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# Microbial nanoparticles: biosynthesis and emerging roles in combating antimicrobial resistance

Alan Raj, Angel Treasa Alex, Venkatesh Kamath, Volety Mallikarjuna Subrahmanyam*
Department of Pharmaceutical Biotechnology, MCOPS, MAHE, Udupi, India.

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**ABSTRACT**

Antimicrobial resistance (AMR) occurs when microorganisms adapt and grow in the presence of drugs that affect them. AMR poses an alarming threat to public health systems throughout the world. Due to factors including overcrowding, increased antibiotic usage and abuse, increased worldwide migration, selection pressure, and inadequate sewage disposal systems, antibiotic resistance has grown globally over the past few decades. Antibiotic resistance may be less of an issue now that nanotechnology has emerged. Antibiotics and nanoparticles can work together to combat infections. According to the studies, metallic nanoparticles of copper, zinc oxide, silver, gold, and other metals can work in concert with medicines to increase their antibacterial effectiveness in vitro, even against bacteria that are resistant to them. This enables the reversal of bacterial resistance by the use of certain combinations.



## 1. INTRODUCTION

Resistance to antimicrobial therapy has increased over the decades, rapidly depleting the antibiotic arsenal. Medicaments that were once effective are becoming ineffective due to increased adaptation of the pathogenic microorganisms. In 2019, the global mortality rate from antibiotic treatment failure was around 7 million fatalities annually; by 2050, that number is predicted to rise to 10 million [1]. Growing incidences of methicillin-resistant and vancomycin-resistant Staphylococci are posing a threat to the world community. The advent of nanotechnology has given hope for treating such resistant forms of pathogens. Laboratory-based studies have shown that metallic nanoparticles have shown synergism with antibiotics, and it has been shown that these combinations reverse bacterial resistance.

## 2. SYNTHESIS OF MICROBIAL NANOPARTICLES

The usage of nanoparticles in the biomedical industry is growing. Particles less than 100 nm are shown to be effective because of their ease of penetration, even though particles between 10 and 1,000 nm are classified as nanoparticles [2]. There are two approaches to making nanoparticles: top-down and bottom-up. There are different methods for creating nanomaterials, viz., mechanical attrition, sol-gel processes, vacuum deposition and vaporisation, gas condensation, chemical vapour deposition, chemical precipitation, and electrodeposition [3].

Nanoparticles can be developed by physical, chemical, or biological means. Using live cells and biological mechanisms to synthesise nanoparticles is a more efficient method. In comparison to existing physical and chemical procedures, the technologies are more stable, nontoxic, economical, and environmentally benign [4].

The processes by which bacteria make nanoparticles include metallic reduction, enzymatic reduction, and capping. Before being transformed into nanoparticles, metal ions are trapped either within or outside of the microbial cells when enzymes are present. The enzyme serves as the nucleation site by providing the metal with electrons for reduction. Biological synthesis of nanoparticles using plant extracts is a widely recognized approach, but this method faces challenges. The natural variability in plant-derived compounds can lead to polydisperse nanoparticles, while seasonal differences in

*Corresponding Author
*Volety Mallikarjuna Subrahmanyam, Department of Pharmaceutical Biotechnology, MCOPS, MAHE, Udupi, India.*
*E-mail: vm.subra @ manipal.edu*

plant chemistry may cause inconsistent production yields [5]. Alternative biological platforms for nanoparticle synthesis include microorganisms such as bacteria, yeast, algae, and fungi, as illustrated in Figure 1. Key characteristics of these biosynthesized nanoparticles are summarized in Table 1, highlighting their distinct properties across different biological systems.

### 2.1. Nanoparticles from bacteria

Microorganisms demonstrate adaptive capabilities under environmental stress, enabling enzymatic production of reduced metal ions through metabolic processes [13]. Notably, silver nanoparticles (AgNPs) fabricated via *Bacillus brevis* bacterium exhibit significant antimicrobial efficacy against multidrug-resistant strains of *Salmonella typhi* and *Staphylococcus aureus* [14]. Different bacteria viz., *Pseudomonas antarctica, Pseudomonas meridiana*, *Pseudomonas proteolytica*, *Arthrobacter gangotriensis,* and *Aerothyris kerguelensis,* act as microbial cell factories with supernatants of their fermented broths, finding application as reducing agents in the synthesis of AgNPs [15,16]. *Pseudomonas stutzeri* accumulated AgNPs through an intracellular mechanism [17]. AgNPs have also been synthesized in the intracellular periplasmic space by a bacterial species [18].

### 2.2. Nanoparticle synthesis by actinomycetes

Current research on Actinomycetes-mediated synthesis of metal nanoparticles remains limited in scope [19]. For gold nanoparticle biosynthesis, studies have identified Actinomycetes species within genera such as *Thermomonospora, Nocardia, Streptomyces*, and *Rhodococcus*, with *Streptomyces* species being particularly notable in this domain [20,21]. The intracellular reduction of metal ions primarily occurs on mycelial surfaces through enzymatic processes [22]. This intracellular nanoparticle formation is hypothesized to result from electrostatic interactions between negatively charged carboxylate groups in mycelial cell wall enzymes and silver ions ($Ag^+$), effectively trapping the ions on the cell surface and enabling subsequent nanoparticle assembly.

### 2.3. Nanoparticle synthesis by fungi

In comparison to bacteria, fungi are more robust for the manufacture of nanoparticles. This could be due to improved production of many bioactive metabolites [23,24]. Several filamentous fungi capable of synthesising AuNP were reported. Also, compounds produced by fungi and media components can be used to stabilize the nanoparticles [25,26]. The observed AuNPs were biosynthesised using three distinct fungal strains: *Aureobasidium pullulans*, *Fusarium oxysporum*, and *Fusarium* sp. Several *F. oxysporum* strains have been used in another study to generate extracellular silver metal nanoparticles in the 20–50 nm range [27].

### 2.4. Nanoparticle synthesis by yeast

Yeast cells can synthesize semiconductor nanoparticles, especially those of cadmium sulfide. Production



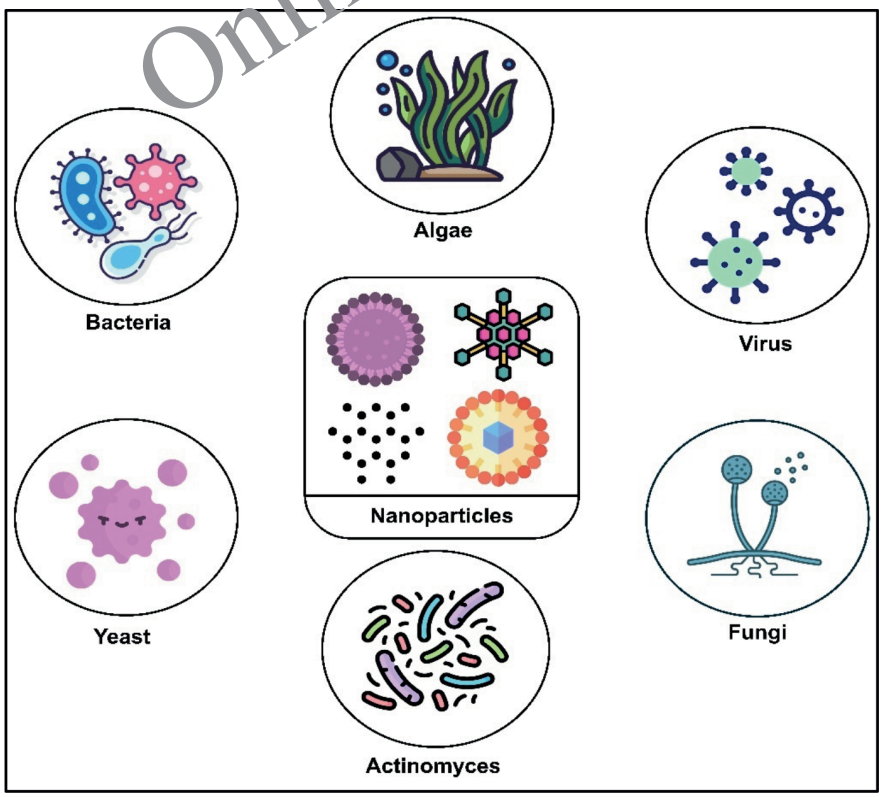


**Figure 1.** Nanoparticle synthesized from different biological sources.

**Table 1.** Properties of biosynthesized nanoparticles.

| Organism type | NP Type | Size range (nm) | Synthesis route | Antimicrobial spectrum | Application |
|---|---|---|---|---|---|
| Bacteria (*Bacillus thuringiensis* SSV1) | $Ag_2O$ | 10–40 | Extracellular biosynthesis | Gram-negative (*E. faecalis, E. coli, P. mirabilis, Pseudomonas sp.*) and Gram-positive (*S. aureus*) | Used as broad-spectrum antimicrobial agents [6]. |
| Bacteria (*Lactobacillus plantarum* TA4) | ZnO | 191.8–291.1 | Using cell biomass and supernatant | Gram-positive (*S. epidermidis, S. aureus*), Gram-negative (*Salmonella sp., E. coli*) | Incorporated in wound dressings and surface disinfectants for antimicrobial protection [7]. |
| Actinobacteria (*Streptomyces* sp.) | CuO | 1.72–80 | cell-free culture supernatant | Bacteria (*E. coli, E. faecalis, P. aeruginosa, S. typhimurium*), fungi (*A. niger, F. solani, R. solani*), yeast (*C. albicans*) | Used in antifungal and antibacterial surface treatments [8]. |
| Fungi (*Fusarium keratoplasticum*) | ZnO | 10–42 (hexagonal) | Extracellular biosynthesis | Gram-positive and Gram-negative bacteria | Shows better antimicrobial activity [9]. |
| Fungi (*Aspergillus niger*) | ZnO | 8–32 (nanorods) | Extracellular biosynthesis | Gram-positive (*B. subtilis, S. aureus*), Gram-negative (*E. coli, P. aeruginosa*) | Shows bactericidal activity based on the shape of nanoparticles [9]. |
| Fungi (*Xylaria acuta*) | ZnO | 34–55 (hexagonal) | Extracellular biosynthesis | *P. aeruginosa, E. coli, S. aureus, B. cereus*, fungi (*Cladosporium cladosporioides*) | Used for antimicrobial and anticancer applications [9]. |
| Yeast (*Yarrowia lipolytica*) | Ag | 15 | Extracellular biosynthesis | Distrupt biofilm formation of *S. paratyphi* | Incorporated into topical antimicrobial formulations [10]. |
| Yeast (*Candida guilliermondii*) | Ag | 10–20 | Extracellular biosynthesis | Broad-spectrum antimicrobial | Compared to biosynthesized particles, chemically produced ones lacking antibacterial properties [11]. |
| Yeast (*Saccharomyces boulardii*) | Ag | 3–10 | Extracellular biosynthesis – cell free extract | Anticancer | Investigated for antimicrobial and anticancer therapies [12]. |



of metal nanoparticles of AgNPs, by yeasts viz., *Candida guilliermondii* [11], *Candida utilis* [28], *Candida lusitaniae* [29], *Candida glabrata* [30], *Candida albicans* [31], *Kluyveromyces marxianus* [32], *Pichia capsulate* [33], *Rhodotorula glutinis*, and *Rhodotorula mucilaginosa* [34], *Saccharomyces boulardii* [12], and *Saccharomyces cerevisiae* [35], was reported. A silver-resistant yeast strain, MKY3, was employed to synthesize AgNPs [36].

### 2.5. Nanoparticle synthesis by Algae

The use of algae for nanoparticle biosynthesis is gaining popularity. For example, *Sargassum muticum* has been utilized to produce ZnO nanoparticles, which have been shown to inhibit angiogenesis and induce apoptosis in HepG2 cells [37].

### 2.6. Nanoparticle synthesis by virus

Viral particles are nanoparticles that exist naturally and range in size from 20 to 500 nanometres. These have desired characteristics of biodegradability, programmable scaffolds, capacity for mass proliferation, biocompatibility, and flexibility of genetic manipulation. Mammalian viruses are primarily utilized for gene delivery applications, whereas bacteriophages and plant viruses have been investigated for their potential in vaccines, immunotherapy, and drug delivery systems [38].

The antimicrobial properties of metallic nanoparticles synthesized from ions of gold, silver, copper, zinc, magnesium, and titanium are widely acknowledged. These nanoparticles exert their antimicrobial effects through various mechanisms, such as forming pores in microbial cell walls, compromising membrane structure, preventing biofilm development, and generating reactive oxygen species (ROS) [39]. As pathogenic strains have become more multidrug resistant (MDR), the hunt for new antibacterial nanoparticles has begun.

### 2.7. Microbial-driven magnetic nanoparticles

Bacteria that move in response to magnetic fields—either an applied magnetic field or the earth's geomagnetic field are known as magnetotactic bacteria (MTB) [40]. In 1963, Salvatore Bellini made the first report on MTB. MTB movement and direction along magnetic field lines were described by Blakemore. Microbial cells may be observed under a microscope near the edge of water droplets in a magnetic field because they passively align and swim along magnetic field lines. This phenomenon, known as magnetotaxis, is how these microorganisms were found to react to magnetic fields [41].

*Pseudomonas aeruginosa* was recovered from clinical samples by Khan *et al.* who also showed that the bacteria could biosynthesise magnetic nanoparticles. *Pseudomonas aeruginosa* flourished on a low pH, carbon-minimum medium that was enhanced with iron. The cells' magnetic characteristics were confirmed when they lined up parallel to a magnetic field. X-ray diffraction, dynamic light scattering, magnetometry, and electron microscopy were used to extract, purify, and characterise the magnetic nanoparticles. Numerous uses for the biosynthesised magnetic nanoparticles exist, such as magnetic resonance imaging, diagnostics, and medicine (such as magnetic hyperthermia) [42].

## 3. POTENTIATION FOR AUGMENTING ANTIBIOTIC ACTIVITY

Innovative therapeutic strategies that enhance the effectiveness of current antibiotics are now essential for combating bacterial resistance. These approaches work by various mechanisms, such as disrupting cell wall formation, blocking protein synthesis by targeting ribosomal subunits, inhibiting nucleic acid production, interfering with metabolic processes, or destabilizing the structure of bacterial membranes [43]. In this manner, antibiotics have saved millions of lives. Bacteria may, however, develop resistance to certain antibacterial drugs through mutation involving resistance determinants or develop resistance naturally. Since current antibacterial medications are no longer as efficient at treating these illnesses, it is possible to observe the growing incidence of infections brought on by MDR bacteria because of the inappropriate use of this class of medications [44].

Given the diverse functionalities of metallic nanoparticles, their combination with antimicrobial agents offers a promising strategy to address the growing problem of bacterial resistance [45]. In a study by [46], demonstrated that AgNPs used in conjunction with antibiotics like amikacin or ampicillin exhibited enhanced, synergistic effects against MDR strains of both Gram-positive bacteria (such as *Enterococcus faecium* and *S. aureus*) and Gram-negative bacteria (including *Acinetobacter baumannii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Morganella morganii*, and *P. aeruginosa*) isolated from clinical specimens. The minimum inhibitory concentration (MIC) of amikacin was lowered by two to thirty-two times when AgNPs and amikacin were combined. The combination of AgNPs and ampicillin only lowered the MIC for *S. aureus* and *E. cloacae* from 1 to 4 times, but it reduced the MICs for the other bacteria by 16 and 32 times, respectively. This activity profile also became evident in the work of [47]. In this study, the researchers first determined the MICs for the antimicrobial agent's chloramphenicol, kanamycin, biapenem, and aztreonam. They then used subinhibitory doses of these drugs in combination with AgNPs to assess potential synergistic effects. The combination of AgNPs with chloramphenicol reduced the growth of *E. coli*, *S. typhimurium*, and *S. aureus* by about 50%, while the AgNPs-kanamycin combination suppressed the growth of these bacteria by roughly 95%. Table 2 shows the application of microbial nanoparticles against MDR strains.

## 4. TOXICITY CONCERNS ON NANOPARTICLE USE IN HUMANS

Strong antimicrobial properties are exhibited by microbial nanoparticles, particularly those made of metals such as silver, gold, copper, and zinc oxide, via a variety of mechanisms, such as disruption of cell membranes, production of ROS, and disruption of microbial DNA and metabolic processes [58]. For instance, it has been demonstrated that AgNPs destroy microbial cell membranes, produce oxidative stress, and damage DNA, all of which result in cell death [59]. However, these same properties can also result in toxicity to human cells and nontarget organisms. In animals, including zebrafish, rats, and Drosophila melanogaster, studies have shown that AgNPs and other metal nanoparticles may induce oxidative stress, DNA damage, and death in mammalian cells. Furthermore, the environmental persistence and bioaccumulation of these nanoparticles raise concerns about their long-term effects on ecosystems and human health [60].

## 5. REGULATORY OVERSIGHT OF MICROBIAL NANOPARTICLES

There are currently no published studies that specifically address the special regulatory difficulties related to bacterially synthesised nanoparticles in therapeutic and drug delivery applications for humans; all the literature that has been found addresses nanomedicine regulation in broad strokes without going into detail about bispecific concerns like endotoxins, host-cell impurities, or genetic safety. Strict rules have been put in place by regulatory bodies like the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for the development, approval, and monitoring of products based on nanoparticles that are meant for human use. Both agencies require comprehensive safety assessments, including studies on cytotoxicity, genotoxicity, immunotoxicity, and biodistribution, before granting approval for clinical applications. For instance, the FDA mandates that manufacturers provide detailed data on nanoparticle characterization, manufacturing processes, and toxicological profiles, emphasizing that nanomaterials are not presumed safe solely due to their nanoscale properties. The EMA similarly requires rigorous preclinical and clinical evaluation, and both agencies maintain ongoing surveillance of approved products to monitor for adverse effects. These regulatory frameworks are designed to ensure that the benefits of nanoparticle-based therapies outweigh potential risks, particularly given the evolving understanding of nanoparticle interactions with biological systems [61–63].

### 5.1. Emerging concerns and the need for harmonized regulations

Despite the progress in regulatory oversight, several challenges remain. The rapid expansion of nanoparticle applications in medicine, agriculture, and environmental remediation has outpaced the development of standardized testing protocols and risk assessment methodologies. There is growing evidence that sub-lethal exposure to nanoparticles can drive the emergence of microbial resistance, like antibiotic resistance, and contribute to genetic mutations and adaptive responses in microbial populations. In addition, the leaching of nanoparticles into soil and water can disrupt microbial communities and potentially co-select for antibiotic resistance genes. To address these concerns, international regulatory bodies advocate for harmonized global guidelines, stricter controls on nanoparticle concentrations, and comprehensive environmental impact assessments [58,64]. Continued collaboration between scientists, industry, and regulators is essential to advance the safe and effective use of microbial nanoparticles while minimizing unintended toxicological and ecological consequences.

## 6. CONCLUSION

With the growing resistance of microbial infections, the arsenal of antibiotics is fast getting depleted. It has

**Table 2.** Application of microbial nanoparticles.

| Sl no | Organism used | Nanoparticle type | Outcome |
|---|---|---|---|
| 1. | *B. subtilis*, *E. coli* and *S. typhimurium* | Polysaccharide capped silver nanoparticles | AgNPs exhibit little to no cytotoxicity against mammalian cells. Even at low doses, it restricts gram-positive and gram-negative bacterial growth and biofilm formation [48]. |
| 2. | Endophytic bacterium *Bacillus cereus* | Silver nanoparticles | Against strains of harmful bacteria, the produced nanoparticles have antibacterial action [49]. |
| 3. | Acidophilic actinomycetes SL19 and SL24 strains | Silver nanoparticles | Silver nanoparticle shows excellent antimicrobial activity in alone and combination with antibiotics [50]. |
| 4. | *Agaricus bisporus* | Silver nanoparticles | Nanoparticles are smaller in size and possess potent antimicrobial activity [51]. |
| 5. | *Bacillus flexu* | Silver nanoparticles | Nanoaprticles exhibit excellent antibacterial activity against MDR bacteria [52]. |
| 6. | Spirulina | Titanium dioxide | It exhibits strong antimicrobial activity against MDR bacteria [53]. |
| 7. | MDR- *P. aeruginosa* | Titanium dioxide | When used in combination with antibiotics, $TiO_2$NPs demonstrated strong antibacterial activity against MDR-Gram-negative bacilli pathogens and a notable fold increase in areas (283%) [54]. |
| 8. | *Aspergillus terreus* | Bimetallic Ag-Cu nanoparticles | Results revealed that these nanoparticles have strong antimicrobial activity [55]. |
| 9. | Fungus *Aspergillus oryzae SZ1* | Silver nanoparticles | Fluconazole and Ag-NPmyc together had a synergistic impact on the pathogenicity of resistant *Candida* sp [56]. |
| 10. | Fungus *Shizophyllum commune* | Silver nanoparticles<br>Copper nanoparticles | These nanoparticle shows excellent antimicrobial activity against MDR pathogens [57]. |



become imperative to develop drug formulations to overcome microbial resistance. Nanotechnology, in recent years, is gaining prominence, and the advantage of the synergism of metal nanoparticles with antimicrobial agents will usher in drug formulations to treat resistant microbial infections. Microbial nanoparticles have rapidly emerged as a pivotal innovation in antimicrobial therapy, offering unique advantages such as green synthesis, biocompatibility, and the ability to synergize with conventional antibiotics. Recent developments demonstrate their diverse mechanisms, which allow them to target a wide range of pathogens, including strains that are resistant to many drugs. These methods range from membrane disruption and ROS production to suppression of biofilm formation and quorum sensing. While nanoparticles, especially silver-based ones, are less prone to sequestration by cellular components like phosphate compared to free ions, the long-term efficacy of nanoparticles in environments rich in phosphate or other anions remains underexplored. This is particularly relevant for clinical settings where phosphate-rich biological fluids may impact nanoparticle stability and antimicrobial action [65]. Batch-to-batch variability, scalability of green synthesis, and comprehensive safety assessments, including long-term toxicity and environmental impact, remain significant challenges for clinical translation.

## 7. CLINICAL RELEVANCE

While most studies on microbial nanoparticles are currently at the in vitro or preclinical stage, their demonstrated efficacy against a broad spectrum of pathogens, including multidrug-resistant strains, highlights their clinical promise. Some nanocellulose-based materials have already reached clinical use for wound healing and burn treatment. For clinical translation, comprehensive safety, toxicity, and pharmacokinetic studies are essential. Batch-to-batch consistency, scalability, and regulatory compliance (e.g., FDA and EMA guidelines) remain challenges that must be addressed to ensure human safety and therapeutic efficacy. Key hurdles include achieving monodispersity, increasing production rates, and ensuring reproducibility. Advances in microbial engineering, bioprocess optimization, and standardized characterization protocols are expected to address these issues, facilitating the clinical adoption of microbial nanoparticles.

## 8. AUTHOR CONTRIBUTION

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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The authors report no financial or any other conflicts of interest in this work.

## 11. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

## 12. DATA AVAILABILITY

All data generated and analysed are included in this review article.

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