, described ZnO NPs and demonstrated their antibacterial efficacy against *S. aureus* and *E. coli*. The bactericidal activity of ZnO NPs was shown to be mediated *via* the generation of ROS and the release of Zn^{2+} ions, according to the study. Mendes *et al*. (2022) looked into the impact of ZnO NPs' size and shape on their antibacterial activity and cytotoxicity profile in a different study published in Scientific Reports. The results of the study demonstrated ZnO NPs and nanorods had the most antibacterial activity against *S. aureus* and *E. coli* when compared to other antibacterial materials, demonstrating the significance of size and shape microparticles.[78] It is well known that pathogenic bacteria's cell surface proteins facilitate colony growth and adhesion. Tiechoic acid and polysaccharides are additional components of the cell wall that protect it from the host defense mechanism and outside influences. The modified surfaces of NPs may be used to induce specific interactions that jeopardize the integrity of the cell wall since they are all charged macromolecules. ZnO NPs directly interact with bacterial cell walls to undermine their integrity. ZnO shows strong bactericidal action against both gram-positive and gram-negative bacteria.[79] The study came to the conclusion that the following factors were mostly manifested in cell killing: (a) Photochemical reactions, (b) nanomaterial morphology, and (c) cell kinds and resistance mechanisms. The morphology of zinc oxide nanorods (ZnO NRs) is shown in Figure 5 in a magnified format, providing a basic example of materials relevant to toxicity. Due to their low toxicity and biocompatibility, ZnO nanoparticles (NMs) are regarded by several researchers as potential medication delivery vehicles. However, some ZnONM topologies can cause cell toxicity, and an overdose can cause necrosis in the cells. Different cells have varying qualities when it comes to losing their ability to survive; some

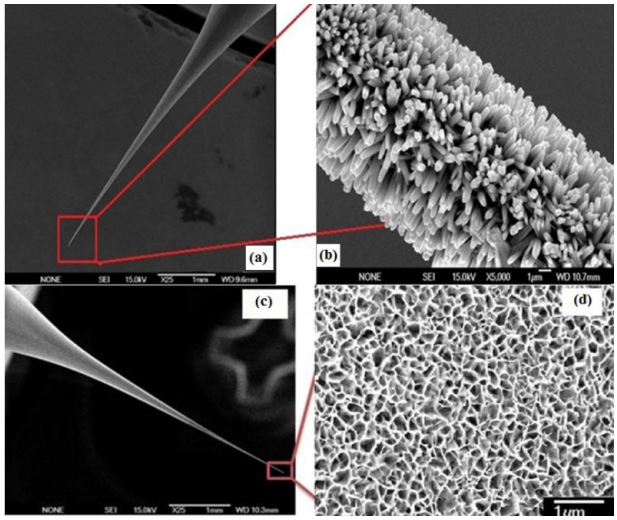

Figure 5: These four distinct morphologies of ZnO nanostructures are: zinc oxide nanoporous (ZnO Nps) (c), generated ZnO NRs in an amplified form of SEM representation (b), and amplified form of ZnO Nps (d).[80]

are less resistant and more readily necrosed, while others have extremely high resistance and can withstand higher dosages of radiation or drugs before dying.

With processes including the current generation of ROS and the Zn^{2+} ions' release playing a major part in their bactericidal action, ZnO NPs have shown considerable antimicrobial properties. Additionally, it has been demonstrated that the form and size of the nanoparticles affect their antibacterial qualities, with smaller nanoparticles having higher antibacterial activity. These results highlight ZnO NPs' potential as strong antibacterial agents with a range of uses.

Bactericidal characteristics of Au NPs

It has been discovered that gold nanoparticles, or Au NPs, exhibit antimicrobial properties against a range of bacterial diseases. The primary reason for Au NPs' antibacterial action is the large ratio of their volume to the surface, which makes it easier for them to enter cell walls and membranes. Au NPs may interact with bacterial surfaces and enter cells because of their tiny size, damaging lipids, proteins, and DNA, among other biological components. The size, shape, and concentration of the nanoparticles affect their antibacterial activities. It has also been discovered that biosynthesized Au NPs possess antibacterial qualities. The nanoparticles' antibacterial activity can be increased by functionalizing them with natural plant chemicals.[81-83] These pathogens' effective minimum inhibitory doses (MICs) ranged from 8 to 64 nM, and it was believed that the disintegration of the bacterial cell was what led to the membrane.[84]

Characterization Techniques

Antibiotic resistance in bacteria is characterized using a variety of methods.

Concentration at which MIC

The quantity of an antibacterial drug that completely prevents the test strain of an organism from growing under precisely

controlled *in-vitro* conditions is known as the MIC, and it is stated as μg/mL, or micrograms per milliliter.[85]

Once a pure culture has been isolated, the MIC is ascertained by cultivating the microorganisms in liquid or on solid growth media plates. The MIC value is a crucial tool for directing antibiotic treatment as it is used to assess a bacteria's sensitivity to antibiotics. When a medicine has a lower value of the MIC, it takes less of the drug to stop the organism from growing, making these drugs more potent antimicrobial agents. To classify microorganisms as drug-resistant, MIC values are compared to the suggested breakpoint concentrations. The MIC approach is often used in drug research and diagnostic labs. It is a vital tool for understanding the processes behind antibiotic resistance and creating successful countermeasures.[86]

Surface-enhanced raman spectroscopy

The technique surface-enhanced Raman Spectroscopy (SERS) enhances the scattering of Raman molecules and is sensitive to surface conditions. It is often used to identify and describe microorganisms that are antimicrobial resistant. SERS is a potent method for examining the chemical makeup of bacterial cells and detecting particular biomolecules, especially those linked to antibiotic resistance since it can detect single molecules.[87,88] In order to enhance the signals associated with Raman of the molecules adsorbed on them. The approach makes use of nanostructured metal surfaces or nanoparticles. This improvement may reach up to 10^{10} to 10^{11}, which makes it possible to identify molecules at very low concentrations. This is especially helpful when researching antibiotic resistance in bacteria.[89] Because of its great sensitivity and specificity, surface plasmon resonance (SPR) has the potential to completely transform antibiotic resistance detection and characterization. It may help with the establishment of focused treatment plans and the tracking of antibiotic resistance in clinical and environmental settings by quickly and accurately identifying bacterial strains and their resistance profiles.[88]

ResFinder and resfams

Two databases are used to predict antibiotic resistance genes (ARGs) in bacterial genomes: ResFinder and resfams. While Resfams is a database that finds antibiotic resistance genes conserved structural domains, ResFinder is a database that concentrates on acquired resistance genes. These databases may be used to determine if bacterial isolates include ARGs and to forecast the resistance profiles of such isolates. Widely employed in diagnostic and drug development labs, ResFinder and Resfams are crucial instruments for understanding the processes behind antibiotic resistance and creating successful countermeasures.[90]

CONCLUSION

In order to fight the growing threat of bacterium resistant to antibiotics infections, the green synthesis of nanoparticles for combatting antibiotic-resistant bacterial infections. Because of their capacity to affect several biological processes, metallic nanoparticles are highlighted in the paper as potentially effective substitutes for conventional antibiotics. It also emphasizes the overwhelming support for the safe and sustainable future, sustainable, and eco-friendly creation of metallic nanoparticles utilizing natural chemicals. The important ramifications of treating antibiotic-resistant bacterial infections are also covered in the conclusion, including the financial cost, restricted treatment alternatives, healthcare burden, and influence on medical advancement. It emphasizes the critical necessity for coordinated efforts to create workable solutions to deal with this serious global health issue. The conclusion aims to emphasize how serious the issue is and how aggressive and creative solutions are needed to fight bacterial illnesses that are resistant to antibiotics.

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