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Bacterial Synthesis of Nanoparticles: Mechanisms and Biomedical Applications

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Abstract

Numerous scientific disciplines have experienced revolutionary changes due to the rapid emergence of nanotechnology, specifically in biotechnology and medicine. The involvement of harmful chemicals and energy-consuming physical methods of nanoparticle manufacturing results in severe toxicological concerns with respect to the environment, ecology, and medicine. Consequently, biological methodologies have become highly efficient, biocompatible, and sustainable alternatives. Through strictly controlled biochemical mechanisms in intracellular and extracellular processes, prokaryotes, more precisely bacteria, have proven to be highly efficient for green, scalable manufacturing of metallic, bimetallic, and metal oxide nanoparticles. These natural processes are facilitated through specialized microbial enzymes, structural proteins, extracellular polymeric substances (EPS), and intracellular metabolic pathways. Natural capping provides high colloidal stability, reduced agglomeration, better biocompatibility, and enhanced biological activity. These are some of the unique physicochemical characteristics of bacterially derived nanoparticles. This comprehensive review addresses the shortcomings in the methods used for characterization, identifies the essential physicochemical and biological aspects influencing the kinetics of nanoparticle formation by bacteria, and systematically reviews the underlying molecular processes involved in such nanoparticle synthesis. Advances in biomedical research are thoroughly addressed with an emphasis on targeted drug delivery, oncological theragnostics, electrochemical biosensing, regenerative tissue engineering, and antimicrobial treatment of multidrug-resistant pathogens. Finally, the current limitations in industry, cytotoxicity concerns, regulatory hurdles, and future trends that leverage machine learning optimization and synthetic biology are critically analyzed.

Keywords: Green synthesis, metallic nanoparticles, bacterial reduction, biomedical applications, targeted drug delivery, antimicrobial resistance.

Introduction

One of the rapidly developing multidisciplinary areas of current research is the field of nanotechnology, which is a blend of essential concepts of engineering of advanced materials, solid-state physics, interface chemistry, and molecular biology. Nanoparticles (NPs) are considered as atoms or molecules, which are constrained within the spatial dimensions of 1 to 100 nm. The properties of the materials vary significantly within this highly small sub-microscopic range. The remarkable inflation of the

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surface-area-to-volume ratio and the strong effects of spatial quantum confinement are the two main quantum-scale phenomena driving these significant changes. As a result, a wide range of high-tech industrial paradigms, such as environmental remediation, catalytic synthesis, semiconductor physics, optoelectronics, and extremely sophisticated clinical biotechnology, have incorporated engineered nanoparticles [1,2].

In earlier times, the most common methods for creating nanoparticles were chemical and physical. Physical vapor deposition (PVD), thermal breakdown, high-energy ball milling, and laser ablation are some physical methods of creating nanoparticles. These physical methods of producing nanoparticles require vacuum-operated machinery [3]. These physical methods of creating nanoparticles also require a lot of electricity. As a result, producing nanoparticles on a large scale is very difficult and costly. Many chemical processes at the time, such as the use of hydrazine or sodium borohydride for reduction, the creation of chemical microemulsions, and sol-gel synthesis, relied excessively on hazardous organic solvents. Additionally, these techniques include capping stabilizers and reducing agents that do not decompose in the natural world. These artificial nanoparticles become harmful to the environment because they contain residual dangerous chemicals on their surface. Utilizing the nanoparticles in actual medical work, human physiology, or conventional in vivo pharmacological procedures is also quite difficult due to this surface contamination.

The concept of "green nanotechnology" has rapidly expanded to genuinely eliminate environmental and biosecurity barriers. Using systems as the primary cellular factories for creating nanomaterials is the current emphasis of green nanotechnology [4]. Bacterial microorganisms stand out among biological resources, including plant extracts, macroalgae, fungi, and viral structures, for their distinct technical and functional advantages. Bacteria have tremendous genetic flexibility, reproduction, easy and well-known cultivation processes, and an innate capacity to withstand and metabolize large concentrations of heavy metals [5]. Because bacteria can swiftly adapt and withstand amounts of heavy metals that might otherwise harm other biological resources, green nanotechnology still depends on microbes. Green nanotechnology has an advantage over other bio-based methods because of this.

To prevent the production of chemical waste, the bacterial synthesis of nanoparticles only occurs in water at body-like temperatures and normal air pressure. This review describes how bacterial nanoparticle manufacturing can alter current medical tests, therapies, and regenerative bioengineering, while providing an up-to-date look at the fundamental biochemical processes that drive it.

Techniques for Bacterial Nanoparticle Synthesis

One essential bacterial defense mechanism against the toxicity of heavy metals is the bioreductive conversion of dissolved and poisonous metal ions to zero-valent, zero-dimensional solid nanoparticles. Enzymatic cascades are involved in both internal and extracellular biocatalytic processes that produce nanoparticles [6]

Intracellular Synthesis

The active transport of soluble metal cation molecules from the exterior microenvironment into the inside of the bacterial cell initiates the cascade of intracellular production. These materials are often transported by concentration gradients, generic ion transport proteins, or specific ABC-type efflux or influx pump mechanisms found in the bacterial plasma membrane. Certain enzymes quickly take up the concentrated metal cations inside the cells and detoxify them. Enzymes such as NADH and NADPH reductase, nitrate reductase, nitrite reductase, and hydrogenases typically start these reactions [7].

The enzyme facilitates the sequential transfer of electrons from NADH/NADPH via an internal electron chain to the target metal ions, thereby reducing them to a zero-valent atomic state (M0). The individual zero-valent metallic atoms swiftly form nuclei, aggregates, and crystalline clusters, which then become nanoparticle clusters. These newly formed nanoparticles are locked inside the cellular cytoplasm or located in the inner and outer layers of the cell membrane [8], necessitating expensive downstream processing like sonication, lysozyme treatment, or detergent extraction [9].

Extracellular Synthesis

However, the extracellular route is highly intriguing for industry because it does not involve the breakdown of the cell wall within the cell [10]. The bacterial secretomes are actively secreted into the surrounding aqueous media during this process. Numerous soluble oxidoreductase enzymes, peptides, proteins, metabolites, and EPS (Extracellular Polymeric Substances), which comprise long-chain polysaccharides, lipids, and nucleic acids, are found in the secretomes.

When exposed to metal ions, microbial cells release proteins and enzymes that act as effective reducing agents. In addition to this mechanism, the EPS matrix's functional groups such as hydroxyl groups (-OH), carboxyl groups (-COOH), amine groups (-NH2), and thiol groups (-SH) offer a powerful electrostatic anchor point for securing the newly generated zero-valent metallic nuclei [11]. The extracellular proteins and polysaccharides coat the developing metallic nucleus in addition to performing the fundamental reduction process. This keeps the nanoparticles from clumping together by giving them natural steric and electrostatic protection, often known as capping.

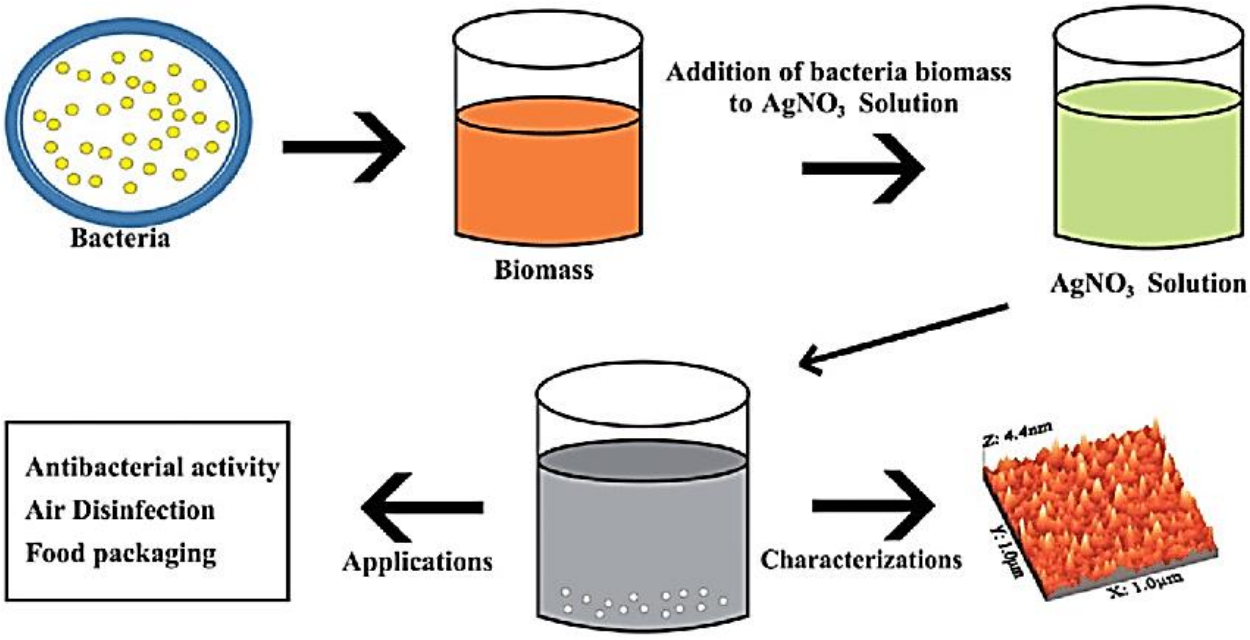


Figure 1. Schematic diagram for the synthesis of Ag-NPs using bacteria.

Bacterial Species Used in Nanoparticle Fabrication

A wide range of bacterial strains are effective biological means of synthesizing elemental and oxide nanoparticles [12]. Gram-positive bacteria have an exceptionally high affinity for passive electrostatic binding and reduction of heavy metal ions due to their thick and durable peptidoglycan layer in their cell walls, which includes highly electronegative teichoic acids. Gram-negative bacteria, on the other hand, have an active periplasmic space that promotes crystal nucleation.

Extremophile bacteria, such as Deinococcus radiodurans and various halophiles, can be increasingly used for nanoparticle synthesis in harsh chemical environments that destroy common biological systems. For instance, strains from the Bacillus genus are widely used because they can form spores and secrete higher amounts of proteins, making their production of silver and gold nanoparticles efficient. The selection of the bacterial strain is thought to be a primary determining factor for the crystalline structure, geometrical morphology, and physical characteristics of the nanoparticles produced.

Key Factors that Affect Nanoparticle Formation

A wide range of physicochemical and biological parameters play a crucial role in controlling the thermodynamic kinetics, growth morphology, yield, and long-term monodispersity of nanoparticles made from bacteria. It is important to optimize these conditions to obtain a consistent structure required for biomedical applications.

Table 1: Parameters for Optimization Altering the Geometrical and Kinetic Output of Bacterial Synthesis

Physicochemical Variable	Operative Range Thresholds	Direct Mechanistic Influence on Nanoparticles	Observed Morphological Shift Patterns
Reaction pH	5.0 – 9.0	Modifies electrical ionization of functional protein groups; alters metal binding affinity.	Alkaline pH promotes rapid nucleation, yielding smaller spherical structures.
Incubation Temperature	25°C – 60°C	Regulates enzyme kinetics and atomic nucleation velocity.	Higher temperatures reduce average particle diameter; extreme heat triggers aggregation.
Metal Salt Concentration	0.5 mM – 5.0 mM	Dictates stoichiometric ratio of metal ions to available microbial reducing enzymes.	Excessive concentration increases particle size and induces polydispersity.
Kinetics Duration	12 h – 72 h	Governs the temporal progression from initial nucleation to crystal growth.	Extended incubation risks secondary crystal growth and shell aggregation.
Microbial Growth Phase	Late Log to Stationary Phase	Dictates cellular metabolic activity and intracellular enzyme expression levels.	Stationary phase cells produce stable, highly monodisperse nanoparticles.

Biosynthesized Nanoparticle Characterization

To verify the nanoparticles' synthesis process and ensure their effectiveness and safety, a trustworthy and thorough method is required [13]. To do this, several characteristics of the nanoparticles must be evaluated. These include their dispersion, chemistry, surface texture, and crystalline nature.

Table 2: Essential Analytical Instrumentation Methods and Their Function in Green Nanoparticle Characterization

Analytical Technique	Targeted Physical Parameter	Direct Operational Purpose & Data Output	Inherent Advantages in Biosynthesis Analysis
UV-Visible Spectroscopy	Surface Plasmon Resonance (SPR)	Confirms initial nanoparticle reduction based on characteristic light absorption spectra.	Rapid, non-destructive validation technique; highly sensitive to local aggregation.
TEM & HR-TEM	Internal Morphology and Lattice Structure	Provides high-resolution imaging of particle geometry, size distributions, and crystal lattices.	Visualizes the natural organic biological capping shell surrounding each nanoparticle core.
SEM & FESEM	Surface Topography & Distribution	Generates detailed 3D topographic surface maps showing spatial nanoparticle dispersion.	Enables qualitative analysis of nanoparticles embedded within bacterial biofilm matrices.
XRD (X-ray Diffraction)	Crystallinity Phase Profile	Identifies specific mineral crystal phases (e.g., FCC vs. BCC) and calculates average grain size.	Differentiates between amorphous bio-precipitates and pure crystalline metallic cores.
FTIR Spectroscopy	Surface Functional Capping Chemistry	Identifies the specific organic functional groups (e.g., amide, hydroxyl) bound to the nanoparticle surface.	Maps the bacterial proteins and biomacromolecules responsible for natural capping and stability.
DLS & Zeta Potential	Hydrodynamic Radius & Charge Stability	Measures the effective particle size in liquid suspension and determines net surface charge.	Predicts long-term colloidal stability and real-time agglomeration risks in physiological fluids.

Utilize in Biomedicine

Nanoparticles produced by bacteria have a distinct surface chemistry and are highly biocompatible, making them potential new platforms for biological applications [14].

Antimicrobial Uses

The efficacy of antibiotics has been significantly compromised by a surge in superbugs that are multi-drug resistant (MDR). Because of their multi-target strategy against microorganisms, biosynthesized nanoparticles of silver (Ag), copper (Cu), and zinc oxide (ZnO) offer an efficient substitute. By producing intracellular damage, localized oxidative stress, and membrane disruption [15], the nanoparticles act on three distinct fronts of toxicity. The nanoparticles create a structural leak of the cellular contents when they encounter the bacterial cell wall because they electrostatically attach to the components of the cell wall's structure. The release of the metallic ions leads to the production of ROS, which cause lipid peroxidation and breakage of the DNA strands.

Systems for Drug Delivery

Bioengineered nanoparticles have gained popularity as a means of transporting genetic material, tiny molecules, and toxic anticancer medications [16]. The targeted ligand, such as a monoclonal antibody, aptamer, or folate molecule, can covalently bind to the organic capping group on the surface of bioengineered nanoparticles. By selectively accumulating in tumors without harming healthy somatic cells, the EPR effect linked to the tumor microenvironment allows for targeted administration of the nanoparticles.

Conclusion

Bacterial synthesis of nanoparticles forms the basis of green nanotechnology. It is environmentally benign and cost-effective, as well as a scalable technology compared to conventional physical and chemical means. Utilizing the intrinsic biochemical capabilities of bacteria permits the reduction of hazardous metals into zero-valent nanomaterials at mild physiological settings. Naturally occurring organic coating of bacteria endows these nanoparticles with high colloidal stability as well as biocompatibility [17-19]. In accordance with the facts offered in this study, green nanoparticles have demonstrated effectiveness against multidrug-resistant infections, providing targeted cancer therapy and diagnostics as well as tissue engineering.

Nevertheless, extensive translation of bacteria-synthesized nanoparticles into clinical practice confronts various hurdles, including those related to large-scale synthesis, subsequent purification processes, and regulation of the product. These problems can be resolved by using machine learning to automate bioreactor dynamics and synthetic biology to optimize bacterial strains. If these issues are resolved, bacterially generated nanoparticles will become essential components of upcoming medicinal and diagnostic technology.

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