

Metal Nanoparticles in Medicine: Biosynthesis and Applications in Chemotherapy, Drug Delivery, and Anticancer, Antibacterial and Antioxidant Chemical Production

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ABSTRACT

In recent years, nanotechnology has become a preeminent field in the maintenance and defense of human health. Nanotechnology with biomedical applications is seen as a viable approach to combat the growing problem of germs that are resistant to antibiotics and to enhance the effectiveness of anti-cancer medications. Nanoparticles have special characteristics that vary depending on their size, which makes them outstanding and essential in many areas of human activity. This review attempts to provide a concise summary of recent advances in the biosynthesis of metal nanoparticles, particularly their usage in biology and medicine, and offers a clear viewpoint for the continued application of these metal nanoparticles in the field of medicine.

Keywords: Nanotechnology; Metal nanoparticles; Biomedicine; Biosynthesis; Anticancer; Antibacterial

INTRODUCTION

The solutions to the difficulties facing the current generation have been found in nanotechnology and nanoscience. Applications of nanotechnology have their origins in all branches of science and technology, ranging from vital human necessities like food and medicine to universal problems like energy, pollution prevention, and remediation. The hunt for novel nanotechnology-based goods and procedures has been sparked by the need for high-quality food on the part of the scientific community, governments, and businesses [1]. Depending on the constituent material, nanomaterials are typically categorized as being made of metal, carbon, organic compound, or composite materials. Due to their size, shape, composition, and density, each of them has distinct characteristics. Because of their many uses, ranging from optomechanical to biomedical, metal nanoparticle-based materials stand out among all others [2,3]. Metal Nanoparticles (MNPs) have grown to be one of the most sought-after nanomaterials due to their unmatched physicochemical and thermodynamic qualities, which make them ideal candidates for usage in a variety of fields including optics, electronics, biology, and catalysis [4-8]. Metal nanoparticles are widely used in biomedical and pharmaceutical areas as alternative antibacterial

techniques as a result of the resurgence of infectious diseases and the emergence of antibiotic-resistant strains [9]. MNPs typically have a metal core made of an inorganic metal element or metal oxide that is surrounded by materials that can be either organic or inorganic [10]. Metal ions can be converted into nanoparticles by physical, chemical, enzymatic, and biological processes [11,12]. In the physicochemical synthesis of MNP, undiluted reducing agents and high radiation levels can be detrimental to the environment as well as to human health [13]. Additionally, these techniques are pricey. Enzymatic synthesis of nanoparticles is known to be more expensive but is safer than other methods [14]. A growing desire to develop environmentally benign processes for the synthesis of nanomaterials has led to an increase in the utilization of biological systems as a novel and dependable approach for producing nanoparticles recently [15]. In order to manufacture different metal-based NPs, aqueous extracts from a variety of living species, including bacteria, fungi, plants (vegetables, tree roots), eggshells, fruit shells, and algae, have been employed. Biosynthesized nanoparticles have their surfaces coated with non-toxic waste materials made from biological extracts. Some drawbacks may later result in the generation of hazardous waste during physical synthesis and the usage of poisonous reagents [16]. Nanotechnology has recently offered a sophisticated and multidisciplinary approach to drug

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Received: 20-Oct-2023, Manuscript No. JNBD-23-27729; **Editor assigned:** 23-Oct-2023, PreQC No. JNBD-23-27729 (PQ); **Reviewed:** 06-Nov-2023, QC No. JNBD-23-27729; **Revised:** 13-Jun-2025, Manuscript No. JNBD-23-27729 (R); **Published:** 20-Jun-2025, DOI: 10.35248/2155-983X.25.15.311

Citation: Pourshahi M, Doraghi Z, Ghaderi M (2025) Metal Nanoparticles in Medicine: Biosynthesis and Applications in Chemotherapy, Drug Delivery, and Anticancer, Antibacterial, and Antioxidant Chemical Production. J Nanomedicine Biotherapeutic Discov. 15:311.

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design and drug delivery that has completely changed the landscape of medical research. Medical researchers are continuously looking for novel, highly efficient, and reasonably priced medicines. The precise targeting of the illness location while sparing the healthy sections of the body is one of the key components of the development of novel medications [17]. Due to its numerous medicinal uses in the areas of medical imaging, antibacterials, and antivirals, metal nanoparticles have drawn particular interest in order to further this objective [18-20]. The biomedical industry has extensively examined copper, titanium, platinum, selenium, and silver nanostructures, which has resulted in their therapeutic application.

LITERATURE REVIEW

To advance the use of these nanoparticles in the treatment of various diseases, we thus sought to present current knowledge about these nanoparticles and the numerous works done with them in the field of nanomedicine.

Silver nanoparticles

Silver Nanoparticles (AgNPs) have become one of the most attractive nanoparticles in the field of biomedicine due to their antimicrobial, anticancer, vaccine adjuvant, antidiabetic agents, biosensors, and their use in increasing the effectiveness of wound healing and bone healing drugs. The synthesis of silver nanoparticles by chemical method through the reduction of silver ions to silver atoms, which includes the two-step process of

nucleation and growth of nanoparticles, is one of the most common methods of synthesis of these nanomaterials. The physical method, including grinding, pyrolysis, and spark discharge, is used for the synthesis of silver nanoparticles with high purity and uniform size.

Plant extracts, sugars, and eco-friendly polymers have been utilized in recent years for the production of silver nanoparticles in accordance with the principles of green chemistry and to reduce the use of chemical solvents and excessive energy consumption. The first scientific study on the use of "hairy" root culture extracts for the environmentally friendly synthesis of silver nanoparticles, as well as research on their stability and biocidal action against pathogenic bacteria, was presented in 2020 by Natalia Kobylinska et al. They employed electrospray ionization time mass spectrometry (UPLC-ESI) in conjunction with Ultra-High-Performance Liquid Chromatography (UHPLC) to determine the structure of the acquired compounds. *Escherichia coli*, *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* were among the bacteria used to test the antibacterial activity of biosynthesized AgNPs. According to the findings of the study on the antibacterial activity of biosynthesized silver nanoparticles (Table 1), silver nanoparticles exhibit high activity (higher inhibition zone) when compared to AgNO₃ solution. Additionally, this study shown that as nanoparticle size is decreased, silver nanoparticle surface activity and antibacterial activity rise, having a higher impact on cell membranes.

Table 1: Comparison of the antimicrobial activity of biosynthesized silver nanoparticles with other samples against different microorganisms.

Tested compounds	Zone of inhibition (mm)			
	<i>C. albicans</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>E. coli</i>
Ciprofloxacin	0	21.3 ± 1.3	29.7 ± 1.3	29.0 ± 1.1
AgNPs (>100)	10.0 ± 0.1	12.3 ± 0.6	10.3 ± 0.6	12.0 ± 0.1
AgNPs (1-20 nm)	14.6 ± 0.6	16.7 ± 0.7	13.3 ± 0.6	12.6 ± 0.6
AgNO ₃ (solution)	11.0 ± 0.1	11.6 ± 0.7	0	10.3 ± 0.6

^a Values are means of triplicate determination ± standard deviations.

Titanium nanoparticles

In recent years, Titanium Dioxide nanoparticles (TiO₂), which are very small nanoparticles with dimensions less than 100 nm, have been a popular nanoparticle in various fields of technology, including medicine, energy, and biosensors, due to their special physical and chemical properties. And various applications of the two crystal structures of rutile and anatase TiO₂ are known, in which the rutile form is considered chemically inert. TiO₂NPs have been used in various fields as photocatalysts, sensors, drug delivery systems for several anticancer drugs (including daunorubicin, temozolomide, doxorubicin, and cisplatin), photovoltaic cells, electrochemical devices, cosmetics, and pharmaceuticals.

Chemotherapy is now constrained for a variety of reasons, which has led to substantial research on the TiO₂ NPs' potential as drug delivery systems. Chemotherapy medications are extremely harmful to the body's constantly expanding and dividing cells, both cancerous and healthy. Chemotherapeutics may occasionally fail to work due to multidrug resistance mechanisms displayed by different cancer-causing tissues. Considering the distinctive features of the disease, the problems related to drug treatment, the serious adverse effects of these drugs on the proliferation of body tissues such as immune cells, and the possibility of drug resistance, the most important challenge in cancer treatment is the targeted delivery of drugs to cancer tissues and cells.

In a 2023 study reported by Mehrab Pourmadadi and colleagues, a pH-sensitive nanocomposite made of starch, PAA, and TiO_2 was fabricated to efficiently deliver curcumin to cancer cells. A composite emulsion in water was used to create nanoparticles with nanodimensional size distribution and spherical morphology. Conventional methods of analysis, including FT-IR, FE-SEM, TEM, XRD, DLS, zeta potential, and LE and EE parameters calculated from experimental data, were used to characterize the synthesized nanocarrier. The design platform's enhanced anticancer activity was tested against human breast cancer cell lines using MTT and flow cytometry techniques. The medicine's bioavailability and effectiveness against MCF-7 cancer cells were both improved by including the drug in the nanocomposite. Based on *in vitro* research, it can be concluded that using the PAA-Starch- TiO_2 -Cur nanocomposite for targeted drug delivery not only decreases the side effects of the drug but also improves its effectiveness. It can also be used to deliver drugs that are poorly soluble or insoluble in biological environments.

In another study conducted in 2023, Reza Qamarpour and her research team investigated the use of Titanium Dioxide (TiO_2) as a UV filter in the composition of cosmetics, especially sunscreens, to investigate the various properties of titanium oxide nanoparticles. The effect of the size of titanium dioxide nanoparticles on the functional characteristics of sunscreens was also investigated because they tend to combine and produce coarse particles to prevent the penetration of nanoparticles into the skin. The research results showed that titanium dioxide can be used as an effective filter against all types of UVA and UVB rays. In addition, it was shown that the UVA and UVB protection of titanium dioxide was improved by reducing the particle size. The majority of sunscreen formulations use titanium dioxide with a particle size above 100 nm in order to decrease the amount of titanium dioxide that penetrates the skin. The use of titanium dioxide in combination with other chemical or physical filters in the formulation, homogenization to reduce titanium dioxide particle size, and high doses of titanium dioxide were all investigated as ways to achieve the highest level of product protection against UVA and UVB rays.

Platinum nanoparticles

In recent years, the drug combination technique has been extensively researched to get beyond the negative effects that using a single medicine can have while also enhancing the therapeutic impact. The co-delivery of medications is highly challenging in clinical settings, and varied *in vivo* kinetics resulting from various pharmacological characteristics can reduce efficacy. As a result, there is a critical need for quick progress in the development of new platinum-based anticancer therapeutics. The chemotherapeutic drug cisplatin has a long history and is crucial in this process. During treatments, normal tissues are frequently harmed in clinical practice due to the non-selective cell-killing effects of cisplatin. Researchers have developed a number of methods to lessen its toxicity or improve its function in order to address the issues with cisplatin in therapies. The physicochemical properties of cisplatin can be chemically altered to reduce its toxicity to the kidneys and liver, but doing so can also significantly impair the drug's efficacy. By

combining it with other anticancer drugs, resistance to cisplatin can be overcome, and the effectiveness of treatment can be improved.

Recently, the two-in-one combination technique has shown better benefits as compared to administering two medications separately. These co-delivery techniques include pro-drug form loading, polymeric pro-drugs encasing another drug in the nanocarrier, and co-loading of drugs in the nanocarrier. These delivery systems offer additional benefits than cocktail-based delivery therapies, such as the predetermined delivery ratio, improved synergistic effects, and diminished adverse effects, all of which help to achieve the best possible synergistic therapy. The dual drug delivery system based on a two-to-one co-delivery strategy, which simultaneously efficiently delivers two drugs with synergistic effects as well as targeted tumor accumulation aids, was reported by Yang and his colleagues during the research they conducted to find a more effective way to kill cancer cells in 2020. For a synergistic effect, the COX-2 selective inhibitor tolafenamic acid (Tolf) was chosen and administered in combination with cisplatin. Tolf is a very effective COX-2 inhibitor with great biosafety and minimal unfavorable side effects, making it an excellent option for combination therapy in this study.

Selenium nanoparticles

In the sciences of physics, chemistry, and biology, the element Selenium (Se) is crucial. Both inorganic (selenite and selenate) and organic (selenomethionine and selenocysteine) forms of selenium are found in nature. In nature, selenium can be found in both crystalline and amorphous polymorphism forms. The crystalline forms of selenium are monoclinic and trigonal. The most stable crystalline form of selenium at ambient temperature is trigonal selenium (t-Se), which is black in color. Figure 1a and b shows the crystal forms of t-Se and m-Se, respectively. The body needs selenium, a trace element that can scavenge free radicals and protect DNA from oxidative damage. Numerous research imply that SeNPs may have special medicinal uses that vary from antioxidant activity to anticancer effects, which are mostly due to its redox modulatory function.

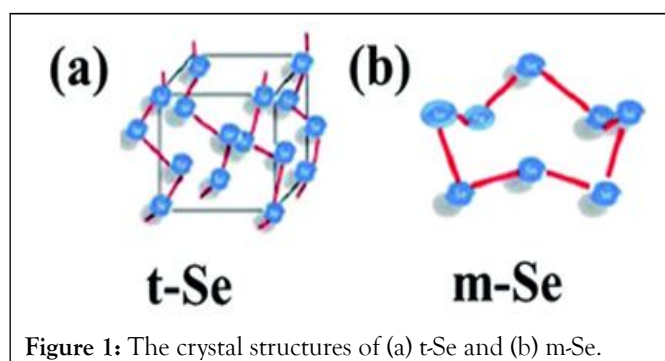


Figure 1: The crystal structures of (a) t-Se and (b) m-Se.

In order to provide better biocompatibility and stability, it is desirable to synthesis SeNPs through a biological pathway. In general, it's thought that biological preparation techniques derived from microorganisms and plant extracts are preferable to chemical ones for meeting the rising demand for inexpensive and safe preparation techniques. It has been claimed that biological extracts function as nanoparticle stabilizers and bio-

reducing agents. The biosynthesis of SeNPs has been extensively studied in the literature.

Biological reagent assisted synthesis is simple because it does not require any particular equipment or circumstances. Bacteria, fungus, algal cells, molecule of protein, and herbal extracts are some of these biological agents. High-quality SeNPs can be made using this process without the use of specialized equipment, with little or no product waste, and without the use of a considerable volume of solvent. As a result, such procedures are thought to be one-step, low-cost, and environmentally benign.

Using chemical and biological processes, Ramorti and his colleagues were able to produce selenium nanoparticles with a

particle size of 100 to 150 nm. They discovered that the size obtained by the biogenic method was slightly larger than the size obtained by the chemical method, but the biogenic method was more efficient due to the fact that the biological strains consisted of several reducing and stabilizing agents. For this reason, biogenic/bioreduction for making SeNPs has been widely considered. Table 2 summarizes the various biological agents used to produce selenium nanoparticles, as well as the precursor and reaction conditions.

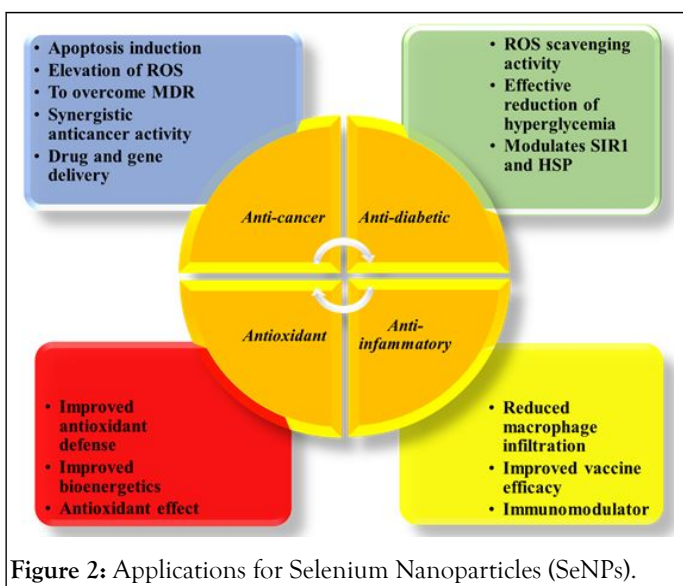
Table 2: An overview of the procedures used by several researchers to synthesize SeNPs using different biological materials.

Se precursor	Biological agents/extract origin	Morphology and size particles	Application
SeO ₂	<i>Bacillus licheniformis</i>	Spherical with a diameter of 10–50 nm, colourless to orange-red	Antimicrobial against foodborne pathogens
SeO ₂	<i>Bacillus licheniformis</i>	Spherical with a diameter of 50–80 nm	Chemopreventive against lung carcinoma
SeO ₂	<i>Trigonella foenum-graecum</i> leaf extract	D=20 nm, nanospheres with a 5–12 nm diameter	Anticancer degradation of sunset yellow FCF
Na ₂ SeO ₃	<i>Terminalia arjuna</i> leaf extract	Size=10-80 nm, dark red	Effect against As (III) toxicity
Na ₂ SeO ₃	Glutathione (GSH)	Nanospheres of 40–100 nm	Prevention of PVC related medical infections
Na ₂ SeO ₃	Glutathione (GSH)	Hemispherical, size=80–200 nm	Cytotoxicity of SeNP coated PVC in rat dermal fibroblasts
Na ₂ SeO ₃	Ethanol extract of bee propolis from <i>Apis mellifera</i> colonies along with ascorbic acid	Brown to orange color change 52–118 nm diameter	Antioxidant, antimicrobial, anti-bacterial, antifungal
Na ₂ SeO ₃	<i>Allium sativum</i> extract	7–45 nm, stable up to 2 months Dark pink color of solution	Antioxidant
Na ₂ SeO ₃	Various cyanobacterial strains	Red spherical NPs with sizes in the range of 11–60 nm depending upon the strain	Antioxidant
Na ₂ SeO ₃	L-Cystine and peptone from soybean	36.2 nm (from XRD) 20–50 nm (TEM)	Protection against irradiation used nephropathy

DISCUSSION

SeNPs have a number of medical advantages, such as anticancer, anti-diabetic, anti-inflammatory and antioxidant effects (Figure 2). Its pro-oxidant features in cancerous cells cause the formation

of reactive oxygen species (ROS), which in turn causes damage to the mitochondria and endoplasmic reticulum, that causes DNA damage and the anticancer action.



Chronic disorders like diabetes are brought on by the excessive levels of glucose that are produced in our bodies as a result of insufficient insulin production or insulin use. The molecule insulin is in charge of keeping blood sugar levels stable. People of all ages suffer from diabetes' negative impacts. Due to selenium's potent ability to decrease blood sugar levels, numerous researchers have reported using it in the treatment of diabetes. Diabetes's long-term effects can harm both large and tiny blood arteries, which can interfere with the proper operation of many organs in the human body. Different disorders of the heart, legs, brain, dental health, kidneys, eyes, skin, digestive system and immune system are caused by diabetes. According to research by Deng et al. mice with diabetes can be treated by oral administration of Se nanoparticle that have been loaded with insulin. Based on the findings of their investigation, insulin was released into the blood in controlled conditions and demonstrated great stability in digesting meal.

Copper nanoparticles

Copper Nanoparticles (Cu-NPs) are one of the most widely used NPs and are utilized in many different products, including catalysis, filtration, aqueous solutions to conduct heat, solar panels, electronics, gas sensors, batteries, ceramics, textiles, and superconducting materials. Multiple chemical, physical, and

mechanical processes are used to create copper nanoparticles. Despite their widespread use, these methods have drawbacks, such as hazardous reaction conditions, the requirement for pricey chemicals and equipment, and lengthy processing periods. In order to prevent this, green chemistry encourages scientists to develop novel manufacturing processes based on biological processes, in which bio creatures like bacteria and plant extracts play a key role in the production of nanoparticles. Unlike other bio-fabrication processes, they have a simpler process because they don't require time-consuming, difficult cell culture procedures.

Therefore, for the biosynthesis of copper nanoparticles from the extract of *M. pinnata* fower through a fast, green and environmentally friendly process, Muthu Thiruvengadam and colleagues reported an interesting research. In this research, copper nanoparticles with an average size of 23 ± 1.10 nm were synthesized without using any toxic chemical reagents and were confirmed through UV-Vis, XRD and TEM analysis. The high antioxidant, antibacterial, antidiabetic and anti-inflammatory activities of these synthesized Cu-NPs are one of the advantages of this research work.

In 2023, Yilmaz KOC AK and his colleagues published a study on the biosynthesis of copper nanoparticles from *P. anisum* and investigating the antibacterial and antioxidant properties of these nanoparticles. *Pimpinella anisum* L (anise) is a flowering plant rich in essential oil that is used in traditional folk medicine to treat various diseases such as cancer, asthma, cholera and cough. In addition, its antibacterial, antioxidant, antiseptic, diuretic and antidepressant effects have been proven. Conventional analyses have been used to characterize copper nanoparticles, and the study of the results of the analyses indicates the correct biosynthesis of copper nanoparticles with a spherical structure and an average size of 10-20 nm without using any chemical solvent. The obtained results confirm the antimicrobial and antioxidant activity of copper nanoparticles against DPPH free radicals and some pathogenic bacteria. As presented in Table 3, copper nanoparticles had better biological activity than the seed extract, especially against the pathogen *Bacillus subtilis*.

Table 3: Compares the diameter of the inhibitory zone (mm) for *P. anisum* seed extract, Cu NPs/PA, and the antibiotic rifampin against pathogenic microorganisms.

Test microorganisms	Zone of inhibition (mm)		
Bacteria	<i>P. anisum</i> extract	Cu NPs/PA	Rifampin
<i>Staphylococcus aureus</i> ATTC 29213	0	8.1 ± 1.2	8.5 ± 1.8
<i>Bacillus subtilis</i> ATCC 6633	8	18.0 ± 2.8	11.0 ± 1.7
<i>Bacillus cereus</i> ATTC 10876	0	8.0 ± 2.1	9.7 ± 2.6
<i>Pseudomonas aeruginosa</i> ATTC 27853	0	0	0

^aValues are means of triplicate determination \pm standard deviations.

CONCLUSION

By using nanoparticles in nanomedicine, fields such as gene transfer, medication delivery, cancer therapy, antibacterial instruments, biosensors, therapeutic facilities, and clinical diagnosis have been completely transformed. The manufacturing of nanoparticles has gained interest because of the numerous ways that modern technology uses them. In the last ten years, a variety of techniques, including physical, chemical, and biological pathways, have been employed in the field of nanotechnology research for their synthesis. Lithography, laser ablation, high-energy radiation, electrochemistry, and chemical regeneration are examples of physicochemical techniques that call for the use of potentially dangerous substances and substantial energy expenditure. So it is inevitable that safe biological techniques or environmentally friendly nanotechnology will be developed. A number of biological resources, including bacteria, yeast, algae, fungi, plants, cell organelles, or enzymes, are utilized in green nanotechnology as eco-friendly bioreactors to promote the creation of nanoparticles.

ACKNOWLEDGMENT

The Mohaghegh Ardabili University Research Council's financial support for this work is much appreciated by the writers.

CONFLICT OF INTEREST

The corresponding author certifies that there is no conflict of interest on behalf of all authors.

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