Biological synthesis of silver nanoparticles and their medical applications (Review)

ADNAN AHMAD[1], MOHAMMAD HANEEF[1], NABEEL AHMAD[2], AZHAR KAMAL[1], SAMRIDDHI JASWANI[1] and FARIYA KHAN[3]

[1]Integral Information and Research Centre (IIRC), Integral University, Lucknow, Uttar Pradesh 226026; [2]Department of Biotechnology, School of Allied Sciences, Dev Bhoomi Uttarakhand University, Dehradun, Uttarakhand 248007; [3]Stem Cell Research Centre, Department of Hematology, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, Uttar Pradesh 226014, India

Received November 1, 2023; Accepted February 21, 2024

DOI: 10.3892/wasj.2024.237

Abstract. The green synthesis of silver nanoparticles (AgNPs) represents a paradigm shift in the field of nanotechnology by offering a sustainable and eco-friendly alternative to traditional methods of synthesis. By harnessing the reducing and stabilizing properties of natural sources, such as plants, fungi and microorganisms, researchers have been able to synthesize AgNPs with reduced toxicity and heightened biocompatibility. These unique nanoparticles have ushered in a new era of possibilities in the medical field. The notable antimicrobial properties of silver render it indispensable for wound healing, infection control, cancer therapy and tissue regeneration applications. Additionally, AgNPs hold great promise as versatile drug carriers for targeted therapies and as contrast agents for advanced medical imaging techniques. In an era characterized by increasing environmental concerns and the need for innovative healthcare solutions, the green synthesis of AgNPs revolutionizes medical practices and aligns with the imperative of sustainability, underscoring its pivotal role at the nexus of nanotechnology and medicine.

Contents

Correspondence to: Professor Nabeel Ahmad, Department of Biotechnology, School of Allied Sciences, Dev Bhoomi Uttarakhand University, Chakrata Road, Dehradun, Uttarakhand 248007, India
E-mail: nabeel.biotech@gmail.com

Key words: nanoparticles, cancer, nanosensors, green synthesis, silver nanoparticles, nanomedicine

1. Introduction

Nanotechnology represents an advanced scientific discipline focused on the fabrication, manipulation and control of particle structures within the size range of 1 to 100 nm. The fundamental building blocks of nanotechnology primarily comprise nanoparticles (1,2). Notably, biological entities, including microorganisms and living cells, stand as exemplary instances of nanoscale machines equipped with functional components. These entities perform an array of tasks, from energy generation to precise material extraction, with exceptional efficiency (3). Various examples illustrate how biological components have been harnessed to synthesize nanoparticles with diverse chemical compositions: Ribosomes are employed in the production of gold nanoparticles (4); bacteria have been utilized in the synthesis of cadmium sulfide (5,6), zinc sulfide (7), magnetite (8), iron sulfide (9) and silver (10,11) nanoparticles (AgNPs); yeasts have played a role in the formation of lead sulfide and cadmium sulfide nanoparticles. Furthermore, the green synthesis of AgNPs utilizing the extract of *Emblica officinalis* herbal fruit exemplifies an alternative approach (12). Notably, individual atoms/molecules and their bulk counterparts exhibit profound disparities in chemical, physical and biological properties as a function of their size. Owing to the emergence of entirely novel or modified characteristics arising from size, classification and morphology, novel applications for nanoparticles and nanomaterials are rapidly expanding, providing compelling evidence of their transformative potential in various scientific domains (13). Nanoparticles have captured the keen interest of researchers due to their versatility in size and form, enabling their sophisticated integration into biotechnological applications. Within the pharmaceutical sector, nanoparticles have gained prominence for their potent antimicrobial properties (14) and their prominent anticancer activity (15,16).

Nanobiotechnology, a multidisciplinary field at the intersection of engineering, physics and biology, focuses on the development of minute physical and biological devices through biomimetic nanofabrication techniques. Biomimicry draws inspiration from the self-assembly of molecules within natural systems, particularly in aqueous environments (17). The synthesis of nanoparticles through microbial involvement underscores the intertwined association between nanotechnology and microbial biotechnology, embodying an environmental friendly approach (18,19).

The continuous advancement of nanoscience and technology has ushered in novel and enhanced nano-methodologies, rendering previous approaches obsolete. Nanotechnology has garnered significant interest due to the unique properties exhibited by nanoscale materials, offering a wide spectrum of potential applications in scientific research. The imperative of adopting a green chemistry approach in the development of nanomaterials cannot be overstated. Within the domain of nanobiotechnology, this approach holds the promise of yielding sustainable nanomaterials that are environment-friendly and poised for widespread acceptance in the realm of nanotechnology. It is crucial to emphasize that the selection of solvents and reducing agents employed in the synthesis of nanoparticles has a profound influence on the resulting particle morphology, encompassing size, physicochemical attributes and shape. This morphology, in turn, has a pivotal impact on the utilization and performance of nanoparticles (20-23).

2. Different strategies for the genesis of nanoparticles

The methodologies of 'top-down' and 'bottom-up' approaches in nanoparticle assembly represent fundamental paradigms. The 'bottom-up' approach entails the initial formation of nanostructure building blocks, which are subsequently assembled to create the final material. Conversely, the top-down approach leverages lithographic and non-lithographic fabrication technologies. Lithography, a cornerstone technology in semiconductor chip and component fabrication, finds application in the top-down approach (24).

The fabrication of micro- and nanoscale system components, spanning from micrometers to nanometers, often relies on the top-down approach. Emerging techniques in material integration, such as artificial methodologies for nanoscale material assembly, introduce additional steps to the process. The degree of control required over the dimensions of nanostructure elements, their spatial arrangement, and their integration into the ultimate material varies significantly, contingent upon the specific requirements of the final product. Broadly, nanoparticle synthesis encompasses three primary approaches: Physical, chemical and biological methods, as represented in Fig. 1 (25).

Physical techniques for nanoparticle synthesis. The 'top-down' approach stands as the conventional and tangible method for nanoparticle assembly, involving the reduction in size of the material through various physical processes, including ultrasonication, microwave irradiation and electrochemical conditions. In this approach, a tube oven, often operated under controlled atmospheric pressure, is employed to combine nanoparticles through a process known as dissolution condensation. Within this framework, two primary physical methods, namely evaporation condensation and laser ablation, emerge as significant techniques.

In the evaporation condensation process, the source material undergoes vaporization within a chamber, subsequently directed onto a furnace to form a carrier gas stream. This vaporized material condenses to yield nanoparticles. Notably, this vapor condensation method has been employed successfully in the production of various nanoparticles, including those composed of silver (Ag), gold (Au), lead (Pb) and cadmium (Cd) (26).

Methodology for the chemical-based synthesis of nanoparticles. In the chemical approach to nanoparticle synthesis, the key constituents involve metallic intermediates, stabilizing agents and reducing agents, encompassing both inorganic and organic compounds. Among the notable reducing agents employed in this methodology are sodium citrate, ascorbate, elemental hydrogen, sodium borohydride, the polyol process, Tollens' reagent, N,N-dimethylformamide and poly (ethylene glycol)-block copolymers (27). These reducing agents play a pivotal role in the controlled reduction of metallic intermediates, facilitating the precise formation of nanoparticles with tailored characteristics and properties.

Biological synthesis of nanoparticles: Sustainable solutions for advanced nanoparticles. In recent years, there has been a growing interest in the development and production of environmentally friendly nanoparticles that do not generate toxic and harmful waste byproducts during their production. Organisms, from simple prokaryotic bacteria to more complex eukaryotic fungi and plants exhibit considerable potential in nanoparticle synthesis. Biological synthesis methods have emerged as a viable approach to obtaining AgNPs, wherein reduction agents sourced from vegetable and fruit extracts are utilized (28). AgNPs find extensive applications in the fields of biomedical engineering, nanomedicine (29), and various biological contexts, offering mechanisms for anti-inflammatory, anti-bacterial, anti-fungal and anticancer activities (30).

As an alternative to traditional physical and chemical methodologies, achieving environmentally benign nanoparticle synthesis necessitates the utilization of biologically safe and ecologically sustainable processes. This approach is integral to the domain of nanobiotechnology, which involves the applications of various biotechnological techniques to fabricate nanomaterials or nanostructures through biological processes, encompassing microorganisms, plants, pathogens and their byproducts, such as proteins and lipids. The bottom-up production of nanomaterials through these biologically inspired methods is inherently more environmentally friendly, as it harnesses the capabilities of biological systems or their derivatives (31).

Research has extensively investigated the role of bacteria in the synthesis of AgNPs. One evident example involved the production of highly stable AgNPs with a diameter of 40 nm through the bioreduction of silver ions in an aqueous solution using the culture supernatant of the non-pathogenic bacterium, *Bacillus licheniformis*. Additionally, well-dispersed silver nanocrystals, ~50 nm, were successfully synthesized utilizing *Bacillus licheniformis* bacteria. The other bacteria

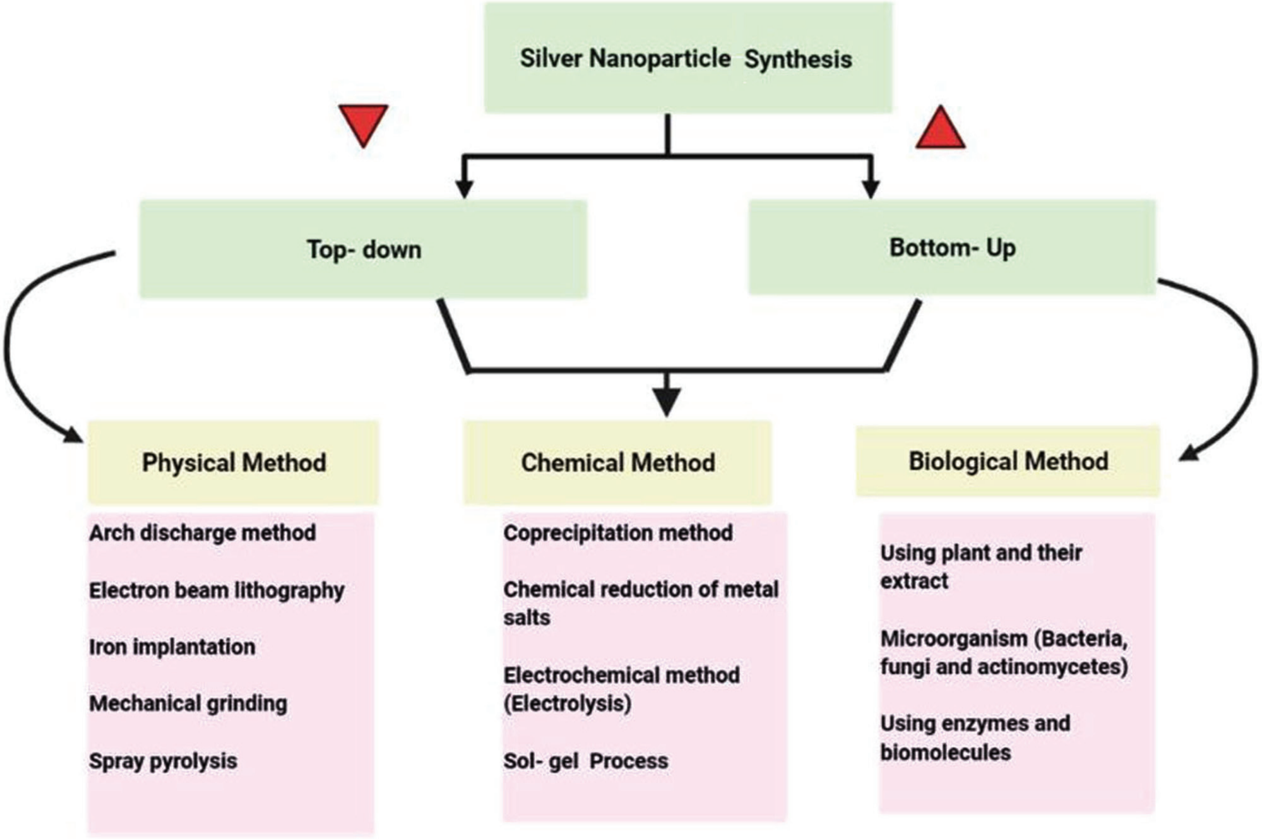

Figure 1. Approaches and method for the synthesis of nanoparticles. The figure has been modified from a figure in a previous study (25).

useful in the synthesis of AgNPs are *Enterobacter cloacae*, *Klebisella pneumoniae* and *Lactobacillus* strains (32).

Not only bacteria, but the synthesis of AgNPs, can also be achieved with the help of fungi. One of the prominent examples of fungi useful in the production of AgNPs is the use of *Aspergillus flavus*. These nanoparticles are stable in water with no significant accumulation for 3 months. Along with this, *Fusarium oxysporum*, *Verticillium sp., Fusarium semitectum* are also utilized for the synthesis of AgNPs (26).

Apart from bacteria and fungi, plants and algae have also been proven to be useful in the green synthesis of AgNPs. The different plants which are useful are *Pinus eldarica*, *Emblica officinalis*, *Aloe vera* leaf extract, *Acalypha indica*, *Pelargonium graveolens*. The AgNPs are produced within 30 min using the leaf extracts of *Acalypha indica*. The advantage of these nanoparticles is that they exhibit exceptional antimicrobial activity against those causative agents or organisms that transmit diseases through water. The different algae used are *Spirulina platensis*, *Oscillatoria willei,* and *Gelidiella acerosa*. Algae are favored for nanoparticle synthesis due to their prominent capacity to accumulate metals and reduce metal ions. Their advantages include rapid and swift growth, ease of handling, and a growth rate greater than that of higher plants (33).

3. Key factors influencing the biological synthesis of nanoparticles

The biological synthesis of nanoparticles relies primarily on three critical factors: The selection of materials, the selection of a reducing agent and the nature of the solvent employed. Within this context, two key processes, Ostwald ripening and oriented attachment play pivotal roles in determining the growth of nanostructures. Oriented attachment is a mechanism wherein two individual nanoparticles self-organize into a single crystal structure, driven by a shared crystallographic orientation. At the nanoscale, this process assumes prominence as a dominant growth mechanism. It is noteworthy that capping agents, which directly influence the nanoparticle surface, can exert a marked and beneficial impact on OA processes. Additionally, the molecular weight of these capping ligands emerges as a crucial factor influencing the assembly behavior of nanoparticles (31).

Surface functionalization stands as a vital facet of nanoparticle synthesis, particularly when designing nanomaterials or nanotubes for specific applications. The production of nanostructured materials, including metal nanoparticles (e.g., silver, gold, copper, platinum and palladium), has garnered immense interest due to their unique attributes, rendering them versatile assets across various domains, including technology and research. This progress in nanomaterials has the potential to revolutionize our tactile, visual, and sensory experiences (34).

The other factors that influence the biological synthesis of nanoparticles are the pH, temperature, reaction time, the purity of ingredients, and the underlying mechanism of the synthesis of nanoparticles.

Sustainable gains: The advantages of biological synthesis in nanoparticle production. Biological synthesis, in contrast to

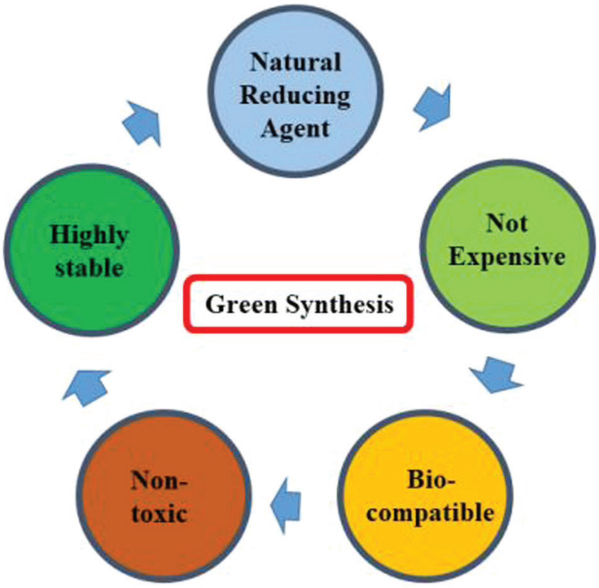

Figure 2. Importance of green nanoparticles.

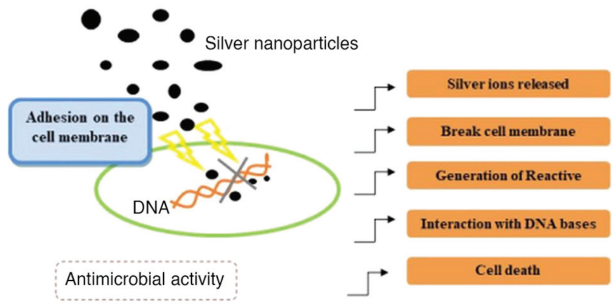

Figure 3. Potential mechanisms for the antimicrobial activity of AgNPs.

chemical and physical methods, offers environmental sustainability by minimizing the ecological impact compared to the physical and chemical methods; it is a cost-effective and widely adopted approach for the large-scale production of nanoparticles, obviating the need for extreme temperatures, pressure or hazardous substances (35).

In the past, the creation of nanoparticles through chemical and physical processes often involved the use of hazardous compounds that posed significant health risks. Research has demonstrated the capability of plant proteins to sequentially reduce metallic ions into nanoparticles, presenting a biologically driven and environmentally benign approach that is not only cost-effective but also safe for human health (36). Nanoparticles synthesized utilizing living organisms have garnered considerable attention due to their notable optical, chemical, photoelectrochemical and electrical properties. This burgeoning field has led to the development of various methods for the synthesis of nanocomposites, involving both nano- and micro-sized inorganic materials. This emerging domain, known as nanocomposites biosynthesis, holds significant promise, provided it can leverage clean, safe and environmentally friendly processes, akin to 'green alchemy'. Such processes may encompass a range of biological contributors, from microorganisms to insects and even plants, facilitating the integration and assembly of nanoparticles (37,38).

Notably, plant-derived nanoparticles exhibit enhanced stability and faster production rates compared to bacterial counterparts, further underscoring their potential in this exciting field of research. The importance of biologically synthesized nanoparticles is summarized in Fig. 2.

4. Unraveling the antimicrobial mechanisms of AgNPs

While the precise mechanisms underlying the antimicrobial action of AgNPs remain partially elucidated, existing research suggests that these nanoparticles exert their effects by disrupting cell membrane permeability, interfering with cellular respiration processes and instigating the production of free radicals. These multifaceted actions collectively contribute to the antibacterial efficacy of silver nanoparticles (39).

Notably, AgNPs possess the capacity to breach the bacterial cell wall, thereby penetrating the cell and inducing significant alterations in the cell membrane, such as increased permeability and ultimately, cell death. This process is often accompanied by the formation of depressions or 'pits' on the cell surface, where nanoparticles accumulate. Additionally, it has been proposed that AgNPs may release silver ions, which can bind to thiol groups found in essential enzymes, rendering them inactive (40).

Silver, which does not react with weak acids, exhibits an innate propensity to react with a base, such as soft bases including sulfur and phosphorus, which constitute key components within most cells. The interaction between these nanoparticles and cellular components can initiate reactions that influence cellular viability. Furthermore, it is worth noting that DNA typically contains sulfur, and nanoparticles may interact with these bases, potentially causing damage to the DNA molecule, and thereby contributing to cell demise (41,42) (Fig. 3).

Several lines of evidence suggest that silver ions play a pivotal role in the antibacterial activity of silver nanoparticles. Notably, the surface area of the nanomaterial emerges as a critical determinant in the antimicrobial toxicity of silver nanoparticles. It has been observed that the highest concentration of released silver ions occurs in conjunction with silver nanoparticles possessing the greatest surface area. For some researchers, the release of silver ions is considered the primary mechanism underpinning the antimicrobial action of silver nanoparticles, with the specific characteristics of individual particles being of secondary importance (43,44).

Determinants of bactericidal properties in AgNPs. Numerous investigations have consistently demonstrated that the shape, size, concentration and colloidal state of AgNPs wield substantial influence over their bactericidal activities (45,46). It has been observed that the stability and biocompatibility of AgNPs are enhanced when their size is reduced. The morphological characteristics of nanoparticles stand as critical determinants of their fundamental physicochemical properties, profoundly affecting their interactions with bacteria, fungi and viruses.

Notably, truncated triangular AgNPs have exhibited superior antibacterial efficacy compared to spherical or rod-shaped counterparts. The variability in AgNP morphologies, despite possessing equivalent surface areas, is attributed to differences

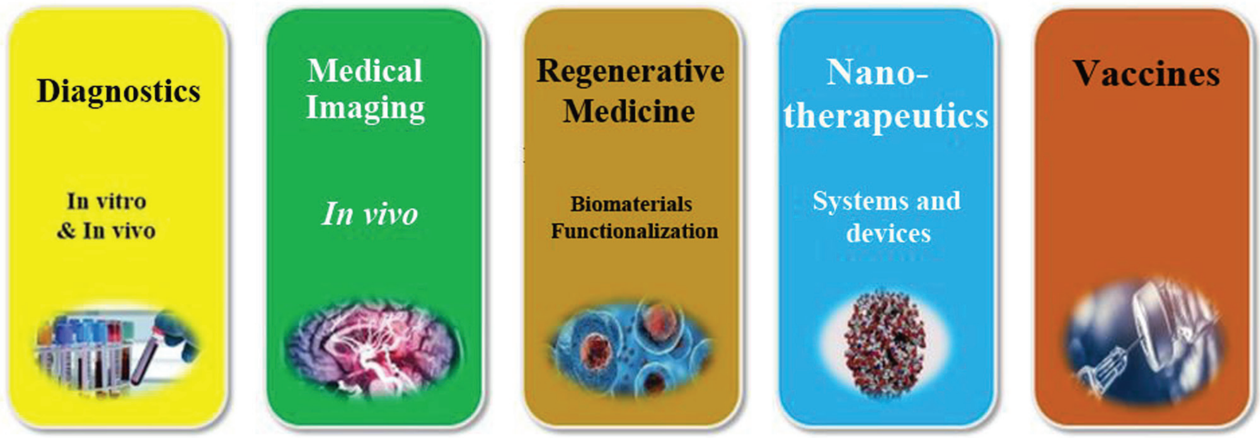

Figure 4. Nanomedicines used in the 21st century.

in effective surface dimensions and dynamic attributes (47). Specifically, AgNPs with diameters falling within the range of 10 to 15 nm have demonstrated heightened stability, biocompatibility and antibacterial activity. Notably, the antibacterial effect is contingent upon the nanoparticle concentration, yet it remains unaffected by the acquisition of drug resistance by bacteria (48,49).

AgNPs exhibit antibacterial properties against a broad spectrum of microorganisms, fungi, as well as viruses. Consequently, they are frequently employed as antimicrobial agents in a wide range of products, such as bandages, textiles, composites, dressings, toothbrushes, cosmetics and surgical instruments. It is worth highlighting that the size and morphology of nanoparticles exert profound influences on their antimicrobial activity, as different morphologies present distinct interaction domains for microorganisms, thereby resulting in variable antibacterial effectiveness (50).

5. Nanotechnology in medicine: Advanced applications and technical insights

In December, 2002, the US National Institutes of Health (NIH) initiated a comprehensive 4-year study encompassing nanoscience and nanotechnology in the context of healthcare (51). In its broadest definition, nanomedicine represents the utilization of molecular structures and insights derived from the human body to identify, treat, and prevent diseases and traumatic injuries, while also alleviating pain and enhancing human vitality. The application of nanotechnology within the realm of medicine is commonly referred to as nanomedicine (52).

Given that various components within cells operate at the nanoscale, nanotechnology emerged as a promising avenue for advancing biology and medicine. The applications of nanotechnology in healthcare and therapeutics encompass drug delivery systems, diagnostic techniques, therapeutic imaging, implantable materials and tissue regeneration technologies. Notably, a diverse array of nanomedicine products have received approval from the US Food and Drug Administration (FDA) and are currently available in the market. However, recent clinical investigations have increasingly focused on more intricate materials, including micelles, protein-based nanoparticles, and various inorganic and silver-based nanoparticles (53). These endeavors underscore the evolving landscape of nanomedicine and its potential to revolutionize healthcare.

Intersecting frontiers: The role of nanomedicine across medical disciplines. Nanomedicine is characterized as a pivotal and highly efficacious instrument within the domains of personalized, targeted and regenerative medicine. It stands at the forefront, ushering in the next generation of medical interventions, therapies and implantable devices, thereby delivering substantial advancements in healthcare (Fig. 4). Furthermore, nanomedicine provides potent and profound methodologies for addressing the challenges posed by demographic aging. It is widely recognized as an indispensable element in achieving superior and economically efficient healthcare systems, thus playing a pivotal role in ensuring the widespread accessibility and affordability of medications and treatments for all individuals (54).

COVID-19 nanomedicines: Advancements in the treatment of the pandemic. The global outbreak of COVID-19 has had profoundly adverse repercussions worldwide, presenting one of the most formidable challenges to global public health in recent memory. Advances in nanotechnology have played a pivotal role in expediting diagnostic testing and, perhaps even more significantly, in the rapid development of vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The global scientific community has responded with notable speed to address the pressing global health crisis.

Nanomedical innovations have greatly contributed to the development of three COVID-19 vaccines. The initial two vaccines, developed by Pfizer/BioNTech and Moderna, utilize lipid nanoparticles to encapsulate, stabilize and deliver mRNA molecules. By contrast, the Novavax vaccine employs a distinct recombinant protein nanoparticle platform to generate antigens derived from the spike protein of SARS-CoV-2 (55). These breakthroughs underscore the pivotal role of nanotechnology in the global effort to combat the COVID-19 pandemic.

Nanomedicine in oncology and progress in cancer therapies. Cancer represents one of the world's most prevalent and lethal diseases, posing a significant risk to >10 million individuals each year (7). The landscape of cancer detection and treatment stands on the brink of a potential revolution, courtesy of advancements in nanotechnology. These advancements, driven by progress in materials science and protein engineering, offer new rays of hope for individuals battling cancer (56).

Lack of specificity, short half-life, cytotoxicity, poor solubility, multi-drug resistance and the formation of stem-like cells are some of the issues that are associated with current chemotherapeutics. To combat these drawbacks, patients with cancer are being treated with nanomaterial-based chemotherapy, targeted therapy, molecular therapy, photothermal therapy, photodynamic therapy, sonodynamic therapy and chemodynamic therapy. With the development of nanotechnology, nanomedicines employed in cancer therapy may be able to lessen the side-effects associated with chemotherapy (57).

The use of nanotechnology in the treatment, diagnosis, or management of cancerous cells enhances the drug concentration within cells, either by active targeting or passive targeting, while minimizing the toxicity to healthy tissue. These targeted nanoparticles can be engineered and modified to be either pH- or temperature-sensitive, allowing for controlled drug release (58).

Conventional cancer therapeutics are often accompanied by severe limitations, driving the exploration and application of various nanotechnologies for more precise and effective cancer treatment, collectively referred to as cancer nanomedicine. Numerous therapeutic nanoparticles have gained acceptance for targeting tumors, encompassing lipid nanoparticles, albumin nanoparticles, polymeric micelles and a plethora of other nanotechnology-enabled treatment modalities. Additionally, approaches such as targeted drug delivery, hyperthermia, radiation therapy, DNA or RNA interference therapies, as well as monoclonal antibodies, are gaining increasing attention within clinical trials and are poised to reshape the landscape of cancer treatment (59). These developments hold the promise of enhancing the efficacy and precision of cancer medicine, potentially improving the outcomes of patients with cancer.

Nanomedicine revolutionizing cardiology. Researchers are actively pursuing less invasive therapies for diseases, such as diabetes and heart-related conditions, and nanotechnology is offering promising avenues for these advancements. In the realm of cardiovascular gene therapy, a multifaceted process is at play, involving the identification of a protein capable of stimulating blood vessel growth, the synthesis and encapsulation of DNA strands containing the gene responsible for producing this protein, and the precise delivery of this DNA to cardiac muscle tissues.

Nanotechnology also facilitates the creation of muscle-powered nanoparticles, which possess the ability to transmit signals into cells, potentially serving as replacements for various tissues that have lost their biological function, such as the sinoatrial node. Additionally, nanotechnology holds the potential to enhance the immunogenicity of cardiac implantable devices and exert control over key limiting factors at the cellular level in procedures, such as percutaneous transluminal coronary angioplasty. This influence may markedly affect the management of infections, particularly those that are often challenging to treat and carry a high risk, such as coronary artery disease (60). Another application of nanotechnology in cardiology involves the detection of complementary DNA strands, relying on the identification of single-walled carbon nanotube complexes containing single-stranded DNA. These innovations underscore the transformative potential of nanotechnology in advancing cardiovascular medicine and diagnosis.

Regenerative nanomedicine and tissue regeneration. Tissue engineering represents a multidisciplinary approach that amalgamates principles from engineering and biological sciences to enhance, restore, or replace the functionality of tissues and organs within the human body. The overarching objective is to provide a customized tissue scaffold that the body recognizes as 'self' and employs to generate 'neo-native' functional cells. The ultimate aim is to enable the body's own cellular components to engage in the process of self-repair. Nevertheless, the demand for transplantable organs far exceeds the available supply, prompting exploration into regenerative therapies as a potential solution to this pressing issue. Nanotechnology emerges as a promising tool capable of accelerating the advancement of organ engineering (61).

The future of advanced healthcare appears poised to leverage nanotechnology, potentially deploying nanorobots implanted within patients to deliver therapies at the cellular level. This innovation offers the prospect of gaining deeper insight into the behavior of cells, bacteria, viruses and other biological entities. It may facilitate the identification and prevention of emerging diseases, restore lost sensory capabilities, streamline genome sequencing processes, enhance the ability to trace and comprehend the underlying biological origins of mental illnesses and spark renewed curiosity and exploration. Nanomaterials have the potential to play a pivotal role in bioengineering, particularly in the field of bioprinting, where nanomaterial-based structures, including proliferation agents, are employed to artificially stimulate cell growth. Progress in nanotechnology-driven tissue engineering holds the promise of extending the lifespan of both humans and other animals (62). These developments represent groundbreaking strides in the pursuit of advanced healthcare solutions.

Nanomedicine as a tool for transforming drug delivery strategies. Nanovehicles, comprising nano-elements engineered for precise localization within specific regions of the body where they are needed to enhance therapeutic outcomes, have emerged as a profoundly significant application of nanotechnology over the past decade. The primary objective of these nanodevices is to enhance treatment effectiveness, while concurrently reducing the levels of toxicity associated with medical interventions (63). Consequently, nanodiagnostics and nanodrugs have been developed to enhance pharmacokinetic properties, thereby facilitating the precise delivery of therapeutic doses, reducing the severe toxicities often associated with conventional drugs in current medical practice, and ultimately improving patient health. This advancement has paved the way for a diverse array of medications that harness nanocarriers and innovative administration routes, marking a transformative shift in healthcare delivery and patient outcomes.

Nanomedicine as a cargo for gene delivery. Traditionally, three primary techniques have been employed for gene transfer: Physical methods, chemical approaches and viral systems. However, recent technological advancements have led to the recognition that nanoparticles hold substantial promise as carriers for delivering various biomolecules, including RNA and DNA, among others. The amalgamation, characterization and functionalization of nanomaterials tailored for applications in targeted gene delivery represent an increasingly deliberate subfield within the domain of nanomedicine.

In the realm of gene transfer, a diverse array of nanostructures has been harnessed, encompassing lipids, polymers, graphene, carbon nanotubes, nanospheres and various inorganic entities. Functionalized nanomaterial-based gene delivery platforms have garnered substantial attention due to their persistent ability to efficiently transfer genetic material to target tissues while maintaining the stability of the genetic cargo.

Despite the immense potential of utilizing nanoparticle-based DNA delivery systems for treating a spectrum of lethal genetic and acquired disorders, it is noteworthy that none of these DNA delivery approaches have received full approval from the FDA. This hesitancy is rooted in concerns regarding the overall toxicity of nanomaterials and their limited capacity for gene transfection *in vivo*.

The burgeoning field of nanomedicine offers promising prospects for the early diagnosis and treatment of ailments, such as Alzheimer's disease, cancer, diabetes and cardiovascular conditions, underscoring its potential to revolutionize healthcare practices and outcomes (61).

6. Conclusion and future perspectives

In recent years, substantial efforts have been directed towards the development of novel methods for green synthesis. The optimal green synthesis approach for AgNPs involves using environmentally friendly methods, such as plant extracts or microorganisms, to reduce silver ions and stabilize the nanoparticles. Green synthesis, as a broader concept, encompasses approaches involving the utilization of microbes or plants, thereby aligning with principles and policies aimed at minimizing adverse environmental impacts and fostering a sustainable approach to nanoparticle synthesis. This approach minimizes the use of hazardous chemicals and promotes sustainable nanotechnology. The present review mainly focused on the growing demand for AgNPs and the diverse array of methodologies employed in their synthesis. Numerous of these methods rely on biomolecules as pivotal agents driving the synthesis process.

However, further comprehensive investigations are warranted to address lingering questions related to the mechanisms, yield and the establishment of suitable reactors for achieving large-scale production. Additionally, extensive research efforts are indispensable for gaining a deeper understanding and assessment of the roles played by various biomolecules as reducing and stabilizing agents. It is worth noting that if external control agents are employed in conjunction with these processes, meticulous attention to the stability of the nanoparticles may be essential. This approach holds the potential to yield nanoparticles of enhanced efficiency.

The controlled and precise synthesis of rootless-mediated nanoparticles may be attainable through the integration of emerging scientific advancements, ultimately contributing to the optimization of the properties and functionalities of these nanoparticles for a wide range of technical applications.

Patent status. The interdisciplinary character of nanotechnology raises new technical and legal questions for the evaluation, classification, and analysis of patent systems worldwide. To guarantee that their ideas are adequately protected, inventors and researchers must abide by the laws now in effect under the patent systems in both their home countries and foreign nations. Over the past 10 years, there has been an average annual growth rate of 25% in the number of researchers working in the area, scientific articles, products, and worldwide in clothing. Moreover, the number of global patent applications has increased at an average annual rate of ~35% (64).

Acknowledgements

The authors are grateful to Professor Syed Waseem Akhtar, Hon'ble Chancellor, and Professor Javed Musarrat, Hon'ble Vice-Chancellor, Integral University (Lucknow, India) for his motivational support and for providing the necessary facility for the literature search.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

All the authors contributed equally in the preparation and design of the manuscript. AA was involved in the conception and design of the study. MH was involved in the articulation of the contents, and in editing the manuscript. NA was involved in editing the technical parts of the manuscript and in the organization of data to be included in the review. AK was involved in drafting and editing the manuscript. SJ was involved in the design of figures and editing the manuscript. FK was involved in editing the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Malik S, Muhammad K and Waheed Y: Nanotechnology: A revolution in modern industry. Molecules 28: 661, 2023.
2. McNeil SE: Nanotechnology for the biologist. J Leukoc Biol 78: 585-594, 2005.
3. Chan WC: Bionanotechnology progress and advances. Biol Blood Marrow Transplant 12 (1 Suppl 1): S87-S91, 2006.

4. Pavel IS: Assembly of gold nanoparticles by ribosomal molecular machines. The University of Texas at Austin, Austin, TX, 2005.
5. Shivashankarappa A and Sanjay KR: Escherichia coli-based synthesis of cadmium sulfide nanoparticles, characterization, antimicrobial and cytotoxicity studies. Braz J Microbiol 51: 939-948, 2020.
6. Kowshik M, Deshmukh N, Vogel W, Urban J, Kulkarni SK and Paknikar KM: Microbial synthesis of semiconductor CdS Nanoparticles, their characterization, and their use in the fabrication of an ideal diode. Biotechnol Bioeng 78: 583-588, 2002.
7. Labrenz M, Druschel GK, Thomsen-Ebert T, Gilbert B, Welch SA, Kemner KM, Logan GA, Summons RE, De Stasio G, Bond PL, *et al*: Formation of Sphalerite (ZnS) deposits in natural biofilms of sulfate-reducing bacteria. Science 290: 1744-1747, 2000.
8. Arakaki A, Nakazawa H, Nemoto M, Mori T and Matsunaga T: Formation of magnetite by bacteria and its application. J R Soc Interface 5: 977-999, 2008.
9. Watson JHP, Cressey BA, Roberts AP, Ellwood DC, Charnock JM and Soper AK: Structural and magnetic studies on heavy-metal-adsorbing iron sulphide nanoparticles produced by sulphate-reducing bacteria. J Magn Mater 214: 13-30, 2000.
10. Kowshik M, Ashtaputre S, Kharrazi S, Vogel W, Urban J, Kulkarni SK and Paknikar KM: Extracellular Synthesis of Silver Nanoparticles by a Silver-Tolerant Yeast Strain MKY3. Nanotechnology 14: 95-100, 2002.
11. Sunkar S and Nachiyar CV: Biogenesis of antibacterial silver nanoparticles using the endophytic bacterium Bacillus cereus isolated from Garcinia xanthochymus. Asian Pac J Trop Biomed 2: 953-959, 2012.
12. Balaprasad A, Chinmay D, Ahmad A and Sastry M: Biosynthesis of gold and silver nanoparticles using Emblica Officinalis fruit extract, their phase transfer and transmetallation in an organic solution. J Nanosci Nanotechnol 5: 1665-1671, 2005.
13. Nikalje AP: Nanotechnology and its applications in medicine. Med Chem 5: 081-089, 2015.
14. Ahmed S, Ahmad M, Swami BL and Ikram S: A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications: A green expertise. J Adv Res 7: 17-28, 2016.
15. Silva GA: Introduction to nanotechnology and its applications to medicine. Surg Neurol 61: 216-220, 2004.
16. Patil MP and Kim GD: Eco-friendly approach for nanoparticles synthesis and mechanism behind antibacterial activity of silver and anticancer activity of gold nanoparticles. Appl Microbiol Biotechnol 101: 79-92, 2017.
17. Khan I, Saeed K and Khan I: Nanoparticles: Properties, applications and toxicities. Arab J Chem 12: 908-931, 2019.
18. Narayanan KB and Sakthivel N: Biological synthesis of metal nanoparticles by microbes. Adv Colloid Interface Sci 156: 1-13, 2010.
19. Shatkin JA: Nanotechnology: Health and environmental risks. 2nd edition. CRC Press, Boca Raton, Fl, 2017.
20. Singh J, Singh T and Rawat M: Green synthesis of silver nanoparticles via various plant extracts for anti-cancer applications. Glob J Nanomed 2: 1-4, 2017.
21. Chattopadhyay KK and Banerjee AN: Introduction to nanoscience and nanotechnology. PHI Learning Pvt. Ltd., 2019.
22. Varma RS: Greener approach to nanomaterials and their sustainable applications. Curr Opin Chem Eng 1: 123-128, 2012.
23. Al-Shmgani HS, Mohammed WH, Sulaiman GM and Saadoon AH: Biosynthesis of silver nanoparticles from Catharanthus roseus leaf extract and assessing their antioxidant, antimicrobial, and wound-healing activities. Artif Cells Nanomed Biotechnol 45: 1-7, 2017.
24. Bhushan B: Introduction to Nanotechnology. In: Springer Handbook of Nanotechnology. Bhushan B (ed). Springer, Berlin, Heidelberg, 2017.
25. Patra JK and Baek KH: Green nanobiotechnology: Factors affecting synthesis and characterization techniques. J Nanomaterials: 219, 2014.
26. Iravani S, Korbekandi H, Mirmohammadi SV and Zolfaghari B: Synthesis of silver nanoparticles: Chemical, physical and biological methods. Res Pharm Sci 9: 385-406, 2014.
27. Gamboa SM, Rojas ER, Martínez VV and Vega-Baudrit J: Synthesis and characterization of silver nanoparticles and their application as an antibacterial agent. Int J Biosen Bioelectron 5: 166-173, 2019.
28. Wasilewska A, Klekotka U, Zambrzycka M, Zambrowski G, Święcicka I and Kalska-Szostko B: Physico-chemical properties and antimicrobial activity of silver nanoparticles fabricated by green synthesis. Food Chem 400, 133960, 2023.
29. Saini R, Saini S and Sharma S: Nanotechnology: The future medicine. J Cutan Aesthet Surg 3: 32-33, 2010.
30. Zhang XF, Liu ZG, Shen W and Gurunathan S: Silver nanoparticles: synthesis, characterization, properties, applications, and therapeutic approaches. Int J Mol Sci 17: 1534, 2016.
31. Kumar KS and Kathireswari P: Biological synthesis of Silver nanoparticles (Ag-NPS) by Lawsonia inermis (Henna) plant aqueous extract and its antimicrobial activity against human pathogens. Int J Curr Microbiol App Sci 5: 926-937, 2016.
32. Kalishwaralal K, Deepak V, Ramkumarpandian S, Nellaiah H and Sangiliyandi G: Extracellular biosynthesis of silver nanoparticles by the culture supernatant of Bacillus licheniformis. Mater Lett 62: 4411-4413, 2008.
33. Mukherjee A, Sarkar D and Sasmal S: A review of green synthesis of metal nanoparticles using algae. Front Microbiol 12: 693899, 2021.
34. Kulkarni N and Muddapur U: Biosynthesis of metal nanoparticles: A review. J Nanotechnol: 2014.
35. Virkutyte J and Varma RS: Green synthesis of nanomaterials: Environmental aspects. In: Sustainable nanotechnology and the environment: advances and achievements. American Chemical Society, pp11-39, 2013.
36. Iravani S: Green synthesis of metal nanoparticles using plants. Green Chem 13: 2638-2650, 2011.
37. Ahmed SF, Mofijur M, Rafa N, Chowdhury AT, Chowdhury S, Nahrin M, Islam ABMS and Ong HC: Green approaches in synthesising nanomaterials for environmental nanobioremediation: Technological advancements, applications, benefits and challenges. Environ Res 204(Pt A): 111967, 2022.
38. Vijayaraghavan K and Nalini SK: Biotemplates in the green synthesis of silver nanoparticles. Biotechnol J 5: 1098-1110, 2010.
39. Singh P, Kim YJ, Singh H, Wang C, Hwang KH, Farh Mel-A and Yang DC: Biosynthesis, characterization, and antimicrobial applications of silver nanoparticles. Int J Nanomedicine 10: 2567-2577, 2015.
40. Prabhu S and Poulose EK: Silver nanoparticles: Mechanism of antimicrobial action, synthesis, medical applications, and toxicity effects. Int Nano Lett 2: 32, 2012.
41. Roy A, Bulut O, Some S, Mandal AK and Yilmaz MD: Green synthesis of silver nanoparticles: Biomolecule-nanoparticle organizations targeting antimicrobial activity. RSC Adv 9: 2673-2702, 2019.
42. Geoprincy G, Srri BV, Poonguzhali U, Gandhi NN and Renganathan S: A review on green synthesis of silver nanoparticles. Asian J Pharm Clin Res 6: 8-12, 2013.
43. Durán N, Durán M, De Jesus MB, Seabra AB, Fávaro WJ and Nakazato G: Silver nanoparticles: A new view on mechanistic aspects on antimicrobial activity. Nanomedicine 12: 789-799, 2016.
44. Franci G, Falanga A, Galdiero S, Palomba L, Rai M, Morelli G and Galdiero M: Silver nanoparticles as potential antibacterial agents. Molecules 20: 8856-8874, 2015.
45. Laxmi V, Singhvi N, Ahmad N, Sinha S, Negi T, Gupta V, Mubashshir M, Ahmad A and Sharma S: emerging field of nanotechnology in environment. Indian J Microbiol 63: 244-252, 2023.
46. Rawat N, Ahmad N, Raturi P, Singhvi N, Sahai N and Kothiyal P: Nanobiomaterials: exploring mechanistic roles in combating microbial infections and cancer. Discov Nano 18: 158, 2023.
47. Dakal TC, Kumar A, Majumdar RS and Yadav V: Mechanistic basis of antimicrobial actions of silver nanoparticles. Front Microbiol 7: 1831, 2016.
48. Tang S and Zheng J: Antibacterial activity of silver nanoparticles: Structural effects. Adv Healthc Mater 7: e1701503, 2018.
49. Slavin YN, Asnis J, Häfeli UO and Bach H: Metal nanoparticles: understanding the mechanisms behind antibacterial activity. J Nanobiotechnology 15: 65, 2017.
50. Raza MA, Kanwal Z, Rauf A, Sabri AN, Riaz S and Naseem S: Size-and shape-dependent antibacterial studies of silver nanoparticles synthesized by wet chemical routes. Nanomaterials (Basel) 6: 74, 2016.
51. Nanomedicine: Grounds for optimism, and a call for papers. Lancet 362: 673, 2003.
52. Freitas RA Jr: What is nanomedicine? Nanomedicine 1: 2-9, 2005.
53. Moghimi SM, Hunter AC and Murray JC: Nanomedicine: Current status and future prospects. FASEB J 19: 311-330, 2005.
54. Kargozar S and Mozafari M: Nanotechnology and Nanomedicine: Start small, think big. Mater Today Proc 5: 15492-500, 2018.

55. Wankar JN, Chaturvedi VK, Bohara C, Singh MP and Bohara RA: Role of Nanomedicine in Management and Prevention of COVID-19. Front Nanotechnol 2: 589541, 2020.
56. Salamanca-Buentello F and Daar AS: Nanotechnology, equity and global health. Nat Nanotechnol 16: 358-361, 2021.
57. Cheng Z, Li M, Dey R and Chen Y: Nanomaterials for cancer therapy: Current progress and perspectives. J Hematol Oncol 14: 85, 2021.
58. Gavas S, Quazi S and Karpiński TM: Nanoparticles for cancer therapy: Current progress and challenges. Nanoscale Res Lett 16: 173, 2021.
59. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R and Langer R: Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol 2: 751-760, 2007.
60. Kandaswamy E and Zuo L: Recent advances in treatment of coronary artery disease: Role of science and technology. Int J Mol Sci 19: 424, 2018.
61. Boulaiz H, Alvarez PJ, Ramirez A, Marchal JA, Prados J, Rodríguez-Serrano F, Perán M, Melguizo C and Aranega A: Nanomedicine: Application areas and development prospects. Int J Mol Sci 12: 3303-3321, 2011.
62. Shi J, Kantoff PW, Wooster R and Farokhzad OC: Cancer nanomedicine: Progress, challenges and opportunities. Nat Rev Cancer 17: 20-37, 2011.
63. Abeer S: Future medicine: Nanomedicine. JIMSA 25: 187-192, 2012.
64. Zhang Y, Sulfab M and Fernandez D: Intellectual property protection strategies for nanotechnology. Nanotechnol Rev 2: 725-742, 2013.