Materials Chemistry Horizons

REVIEW

Bacterial Synthesis of Metallic Nanoparticles for Biomedical Applications

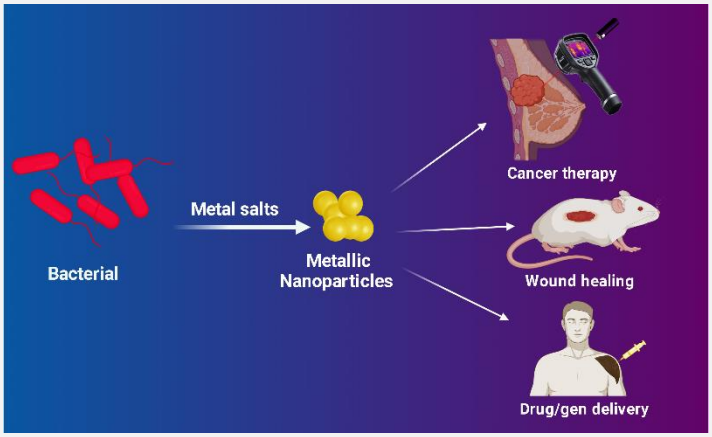
Minmin Shao[1],Guofeng Xiong[1],Guiqing He[2,3*]

[1]Department of Otorhinolaryngology,The Dingli Clinical College of Wenzhou Medical University(The Second Affiliated Hospital of Shanghai University,Wenzhou Central Hospital), Wenzhou, Zhejiang Province 325000,China
[2]Department of Infectious Diseases, Wenzhou Central Hospital, The Dingli Clinical College of Wenzhou Medical University, The Second Affiliated Hospital of Shanghai University, Wenzhou, Zhejiang Province 325000, China
[3]Laboratory of Infectious Diseases, Wenzhou Central Hospital, The Dingli Clinical College of Wenzhou Medical University, The Second Affiliated Hospital of Shanghai University, Wenzhou, Zhejiang Province 325000, China

Corresponding author: shaominmin2005@163.com (M.Shao)

Mater. Chem. Horizons, 2023,2(4), 303-313 10.22128/MCH.2024.769.1055 OPEN ACCESS

ABSTRACT



Metallic nanoparticles, especially silver and gold, have promising applications in biomedicine due to their unique optical, electronic, and chemical properties. Conventionally, physical and chemical methods have been used to synthesize these nanoparticles; however, bacterial synthesis has recently emerged as an environmentally friendly, cost-effective, and facile alternative. In this review, we summarize recent progress in understanding the mechanisms underlying microbial nanoparticle biosynthesis and highlight key bacterial strains that have been exploited for efficient, controlled nanoparticle fabrication, including *Escherichia coli*, *Bacillus subtilis*, and *Geobacillus sp*. We discuss current genetic and process engineering strategies to improve the quality, yield, and mono-dispersity of bacterially synthesized metallic nanoparticles. Furthermore, we overview promising biomedical uses of these nanoparticles being actively explored, ranging from drug delivery vehicles, bioimaging tracers, diagnostics, and biosensors, to antibacterial agents and materials with accelerated wound healing capacity. Finally, we outline prospects and challenges toward scale-up, regulation, and adoption of green, biosynthesized metallic nanomaterials for various healthcare applications.

Keywords: Metallic nanoparticles, biosynthesis, bacterial, biomedical application

1. Introduction

Nanoparticles, defined as materials with at least one dimension measuring between 1-100 nm, possess remarkably unique optical, electrical, and catalytic properties compared to their bulk counterparts [1,2]. Research interest in fabricated nanomaterials has recently surged across diverse fields due to their multifunctionality and potential integration into innovative commercial products. Of the various nanoparticles studied, metallic nanoparticles are exceptionally valuable given properties like localized surface plasmon resonance, high electron conductivity, and chemical stability that lend them to sensing and catalysis roles [3].

Additionally, the biocompatibility and facile surface chemistry of metals has enabled the employ of metallic nanoparticles like silver, iron oxide, and gold for myriad biomedical uses including bioimaging, drug delivery, pathogen detection via biosensors, photothermal ablation of cancer cells, and antimicrobial agents [4]. They serve as indispensable materials at the intersection of nanotechnology and biomedicine.

Conventionally, metallic nanoparticles have relied on top-down physical and bottom-up wet chemical synthesis methods [5]. However, burgeoning eco-toxicity concerns regarding these approaches have necessitated a paradigm

Received: December 26, 2023
Received in revised: January 07, 2024
Accepted: January 09, 2024

shift. Biological or 'green' production strategies utilizing microbial cells are emerging as viable alternatives [6]. Microbial nanoparticle biosynthesis leverages bacterial oxidation-reduction machinery normally operating during metabolism to bio-transform metal salts into nano-dimensions [6]. Key advantages of microbial synthesis include negligible toxic waste discharge, ambient reaction conditions, excellent nanoparticle yield, dispersity control, and one-step production with inherent capping/stabilization [7].

This review specifically focuses on recent research on employing bacteria including extremophiles for efficient extracellular and intracellular metallic nanoparticle fabrication. Further, common mechanistic pathways adopted by bacteria for nanoparticle nucleation and assembly are elucidated. Key recent biomedical applications using bacteria-mediated metallic nanoparticles like biosensing, antimicrobial function, antioxidant/anticancer activity, wound healing, and neurotherapeutic effects are discussed. Finally, critical challenges facing large-scale biosynthesis are outlined and upcoming advances like genetically engineering bacteria to produce custom nanoparticles are highlighted.

2. Synthesis of nanoparticles

There are three main approaches for synthesizing nanoparticles: physical, chemical, and biological. These approaches fall under either top-down or bottom-up methods (**Figure 1**). The top-down method reduces size by progressively breaking down bulk materials into nanoscale structures. In contrast, the bottom-up method involves assembling atoms or molecules into nanoscale molecular structures.

Bottom-up approaches rely on chemical and biological nanoparticle synthesis, while top-down methods typically use physical or chemical routes [8,9]. Techniques like UV irradiation, sonochemistry, radiolysis, and laser ablation employ a physical approach to synthesizing metallic nanoparticles [10]. However, these methodologies have limitations. Although physical and chemical methods can generate high-purity nanoparticles of desired sizes, the processes are often costly and utilize toxic chemicals. Chemical synthesis may result in toxic residues on the nanoparticle surfaces that could cause detrimental medical effects. The nanoparticles could also directly interact with the human body, raising toxicity concerns. Thus, a key nanotechnology objective is developing an eco-friendly production process for low-toxicity nanoparticles. Several researchers have focused on biological nanoparticle synthesis methods to achieve this aim. These are fast, cost-effective, and eco-friendly. The biological synthesis of nanoparticles encompasses a vast range of natural species, including viruses, bacteria, fungi, algae, and plants (using their enzymes, proteins, DNA, lipids, carbohydrates, etc.). Bacteria that reduce metals serve as environmentally friendly catalysts for bioremediation and materials synthesis. Microbes can assist in synthesizing diverse metal oxides through respiration processes [11]. Microbial dissimilatory anaerobic respiration involves electron transfer from reduced organic to oxidized inorganic compounds, driving crystal/nanoparticle formation alongside bioremediation. Well-documented examples are Shewanella species that oxidize organic acids as electron donors while reducing inorganic metals as electron acceptors [12].

Additionally, microorganisms like bacteria have developed detoxification mechanisms to reduce toxic metal species into metal nanoparticles, thereby making their immediate cellular environment safer[13]. Bacterial biomolecules have also been utilized as capping and stabilizing agents in nanoparticle synthesis. In microbial nanoparticle synthesis, metal ions are first trapped on microbial cell surfaces or interiors. Enzymes then reduce the trapped metal ions into nanoparticles. Generally, microorganisms impact mineral formation in two ways: By changing solution composition to increase supersaturation concerning a specific phase, and by generating organic polymers that control nucleation by stabilizing the first mineral seeds (inhibiting or promoting nanoparticle formation). Bacteria, as potent eco-friendly green nanofactories, can regulate the size and shape of biologically synthesized nanoparticles. Although plant-extract mediated nanoparticle synthesis is a well-established biological platform, the resulting nanoparticles risk becoming polydisperse owing to phytochemicals. Nanoparticle yields may also vary due to seasonal fluctuations [14]. In contrast, bacteria synthesis offers advantages like controlled nanoparticle size/shape and consistent yield. Thus, many microorganisms are considered prime candidates for nanoparticle generation [15].

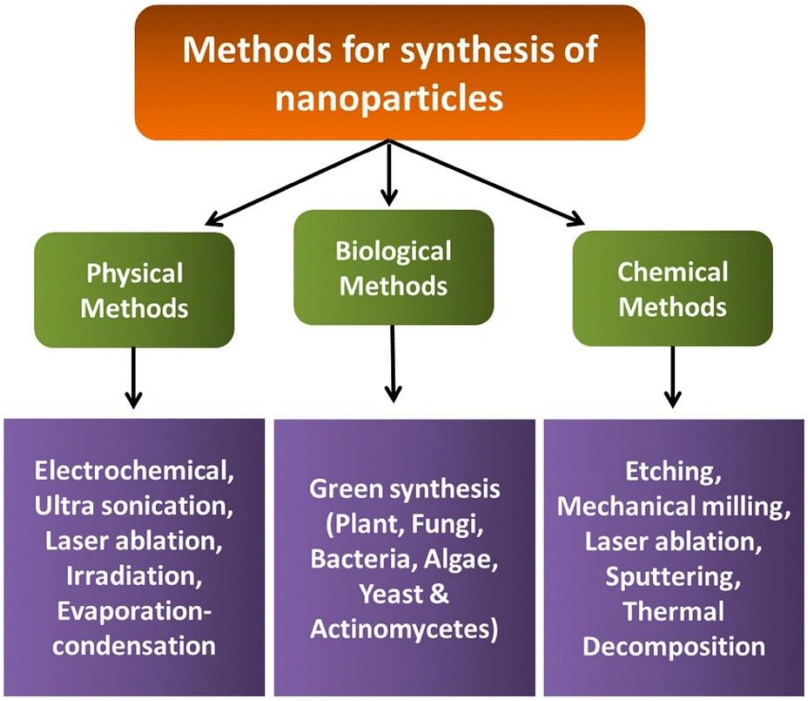


Figure 1. The approaches are broadly categorized into physical, chemical, and biological routes. Top-down physical techniques involve directly breaking down bulk metal sources into nano-dimensions using mechanical fabrication methods or energy sources like ultrasound, lasers, gamma rays, etc. Bottom-up chemical methods rely on chemically reducing metal salts to generate metal atoms that assemble into nanoparticles. Variants use different reducing agents, stabilizers, and application of external stimuli. Biological approaches leverage whole microbial cells or their extracts to biosynthesize metal nanoparticles through enzymatic metal ion reduction coupled with capping by innate biomolecules. This enables an eco-friendly, sustainable nanoparticle production strategy. Reprinted with permission from [16].

2.1. Bacterial synthesis of metallic nanoparticles

Bacteria's remarkable ability to adapt to environmental stresses enables them to generate reduced metal ions [17]. Supernatants from species like *Pseudomonas proteolytica*, *Pseudomonas meridiana*, *Pseudomonas Antarctica*, *Arthrobacter gangotriensis*, and *Arthrobacter kerguelensis* have served as microbial cell factories and reducing agents to synthesize silver nanoparticles [18]. Recently, *Bacillus brevis*-produced silver nanoparticles exhibited potent antimicrobial properties against multidrug-resistant *Staphylococcus aureus* and *Salmonella typhi* [19]. Through an intracellular mechanism, *Pseudomonas stutzeri* has also accumulated silver nanoparticles [20]. *Bacillus* species have likewise biosynthesized silver nanoparticles in intracellular periplasmic spaces [21].

Organisms dwelling in gold mines resist soluble gold toxicity and can proficiently generate gold nanoparticles [22]. With the bacterium Acinetobacter sp. SW30, varying cell densities, and gold chloride concentrations dramatically impacted the color of the gold nanoparticle (AuNP) containing solutions, indicating differences in AuNP size and shape. Strikingly, at the lowest cell density and gold salt concentration, monodisperse spherical AuNPs of ~19 nm formed, while higher cell numbers resulted in polyhedral AuNPs (~39 nm) [23]. Amino acids likely enabled gold salt reduction, and amide groups assisted AuNP stabilization.

Other reports describe the intracellular biosyntheses of silver, gold, and silver-gold alloy nanocrystals within lactic acid bacteria [24]. Two separate *Pseudomonas aeruginosa* strains in one sample yielded AuNPs of distinct sizes [25]. Spherical (10-50 nm) and triangular platelet (50-400 nm) AuNPs were also extracellularly synthesized using *Rhodopseudomonas capsulata* [26].

A radioresistant microbe, *Deinococcus radiodurans*, was studied for its capacity to generate gold nanoparticles (AuNPs) from aqueous gold salt solutions [27]. Ultraviolet-visible absorption spectra, microscopy, X-ray diffraction, light scattering, infrared spectroscopy, and X-ray photoelectron spectroscopy measured nanoparticle formation, properties, and localization within the bacterial cells. The bacteria efficiently synthesized AuNPs with varied morphologies after 8 hours of exposure to 1 millimolar Au(III). Dynamic light scattering quantified an average 43.75

nm diameter and moderate dispersity. The nanoparticles were found throughout the cell envelope, cytosol, and extracellular environment, with X-ray diffraction supporting their crystalline metallic nature. Purified nanoparticles displayed antibacterial qualities against model Gram-positive and Gram-negative species by compromising cytoplasmic membrane integrity. Therefore, the extreme durability of *D. radiodurans* could enable straightforward and scalable biological synthesis of AuNPs with potential biomedical functions like bactericidal capability (**Figure 2**) [28].

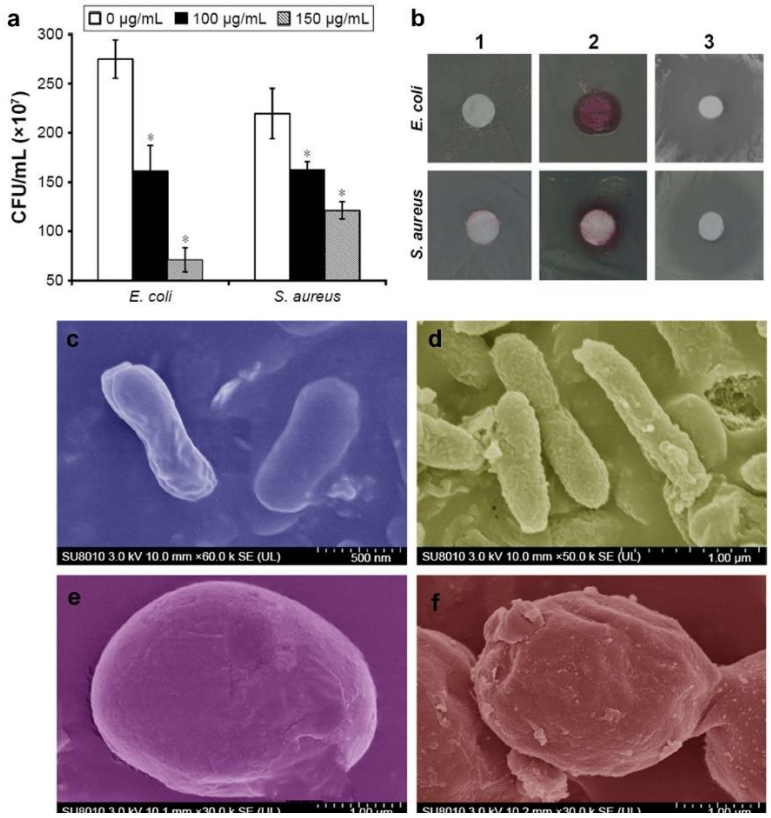


Figure 2. The image displays the antibacterial properties of gold nanoparticles (AuNPs). (a) shows the survival rate of *Escherichia coli* and *Staphylococcus aureus* when exposed to two different concentrations of AuNPs, with asterisks indicating statistical significance. (b) exhibits the inhibition zones created by AuNPs, phosphate-buffered saline, and chloramphenicol on cultures of the bacteria. Scanning electron microscope images illustrate the morphological effects of a 30-minute, 100 µg/mL AuNP treatment on *E. coli* (c and d) and *S. aureus* (e and f), before and after exposure. Scale bars are included. Reprinted with permission from [28].

Using *Serratia ureilytica*, ZnO nanoflowers were synthesized and integrated into cotton fabrics, conferring anti-E.coli and anti-Staphylococcus aureus properties [29]. *Lactobacillus plantarum* biosynthesized ZnO nanoparticles as well [30], alongside *Aeromonas hydrophila's* generation of antimicrobial ZnO nanoparticles [31]. Triangular copper oxide nanoparticles from *Halomonas elongata* displayed activity against *Escherichia coli* and *Staphylococcus aureus* too [32]. In another study, *Bacillus cereus* produced ~29.3 nm superparamagnetic iron oxide nanoparticles that exhibited anti-cancer effects against MCF-7 breast cancer cells and 3T3 mouse fibroblasts, in a dose-dependent manner [33]. Using *Streptomyces* species intracellularly, convenient and rapid manganese and zinc nanoparticle synthesis was achieved from the respective metal sulfates. The nanoparticles ranged between 10-20 nm [34]. Surfactin-generating *Bacillus amyloliquefaciens* KSU-109 strain enabled 3-4 nm cadmium sulfide nanoparticle production [35]. *Escherichia coli* E-30 and *Klebsiella pneumoniae* K-6 synthesized 3.2 to 44.9 nm cadmium sulfide nanoparticles having antimicrobial effects on *Aspergillus fumigatus*, *Geotrichum candidum*, *Bacillus subtilis*, *Staphylococcus aureus,* and *E.coli* [36].

Other reports describe *Serratia marcescens*-mediated antimony sulfide nanoparticles under 35 nm [37], alongside 96 nm selenium nanoparticles using *Pseudomonas aeruginosa* ATCC 27853 [38]. *Cocos nucifera* enabled 47 nm lead nanoparticle fabrication possessing anti-*Staphylococcus aureus* function. Finally, Egyptian desert bacterial isolates synthesized 2.9 to 21.13 nm uranium nanoparticles intracellularly [39].

In summary, bacteria adapt to stresses by generating metal and metal compound nanoparticles through extracellular and intracellular approaches. Diverse bacteria serve as microbial nanofactories for fabricating technologically relevant nanomaterials. Cyanobacteria have been extensively studied for their nanoparticle synthesis capacities owing to bioactive components that aid nanoparticle stabilization and functionalization, resulting in fewer synthesis steps. Their rapid growth also enables substantial biomass generation to assist nanoproduction. Typically, cell-free extracts of the cyanobacterial biomass are utilized for nanosynthesis.

Silver nanoparticle reduction and subsequent stabilization were achieved using aqueous extracts of the cyanobacterium *Oscillatoria limnetica*. The 3.30–17.97 nm nanoparticles displayed anti-cancer and antimicrobial properties [40]. With *Microchaete sp*. NCCU-342 aqueous biomass extracts, 60-80 nm spherical, polydispersed silver nanoparticles formed similarly [41]. Desertifilum sp.-derived 4.5-26 nm silver nanoparticles exhibited antibacterial effects and cytotoxicity against HepG2, MCF-7, and Caco-2 cancer cell lines [42]. Other explored cyanobacterial strains include *Scytonema sp*., *Nostoc sp*., and *Phormidium sp*. [43].

In an interesting study, the *filamentous Plectonema boryanum* (UTEX 485) biomass reacted with silver nitrate, precipitating silver nanoparticles on the exterior and interior. Intracellular nanoparticles were <10 nm, while extracellular ones ranged from 1-200 nm [44]. *P. boryanum* can also intracellularly reduce gold (III) chloride to gold nanoparticles via gold (I) sulfide formation. This species produces platinum and palladium nanoparticles too [45].

Therefore, cyanobacteria constitute a promising biogenic nanosynthesis platform with widespread utility. Their biosynthesis mechanisms for diverse technologically relevant nanomaterials warrant further investigation.

3. Mechanism of metallic nanoparticle formation by bacteria

Bacteria facilitate metallic nanoparticle fabrication through various extracellular and intracellular mechanisms (**Figure 3**). Redox-active enzymes play a central role in nanoparticle nucleation and development in most pathways adopted by bacteria.

Extracellular biosynthesis: Bacteria secreted enzymes like nitrate reductase catalyze metal ion reduction to produce metal atoms (Nucleation). Subsequent metal atom aggregation driven by factors like reaction condition parameters results in nanoparticle seed formation. Concurrently, bacterial secretion of stabilizing polymers like proteins, polysaccharides, etc stabilizes growing nanoparticle seeds preventing aggregation (Growth and Stabilization) [46]. Characteristic capping engenders further nanoparticle enlargement by oriented attachment. For example, *Pseudomonas stutzeri* AG259 nitrate reductase reduces silver ions to silver nanoparticles extracellularly, confirmed using enzyme inhibitors that ceased nanoparticle synthesis [47]. *Escherichia coli* and *Salmonella* Typhimurium nitrate reductases generating silver nanocrystals, verified by mutant strains lacking nitrate reductase failing to produce nanoparticles [48].

Intracellular biosynthesis: Metal ions traversing bacterial cell walls interact with cytoplasmic reducing enzymes or cellular components to form metal atoms (Nucleation) [49]. Early nucleation likely occurs near redox enzyme sites like Glutathione clusters. Accumulating metal atoms then coalesce into oligomeric metal clusters eventually developing into nanoparticle seeds (Nucleation and Growth). Next, nanoparticle enlargement happens aided by enzymes while bacterial biomolecules (proteins, peptides, organics) offer capping/stabilization functionality, preventing aggregation in a cellular milieu (Growth and Stabilization). For example, *cyanobacteria* species intracellularly form gold nanoparticles, confirmed by X-ray photoelectron spectroscopy revealing gold-sulfur bonds from constituent biomolecule capsiding nanoparticles [50]. *Bacillus licheniformis* generates silver nanoparticles intracellularly, verified through Fourier transform infrared spectroscopy demonstrating cellular proteins covering synthesized nanoparticles [51]. Thus bacteria demonstrate excellent nanoparticle productivity stemming from orchestrated biomolecular mechanisms for systematic nanoparticle nucleation, growth, recovery, and stabilization. Elucidating these complex biochemical pathways warrants further studies and can enable rational engineering routes for custom nanoparticles.

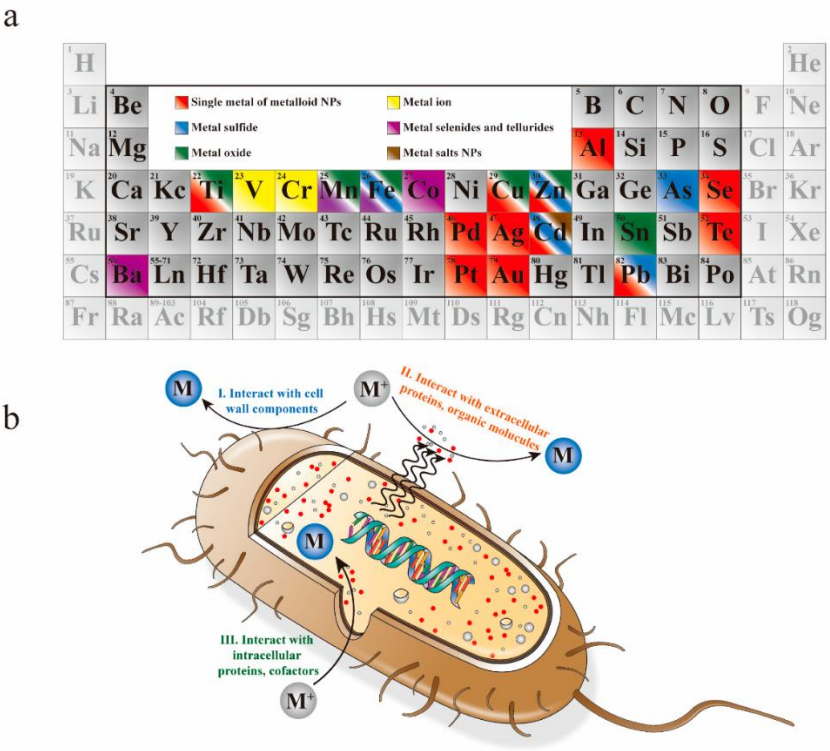


Figure 3. showcases the diverse array of nanoparticles that bacteria can generate. Part (a) presents a periodic table highlighting elemental nanoparticles synthesized using bacterial platforms. Bacteria demonstrate the remarkable capacity to produce nanoparticles spanning various metals, metalloids, and even radionuclides. Part (b) schematically encapsulates nanoparticle biosynthesis mechanisms adopted by bacteria, both extracellular and intracellular. Extracellularly, bacterial cells secrete reducing enzymes that transform ionic precursors into elemental atoms, subsequently agglomerating into nanoparticles. Concurrently, other secreted biomolecules provide capping functionality. Intracellularly, cellular entry of precursors allows enzyme-mediated nanoparticle generation within bacteria. Internally synthesized nanoparticles later get secreted outside bacterial cells, enabled by biomolecules again preventing uncontrolled aggregation. Thus bacteria implement elegant biochemical pathways for systematic nanoparticle nucleation, recovery, and stabilization either inside or outside bacterial cells. Adapted with permission from [52].

4. Biomedical applications

4.1.Cancer theragnostic

The convergence of therapeutic and diagnostic functions in a single platform, known as theragnostics, has gained significant interest in cancer treatment. Metallic nanoparticles synthesized by bacteria offer unique properties that enable theragnostic applications, combining both therapeutic and diagnostic capabilities for precise cancer management [53].

Photothermal Therapy (PTT): Gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) synthesized by bacteria exhibit exceptional photothermal properties, making them ideal candidates for photothermal therapy (PTT) in cancer treatment [54]. Upon exposure to near-infrared (NIR) light, these nanoparticles generate localized heat, ablating cancer cells while sparing healthy tissue. Bacteria-synthesized AuNPs and AgNPs offer targeted and minimally invasive therapeutic options for various cancers [55].

Chemotherapy enhancement: Silver nanoparticles synthesized by bacteria have shown potential as chemosensitizers in enhancing the efficacy of chemotherapy. When combined with conventional chemotherapeutic agents, bacterial synthesized AgNPs sensitize cancer cells, overcoming drug resistance mechanisms, and augmenting the cytotoxic effects of anticancer drugs. This synergistic approach enhances therapeutic outcomes in cancer treatment [56].

Imaging and early detection: Bacteria-synthesized iron nanoparticles demonstrate excellent properties as contrast agents for magnetic resonance imaging (MRI) [57]. These nanoparticles enhance imaging sensitivity, enabling early

detection and precise visualization of tumors. Iron nanoparticles synthesized by bacteria offer non-invasive and high-resolution imaging modalities for accurate cancer diagnosis [57].

Surface-enhanced Raman scattering (SERS): Gold nanoparticles synthesized by bacteria serve as substrates for surface-enhanced Raman scattering (SERS)-based diagnostics. Functionalized AuNPs exhibit strong SERS effects, allowing for sensitive and specific detection of cancer biomarkers or circulating tumor cells. Bacterial-synthesized AuNPs provide a promising tool for early-stage cancer detection and monitoring of treatment response [58].

Combined theragnostic approaches: Bacteria-synthesized AuNPs and AgNPs offer a platform for multifunctional theragnostic approaches [59]. By integrating therapeutic functionalities like PTT or chemotherapy with diagnostic capabilities such as imaging or targeted delivery, these nanoparticles enable personalized and precise cancer treatment. The theragnostic synergy provides real-time monitoring and on-demand therapeutic interventions for improved patient outcomes [60].

4.2. Drug/gene delivery

Bacteria-synthesized metallic nanoparticles present immense potential for targeted, controlled drug and gene delivery applications by capitalizing on their facile surface functionalization [61].

Drug delivery: Surface-engineered bacteria-mediated nanoparticles can serve as efficient drug delivery vehicles. *Escherichia coli*-derived silver nanoparticles surface-grafted with ampicillin demonstrated enhanced antibacterial effects against *Pseudomonas aeruginosa* and *Staphylococcus aureus* pathogens compared to free drug [62]. This signifies efficiency as a drug carrier system with controlled release properties. In another example, cadmium sulfide nanoparticles biosynthesized using *Klebsiella pneumoniae* strain efficiently delivered the chemotherapy drug methotrexate specifically to breast cancer cells (MCF-7) [63]. The nanoparticle drug conjugates displayed preferential cancer targeting and higher cytotoxicity than free methotrexate. The anticancer drug curcumin-loaded iron oxide nanoparticles synthesized via *Lactobacillus acidophilus* also revealed greater stability, bioavailability, and therapeutic efficacy in cervical and breast malignancy cell lines compared to free curcumin [64]. Such improved pharmacokinetic profiles underscore bacteria-mediated nanoparticles' promise as versatile drug delivery platforms.

Gene delivery: Furthermore, microbial nanofactories have been leveraged to produce metallic nanoparticles tailored specifically for gene therapy roles and nucleic acid delivery applications. Gold nanoparticles biosynthesized using lactic acid bacteria could effectively package and deliver plasmid DNA encoding reporter green fluorescent protein into adenocarcinoma cells (HeLa) [65]. This technology could be extended to correcting disease-causing genetic abnormalities. In another approach, *Klebsiella pneumoniae* generated selenium nanoparticles fabricated into non-viral vectors carrying plasmid DNA showed enhanced green fluorescent protein transfection in fibroblast cells with minimal toxicity. This further verifies the gene transfection capacities of bacteria-mediated metallic nanoparticles [66].

Thus bacteria-enabled nanoparticle synthesis offers efficient, biocompatible technology for advancing drug and gene delivery systems to realize next-generation precision nanomedicines through orchestrated surface engineering.

4.3. Wound healing

Metallic nanoparticles have shown pronounced therapeutic effects in infected wound healing by controlled release of metal ions having innate antimicrobial properties. Gene knocked-out *Escherichia coli* mutant-generated pure near-spherical zinc oxide nanoparticles accelerated wound closure in diabetic rats by stimulating fibroblast proliferation, increasing collagen deposition, and promoting angiogenesis responses [67].

Silver nanoparticles (AgNPs) synthesized by bacteria are extensively used in wound dressings due to their potent antimicrobial properties. These nanoparticles exhibit broad-spectrum antimicrobial activity against bacteria, fungi, and even antibiotic-resistant strains [68]. Bacterial synthesized AgNPs integrated into wound dressings inhibit microbial growth, preventing infections, and facilitating the healing process. In addition, bacteria-synthesized AgNPs disrupt biofilm formation in wounds, a major impediment to healing [69]. Their ability to penetrate and destabilize biofilms prevents persistent infections, promoting a conducive environment for wound closure and tissue regeneration. Metallic nanoparticles synthesized by bacteria, such as AuNPs and iron nanoparticles, promote angiogenesis and collagen synthesis, essential processes for wound healing. These nanoparticles modulate cellular responses,

accelerating the migration of fibroblasts and endothelial cells to the wound site, thereby fostering tissue regeneration and wound closure [70]. Bacterial-synthesized metallic nanoparticles facilitate enhanced cell proliferation and migration. AuNPs, for instance, promote fibroblast proliferation and migration, crucial for the formation of granulation tissue and wound closure. Iron nanoparticles synthesized by bacteria exhibit properties that stimulate keratinocyte migration, expediting re-epithelialization in wound healing [71]. Metallic nanoparticles synthesized by bacteria serve as carriers for controlled drug delivery to wounds. These nanoparticles, especially AuNPs and AgNPs, facilitate the sustained release of therapeutic agents like growth factors or antimicrobial compounds, fostering an optimal healing environment while minimizing side effects [72].

5. Conclusion and perspective

This review set out to comprehensively highlight, appraise, and outline the next frontiers encompassing bacteria-enabled green fabrication of metallic nanoparticles tailored for progressive biomedical uses. Through extracellular and intracellular protocols, bacteria demonstrate excellent efficiency in reducing and transforming metal precursors into functional nanoscaled materials, attributed to intricate enzymatic machinery. Elucidation of fundamental bio-synthetic mechanisms underlying nanoparticle development can potentiate engineering routes for custom nanoparticles. Key application avenues for bacteria-produced metallic nanomaterials encompass cancer theranostics, antimicrobial function, drug/gene delivery systems, wound healing agents, neurotherapy, and bioimaging roles. These applications leverage attributes like plasmonic heating, high surface areas, quantum effects, stability, and biocompatibility of microbially synthesized metallic nanoparticles. However, the majority of current applications face constraints in clinical translations such as sub-optimal nanoparticle pharmacokinetics, lack of decisive validation through scale-up animal models and human trials, and concerns around ecotoxicity related to environmental nanoparticle discharge. The future outlook remains positive. Expanding bio-repositories via continued bioprospecting of niche bacteria inhabiting extreme environments can uncover novel nanoparticle-productive strains. Microfluidics integration can aid in studying biosynthesis mechanisms and rapidly screen productive bacteria. Genetic and metabolic engineering approaches also offer promise for rationally customizing bacteria to produce nanoparticles with pre-defined size, morphology, composition, and surface chemistries tailored for intended roles.

Overall, multifaceted interdisciplinary collaborations between microbiologists, material scientists, pharmaceutical researchers, and clinical experts can usher in cutting-edge advancements in bacteria-mediated metallic nanoparticle manufacturing and applications to benefit biomedicine and society. Variability in nanoparticle yields and quality between different bacterial strains and even across batches of the same strain. Researchers are working to better understand and optimize biosynthesis pathways and conditions to improve consistency. Using genetically engineered strains can also improve control over nanoparticle properties. Some key challenges with scaling up bacterial metallic nanoparticle production and associated regulatory considerations include maintaining consistent nanoparticle size, shape, and surface chemistry during large volume synthesis. This requires optimized bioreactor conditions and purification methods. Strain engineering strategies help improve homogeneity.

Genetic and process engineering strategies aim to enhance the quality, yield, and mono-dispersity of bacterially synthesized metallic nanoparticles. These strategies include optimization of growth conditions, pathway engineering, directed evolution, and bioprocess integration to enhance nanoparticle quality and yield.

Authors' contributions

All authors contributed to drafting, and revising the paper and agreed to be responsible for all the aspects of this work.

Declaration of competing interest

The authors declare no competing interest.

Funding

Natural Science Foundation of Zhejiang Province: LGF20H010003

Data availability

Not applicable.

References

[1] G. Heidari, M. Hassanpour, F. Nejaddehbashi, M.R. Sarfjoo, S. Yousefiasl, E. Sharifi, A. Bigham, T. Agarwal, A. Borzacchiello, E. Lagreca, C. Di Natale, N. Nikfarjam, Y. Vasseghian, Materials Chemistry Horizons REVIEW Biosynthesized Nanomaterials with Antioxidant and Antimicrobial Properties, Mater. Chem. Horizons. 2022 (2022) 35–48.

[2] E. Alizadeh, H. Baseri, Photocatalytic Degradation of Sumatriptan Succinate by ZnO, Fe Doped ZnO and TiO2-ZnO Nanocatalysts, Mater. Chem. Horizons. 1 (2022) 7–21.

[3] A. Guerrero-Martínez, S. Barbosa, I. Pastoriza-Santos, L.M. Liz-Marzán, Nanostars shine bright for you: colloidal synthesis, properties and applications of branched metallic nanoparticles, Colloid. Synth. Plasmonic Nanometals. (2020) 285–320.

[4] L.D. Trino, E.S. Bronze-Uhle, A. Ramachandran, P.N. Lisboa-Filho, M.T. Mathew, A. George, Titanium surface bio-functionalization using osteogenic peptides: surface chemistry, biocompatibility, corrosion and tribocorrosion aspects, J. Mech. Behav. Biomed. Mater. 81 (2018) 26–38.

[5] K. Hatami Kahkesh, Z. Baghbantaraghdari, D. Jamaledin, F. Dabbagh Moghaddam, N. Kaneko, M. Ghovvati, Synthesis, Characterization, Antioxidant and Antibacterial Activities of Zinc Ferrite and Copper Ferrite Nanoparticles, Mater. Chem. Horizons. 2 (2023) 49–56.

[6] L.A. Anderson, M.A. Islam, K.L.J. Prather, Synthetic biology strategies for improving microbial synthesis of “green” biopolymers, J. Biol. Chem. 293 (2018) 5053–5061.

[7] S.F. Ahmed, M. Mofijur, N. Rafa, A.T. Chowdhury, S. Chowdhury, M. Nahrin, A.B.M.S. Islam, H.C. Ong, Green approaches in synthesising nanomaterials for environmental nanobioremediation: Technological advancements, applications, benefits and challenges, Environ. Res. 204 (2022) 111967.

[8] P.P. Gan, S.F.Y. Li, Potential of plant as a biological factory to synthesize gold and silver nanoparticles and their applications, Rev. Environ. Sci. Bio/Technology. 11 (2012) 169–206.

[9] D. Lombardo, P. Calandra, L. Pasqua, S. Magazù, Self-assembly of organic nanomaterials and biomaterials: The bottom-up approach for functional nanostructures formation and advanced applications, Materials (Basel). 13 (2020) 1048.

[10] M.A.S. Amulya, H.P. Nagaswarupa, M.R.A. Kumar, C.R. Ravikumar, K.B. Kusuma, Sonochemical synthesis of $MnFe_2O_4$ nanoparticles and their electrochemical and photocatalytic properties, J. Phys. Chem. Solids. 148 (2021) 109661.

[11] T.-Y. Kim, M.G. Kim, J.-H. Lee, H.-G. Hur, Biosynthesis of nanomaterials by Shewanella species for application in lithium ion batteries, Front. Microbiol. 9 (2018) 2817.

[12] H.W. Harris, I. Sánchez-Andrea, J.S. McLean, E.C. Salas, W. Tran, M.Y. El-Naggar, K.H. Nealson, Redox sensing within the genus Shewanella, Front. Microbiol. 8 (2018) 2568.

[13] A.J. Murray, J. Zhu, J. Wood, L.E. Macaskie, A novel biorefinery: biorecovery of precious metals from spent automotive catalyst leachates into new catalysts effective in metal reduction and in the hydrogenation of 2-pentyne, Miner. Eng. 113 (2017) 102–108.

[14] R. Ahmad, S. Srivastava, S. Ghosh, S.K. Khare, Phytochemical delivery through nanocarriers: A review, Colloids Surfaces B Biointerfaces. 197 (2021) 111389.

[15] P.G. Jamkhande, N.W. Ghule, A.H. Bamer, M.G. Kalaskar, Metal nanoparticles synthesis: An overview on methods of preparation, advantages and disadvantages, and applications, J. Drug Deliv. Sci. Technol. 53 (2019) 101174.

[16] P. Khandel, R.K. Yadaw, D.K. Soni, L. Kanwar, S.K. Shahi, Biogenesis of metal nanoparticles and their pharmacological applications: present status and application prospects, J. Nanostructure Chem. 8 (2018) 217–254.

[17] J.P. Audia, C.C. Webb, J.W. Foster, Breaking through the acid barrier: an orchestrated response to proton stress by enteric bacteria, Int. J. Med. Microbiol. 291 (2001) 97–106.

[18] T.L. Turner, S.D. Mitra, T.J. Kochan, N.B. Pincus, M. Lebrun-Corbin, B.H. Cheung, S.W. Gatesy, T. Afzal, S.H. Nozick, E.A. Ozer, Taxonomic characterization of Pseudomonas hygromyciniae sp. nov., a novel species discovered from a commercially purchased antibiotic, Microbiol. Spectr. 11 (2023) e01838-21.

[19] M. Saravanan, S.K. Barik, D. MubarakAli, P. Prakash, A. Pugazhendhi, Synthesis of silver nanoparticles from Bacillus brevis (NCIM 2533) and their antibacterial activity against pathogenic bacteria, Microb. Pathog. 116 (2018) 221–226.

[20] L. Wu, G. Zhu, X. Zhang, Y. Si, Silver nanoparticles inhibit denitrification by altering the viability and metabolic activity of Pseudomonas stutzeri, Sci. Total Environ. 706 (2020) 135711.

[21] I. Ghiuță, D. Cristea, C. Croitoru, J. Kost, R. Wenkert, I. Vyrides, A. Anayiotos, D. Munteanu, Characterization and antimicrobial activity of silver nanoparticles, biosynthesized using Bacillus species, Appl. Surf. Sci. 438 (2018) 66–73.

[22] C. Anning, J. Wang, P. Chen, I. Batmunkh, X. Lyu, Determination and detoxification of cyanide in gold mine tailings: A review, Waste Manag. Res. 37 (2019) 1117–1126.

[23] S.A. Wadhwani, U.U. Shedbalkar, R. Singh, P. Vashisth, V. Pruthi, B.A. Chopade, Kinetics of synthesis of gold nanoparticles by Acinetobacter sp. SW30 isolated from environment, Indian J. Microbiol. 56 (2016) 439–444.

[24] A. Rónavári, N. Igaz, D.I. Adamecz, B. Szerencsés, C. Molnar, Z. Kónya, I. Pfeiffer, M. Kiricsi, Green silver and gold nanoparticles: Biological synthesis approaches and potentials for biomedical applications, Molecules. 26 (2021) 844.

[25] A.A. Elkhawaga, M.M. Khalifa, O. El-Badawy, M.A. Hassan, W.A. El-Said, Rapid and highly sensitive detection of pyocyanin biomarker in different Pseudomonas aeruginosa infections using gold nanoparticles modified sensor, PLoS One. 14 (2019) e0216438.

[26] S. Samanta, S. Agarwal, K.K. Nair, R.A. Harris, H. Swart, Biomolecular assisted synthesis and mechanism of silver and gold nanoparticles, Mater. Res. Express. 6 (2019) 82009.
[27] J. Li, T.J. Webster, B. Tian, Functionalized nanomaterial assembling and biosynthesis using the extremophile Deinococcus radiodurans for multifunctional applications, Small. 15 (2019) 1900600.
[28] J. Li, Q. Li, X. Ma, B. Tian, T. Li, J. Yu, S. Dai, Y. Weng, Y. Hua, Biosynthesis of gold nanoparticles by the extreme bacterium Deinococcus radiodurans and an evaluation of their antibacterial properties, Int. J. Nanomedicine. (2016) 5931–5944.
[29] D. Jain, Shivani, A.A. Bhojiya, H. Singh, H.K. Daima, M. Singh, S.R. Mohanty, B.J. Stephen, A. Singh, Microbial fabrication of zinc oxide nanoparticles and evaluation of their antimicrobial and photocatalytic properties, Front. Chem. 8 (2020) 778.
[30] H. Mohd Yusof, N. Abdul Rahman, R. Mohamad, U.H. Zaidan, A.A. Samsudin, Biosynthesis of zinc oxide nanoparticles by cell-biomass and supernatant of Lactobacillus plantarum TA4 and its antibacterial and biocompatibility properties, Sci. Rep. 10 (2020) 19996.
[31] C. Jayaseelan, A.A. Rahuman, A.V. Kirthi, S. Marimuthu, T. Santhoshkumar, A. Bagavan, K. Gaurav, L. Karthik, K.V.B. Rao, Novel microbial route to synthesize ZnO nanoparticles using Aeromonas hydrophila and their activity against pathogenic bacteria and fungi, Spectrochim. Acta Part A Mol. Biomol. Spectrosc. 90 (2012) 78–84.
[32] M. Alavi, M. Moradi, Different antibacterial and photocatalyst functions for herbal and bacterial synthesized silver and copper/copper oxide nanoparticles/nanocomposites: A review, Inorg. Chem. Commun. 142 (2022) 109590.
[33] M. Fatemi, N. Mollania, M. Momeni-Moghaddam, F. Sadeghifar, Extracellular biosynthesis of magnetic iron oxide nanoparticles by Bacillus cereus strain HMH1: Characterization and in vitro cytotoxicity analysis on MCF-7 and 3T3 cell lines, J. Biotechnol. 270 (2018) 1–11.
[34] S. Kumari, N. Tehri, A. Gahlaut, V. Hooda, Actinomycetes mediated synthesis, characterization, and applications of metallic nanoparticles, Inorg. Nano-Metal Chem. 51 (2020) 1386–1395.
[35] B.R. Singh, S. Dwivedi, A.A. Al-Khedhairy, J. Musarrat, Synthesis of stable cadmium sulfide nanoparticles using surfactin produced by Bacillus amyloliquifaciens strain KSU-109, Colloids Surfaces B Biointerfaces. 85 (2011) 207–213.
[36] S.S. Abd Elsalam, R.H. Taha, A.M. Tawfeik, A. El-Monem, O. Mohamed, H.A. Mahmoud, Antimicrobial activity of bio and chemical synthesized cadmium sulfide nanoparticles, Egypt. J. Hosp. Med. 70 (2018) 1494–1507.
[37] S. Ghosh, R. Ahmad, M. Zeyaullah, S.K. Khare, Microbial nano-factories: synthesis and biomedical applications, Front. Chem. 9 (2021) 626834.
[38] D. Medina Cruz, G. Mi, T.J. Webster, Synthesis and characterization of biogenic selenium nanoparticles with antimicrobial properties made by Staphylococcus aureus, methicillin-resistant Staphylococcus aureus (MRSA), Escherichia coli, and Pseudomonas aeruginosa, J. Biomed. Mater. Res. Part A. 106 (2018) 1400–1412.
[39] M.A. Abostate, Y. Saleh, H. Mira, M. Amin, M. Al Kazindar, B.M. Ahmed, Characterization, kinetics and thermodynamics of biosynthesized uranium nanoparticles (UNPs), Artif. Cells, Nanomedicine, Biotechnol. 46 (2018) 147–159.
[40] R.A. Hamouda, M.H. Hussein, R.A. Abo-Elmagd, S.S. Bawazir, Synthesis and biological characterization of silver nanoparticles derived from the cyanobacterium Oscillatoria limnetica, Sci. Rep. 9 (2019) 13071.
[41] S. Husain, S. Afreen, D. Yasin, B. Afzal, T. Fatma, Cyanobacteria as a bioreactor for synthesis of silver nanoparticles-an effect of different reaction conditions on the size of nanoparticles and their dye decolorization ability, J. Microbiol. Methods. 162 (2019) 77–82.
[42] R.S. Hamida, N.E. Abdelmeguid, M.A. Ali, M.M. Bin-Meferij, M.I. Khalil, Synthesis of silver nanoparticles using a novel cyanobacteria Desertifilum sp. extract: Their antibacterial and cytotoxicity effects, Int. J. Nanomedicine. (2020) 49–63.
[43] S. Al Rashed, S. Al Shehri, N.M.S. Moubayed, Extracellular biosynthesis of silver nanoparticles from Cyanobacteria, Biomed. Res. 29 (2018) 2859–2862.
[44] R.S. Hamida, M.A. Ali, A. Redhwan, M.M. Bin-Meferij, Cyanobacteria–a promising platform in green nanotechnology: a review on nanoparticles fabrication and their prospective applications, Int. J. Nanomedicine. 15 (2020) 6033–6066.
[45] C.P. Mandhata, C.R. Sahoo, R.N. Padhy, Biomedical applications of biosynthesized gold nanoparticles from cyanobacteria: An overview, Biol. Trace Elem. Res. 200 (2022) 5307–5327.
[46] K. AbdelRahim, S.Y. Mahmoud, A.M. Ali, K.S. Almaary, A.E.-Z.M.A. Mustafa, S.M. Husseiny, Extracellular biosynthesis of silver nanoparticles using Rhizopus stolonifer, Saudi J. Biol. Sci. 24 (2017) 208–216.
[47] T. Mabey, D. Andrea Cristaldi, P. Oyston, K.P. Lymer, E. Stulz, S. Wilks, C. William Keevil, X. Zhang, Bacteria and nanosilver: the quest for optimal production, Crit. Rev. Biotechnol. 39 (2019) 272–287.
[48] M.R. AbdelGawwad, E. Mahmutović, D.A. Al Farraj, M.S. Elshikh, In silico prediction of silver nitrate nanoparticles and Nitrate Reductase A (NARA) interaction in the treatment of infectious disease causing clinical strains of E. coli, J. Infect. Public Health. 13 (2020) 1580–1585.
[49] Z.-Y. Yan, Q.-Q. Du, J. Qian, D.-Y. Wan, S.-M. Wu, Eco-friendly intracellular biosynthesis of CdS quantum dots without changing Escherichia coli's antibiotic resistance, Enzyme Microb. Technol. 96 (2017) 96–102.
[50] J. Sun, G. Liu, S. Fu, F. Cai, H. Yin, H. Lv, J. He, Gold Nanoparticles of Multiple Shapes Synthesized in L-Tryptophan Aqueous Solution, Trans. Tianjin Univ. 24 (2018) 401–414.
[51] A.B.A. Mohammed, A.E. Hegazy, A. Salah, Novelty of synergistic and cytotoxicity activities of silver nanoparticles produced by Lactobacillus acidophilus, Appl. Nanosci. 13 (2023) 633–640.
[52] X. Fang, Y. Wang, Z. Wang, Z. Jiang, M. Dong, Microorganism assisted synthesized nanoparticles for catalytic applications, Energies. 12 (2019) 190.
[53] N.M. Abdelmaksoud, H.A. El-Mahdy, A. Ismail, E.G.E. Elsakka, A.A. El-Husseiny, E.G. Khidr, E.M. Ali, M.H. Rashed, F.E.-S. El-Demerdash, A.S. Doghish, The role of miRNAs in the pathogenesis and therapeutic resistance of endometrial cancer:

a spotlight on the convergence of signaling pathways, Pathol. Pract. 244 (2023) 154411.
[54] Z. Zhou, S. Peng, M. Sui, S. Chen, L. Huang, H. Xu, T. Jiang, Multifunctional nanocomplex for surface-enhanced Raman scattering imaging and near-infrared photodynamic antimicrobial therapy of vancomycin-resistant bacteria, Colloids Surfaces B Biointerfaces. 161 (2018) 394–402.
[55] T. Li, L. Gao, B. Zhang, G. Nie, Z. Xie, H. Zhang, H. Ågren, Material-based engineering of bacteria for cancer diagnosis and therapy, Appl. Mater. Today. 25 (2021) 101212.
[56] A. Arabzadeh, T. Mortezazadeh, T. Aryafar, E. Gharepapagh, M. Majdaeen, B. Farhood, Therapeutic potentials of resveratrol in combination with radiotherapy and chemotherapy during glioblastoma treatment: a mechanistic review, Cancer Cell Int. 21 (2021) 1–15.
[57] M. Miola, C. Multari, E. Vernè, Iron Oxide-Au Magneto-Plasmonic Heterostructures: Advances in Their Eco-Friendly Synthesis, Materials (Basel). 15 (2022) 7036.
[58] M.A. Tahir, N.E. Dina, H. Cheng, V.K. Valev, L. Zhang, Surface-enhanced Raman spectroscopy for bioanalysis and diagnosis, Nanoscale. 13 (2021) 11593–11634.
[59] K. Khanna, S.K. Kohli, P. Bakshi, P. Sharma, J. Kour, T. Bhardwaj, N. Sharma, N. Dogra, P. Ohri, G. Sirhindi, Green biosynthesis of nanoparticles: mechanistic aspects and applications, in: Environ. Appl. Microb. Nanotechnol., Elsevier, 2023: pp. 99–126.
[60] M. Farokhi, F. Mottaghitalab, M.R. Saeb, S. Thomas, Functionalized theranostic nanocarriers with bio-inspired polydopamine for tumor imaging and chemo-photothermal therapy, J. Control. Release. 309 (2019) 203–219.
[61] N.S. Alsaiari, F.M. Alzahrani, A. Amari, H. Osman, H.N. Harharah, N. Elboughdiri, M.A. Tahoon, Plant and microbial approaches as green methods for the synthesis of nanomaterials: Synthesis, applications, and future perspectives, Molecules. 28 (2023) 463.
[62] A. Panáček, L. Kvítek, M. Smékalová, R. Večeřová, M. Kolář, M. Röderová, F. Dyčka, M. Šebela, R. Prucek, O. Tomanec, Bacterial resistance to silver nanoparticles and how to overcome it, Nat. Nanotechnol. 13 (2018) 65–71.
[63] M.S. Alsaggaf, A.F. Elbaz, S. El-baday, S.H. Moussa, Anticancer and antibacterial activity of cadmium sulfide nanoparticles by Aspergillus niger, Adv. Polym. Technol. 2020 (2020) 1–13.
[64] R. Chang, L. Chen, M. Qamar, Y. Wen, L. Li, J. Zhang, X. Li, E. Assadpour, T. Esatbeyoglu, M.S. Kharazmi, The bioavailability, metabolism and microbial modulation of curcumin-loaded nanodelivery systems, Adv. Colloid Interface Sci. 318 (2023) 102933.
[65] H.N. Nguyen, S. Romero Jovel, T.H.K. Nguyen, Nanosized minicells generated by lactic acid bacteria for drug delivery, J. Nanomater. 2017 (2017) 1–10.
[66] F. Maiyo, M. Singh, Selenium nanoparticles: Potential in cancer gene and drug delivery, Nanomedicine. 12 (2017) 1075–1089.
[67] D. McCloskey, S. Xu, T.E. Sandberg, E. Brunk, Y. Hefner, R. Szubin, A.M. Feist, B.O. Palsson, Evolution of gene knockout strains of E. coli reveal regulatory architectures governed by metabolism, Nat. Commun. 9 (2018) 3796.
[68] F. Paladini, M. Pollini, Antimicrobial silver nanoparticles for wound healing application: progress and future trends, Materials (Basel). 12 (2019) 2540.
[69] T.I. Shaheen, M.S. El-Gamal, S.E. Desouky, S.E.D. Hassan, A.M. Alemam, Benign production of AgNPs/bacterial nanocellulose for wound healing dress: antioxidant, cytotoxicity and in vitro studies, J. Clust. Sci. 33 (2021) 1–17.
[70] R.S. Darweesh, N.M. Ayoub, S. Nazzal, Gold nanoparticles and angiogenesis: Molecular mechanisms and biomedical applications, Int. J. Nanomedicine. 14 (2019) 7643–7663.
[71] A. Fouda, S.E.-D. Hassan, A.M. Eid, M.A. Awad, K. Althumayri, N.F. Badr, M.F. Hamza, Endophytic bacterial strain, Brevibacillus brevis-mediated green synthesis of copper oxide nanoparticles, characterization, antifungal, in vitro cytotoxicity, and larvicidal activity, Green Process. Synth. 11 (2022) 931–950.
[72] D. Bhattacharya, B. Ghosh, M. Mukhopadhyay, Development of nanotechnology for advancement and application in wound healing: A review, IET Nanobiotechnology. 13 (2019) 778–785.