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REVIEW

Metal Nanoparticles: From Endophytic Fungi-Mediated Biosynthesis to Their Therapeutic Applications in Oncology

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Abstract: Metal nanoparticles possess unique properties and usage patterns compared to traditional materials owing to their distinctive structures. In recent years, their application scenarios and dosages have considerably expanded. Biosynthetic nanoparticles, particularly those derived from endophytic fungi that help host organisms in adapting to heavy metal environments, hold substantial value and potential for application. This is largely attributed to their simplicity, cost-effectiveness, and energy efficiency. The present review provides an overview of the entire process of metal nanoparticle biosynthesis by plant endophytic fungi and illustrates various scenarios of their applications in oncology treatment. In addition to focusing on the preparation of metal nanoparticles using plant endophytic fungi, this review also explores the characterization of these nanoparticles and clarifies the synthesis mechanisms, including the synthetic pathways and the roles of fungal enzymes. It also comprehensively summarizes the application of biosynthetic metal nanoparticles in cancer, covering their role in diagnosis, enhancement of drug biocompatibility, and improvement of therapeutic efficacy. These nanoparticles exhibit toxicity toward cancer cells by generating reactive oxygen species and inducing oxidative stress, ultimately leading to the death of malignant cells. The biosynthesis of metal nanoparticles by plant endophytic fungi represents a promising, green, and environmentally friendly approach with potential applications in various fields, including cancer treatment, in the future.

Keywords: endophytic fungi, metal nanoparticles, biosynthesis, cancer therapy

Introduction

Nanotechnology represents an interdisciplinary field operating at the nanoscale, integrating principles from chemistry, biology, physics, and materials science. Nanoparticles are minute particles with sizes ranging from 1 to 100 nm. They can be categorized into various types based on their chemical and physical characteristics, including metal, ceramic, and polymer nanoparticles.[1] Nanomaterials address certain limitations associated with traditional materials and enhance the functionality of various products, owing to their unique properties and diverse applications.[2] Specifically, their high surface-to-volume ratio enables broader applications in structural and functional materials, such as residential buildings, automotive components, solar cells, and coatings.[3] Additionally, nanomaterials possess a high refractive index, resulting in visible light scattering, making them advantageous for use in dyes and ultraviolet protection at approximately 50 nm.[4] Their superior mobility enables effective nanoparticle-based drug delivery and therapeutic interventions.[5] Moreover, nanocomposites can be tailored through surface modifications to achieve tissue-specific and controlled delivery.[6] Notably, the minute size of nanomaterials enables the establishment of innovative and functional structures, devices,

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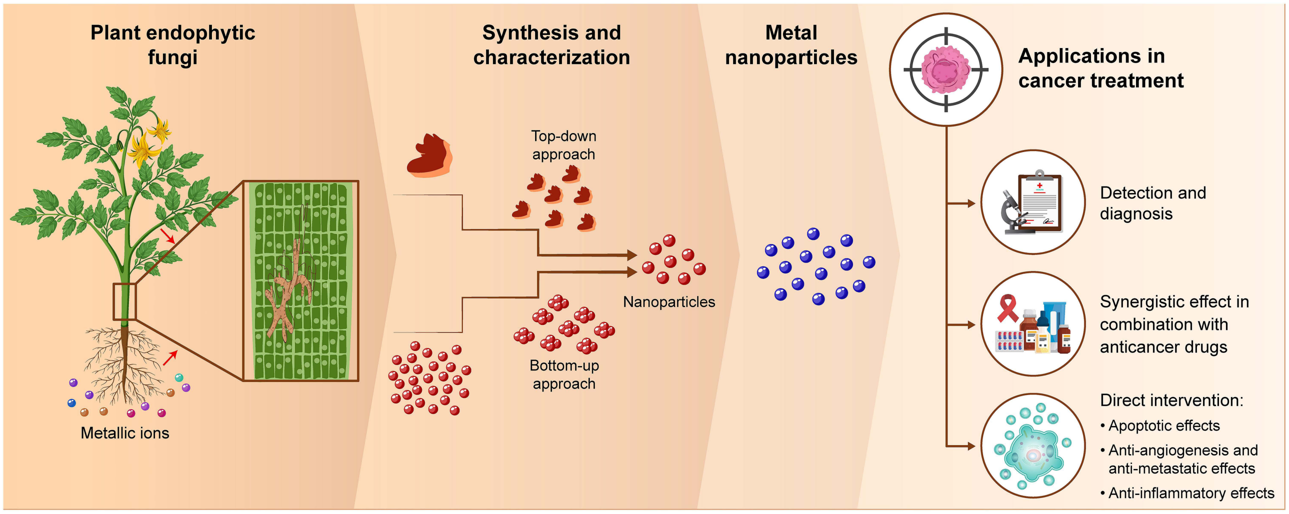
Graphical Abstract



and systems, overcoming key issues in contemporary biology.[7] Currently, a primary focus in modern nanotechnology is the development of nanoparticles that are stable, effective, and uniform in size.[8]

Nanoparticles can be prepared through various physicochemical methods.[9] However, the synthesis process is increasingly shifting toward non-toxic and environmentally friendly biological methods, particularly for invasive biomedical applications. Successful biosynthetic pathways have been established for nanoparticle synthesis,[10] involving reactions between metal salt solutions and biomass. Various sources, such as plants, plant tissues, plant extracts, and seaweed, have been utilized for this purpose.[11] Among these natural biological resources, fungi demonstrate remarkable efficiency, making them particularly well-suited for synthesizing metallic nanoparticles.[12] Specifically, fungi exhibit relatively rapid growth rates and can produce substantial quantities of proteins, enhancing the productivity and stability of the resulting particles.[13] Furthermore, fungal hyphae are resilient in harsh bioreactor environments, facilitating easier processing during downstream manufacturing than plant materials and other microorganisms.[14] Consequently, significant advancements have been made in fungal biosynthesis for nanomaterial production, presenting a viable alternative to physicochemical synthesis methods. As natural microorganisms, plant endophytes perform functions analogous to their symbiotic hosts.[15] Using endophytes for nanoparticle synthesis can effectively reduce the reliance on chemicals, enhance environmental performance, lower production costs, and support large-scale production, thus aligning with sustainable development principles.[16]

The present review offers a comprehensive overview of the entire process of metal nanoparticle biosynthesis by plant endophytic fungi and highlights their potential applications in oncology treatment. Specifically, we outlined the methods, conditions, and mechanisms involved in nanoparticle synthesis by plants and their endophytic fungi. We summarized the applications of metal nanoparticles synthesized by endophytic fungi (Figure 1), focusing on promising prospects in cancer research. This review provides a new biosynthetic approach for sourcing anticancer nanoparticles.

Synthesis Methods

Nanoparticle preparation methods can be categorized into two primary types: top-down and bottom-up (Figure 2).[17] Top-down methods involve disintegrating larger materials into nanoscale particles through techniques such as mechanical grinding, soft lithography, and quenching. However, these methods lack precision in controlling the particle shape and size.[18] Conversely, bottom-up techniques involve the self-assembly of atoms and their growth into nanoparticles, representing a gradual construction process starting at the atomic level. This group primarily encompasses chemical

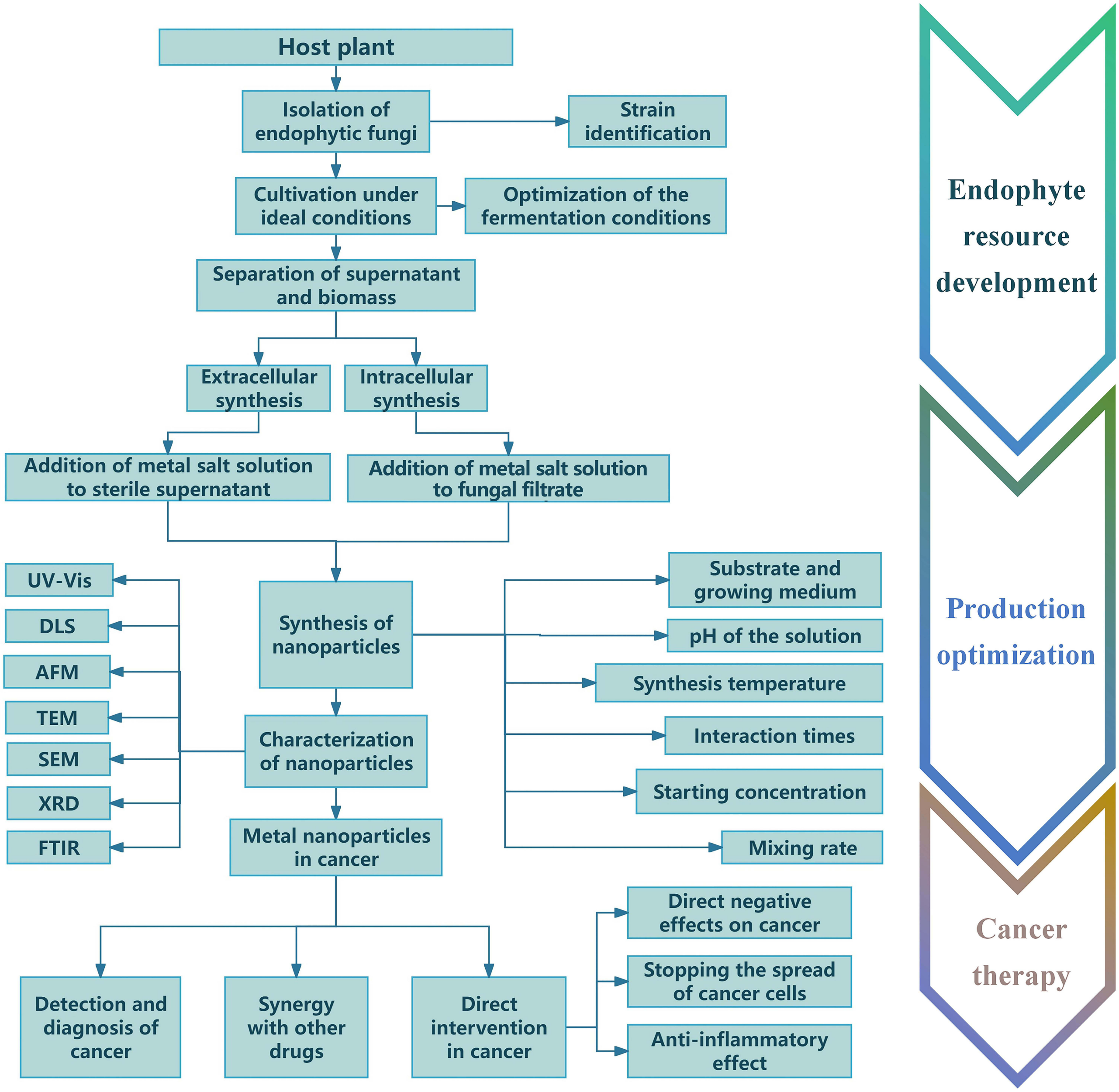


Figure 1 Schematic diagram of nanoparticles synthesized by plant fungal endophytes.

synthesis and biosynthesis methods. Nanoparticles synthesized through physical, chemical, and biological means each possess specific advantages and disadvantages (Figure 3).[19] Among these, the environmentally friendly synthesis of nanoparticles using plant endophytic fungi represents a novel and promising synthetic pathway.

Biosynthesis represents a predominantly bottom-up approach to nanoparticle synthesis, relying on reactions facilitated by organisms, including plants, fungi, bacteria, actinomycetes, and algae. This method allows for precise control over nanoparticle morphology and dimensions by adjusting cultivation parameters,[20] making it a preferred approach for sustainable nanoparticle fabrication. Biosynthesis is relatively environmentally friendly, energy-efficient, cost-effective, scalable, biocompatible, easy to manipulate, and avoids the production of harmful by-products.[11] Although fungi exhibit a slower growth rate than bacteria, they offer advantages in nanoparticle synthesis owing to the simplicity of their cultivation, substantial biomass production, enzyme excretion, and mycelial network resilience to shear stress.[21] Filamentous fungi can produce highly stable nanoparticles that prevent molecular aggregation, even after prolonged

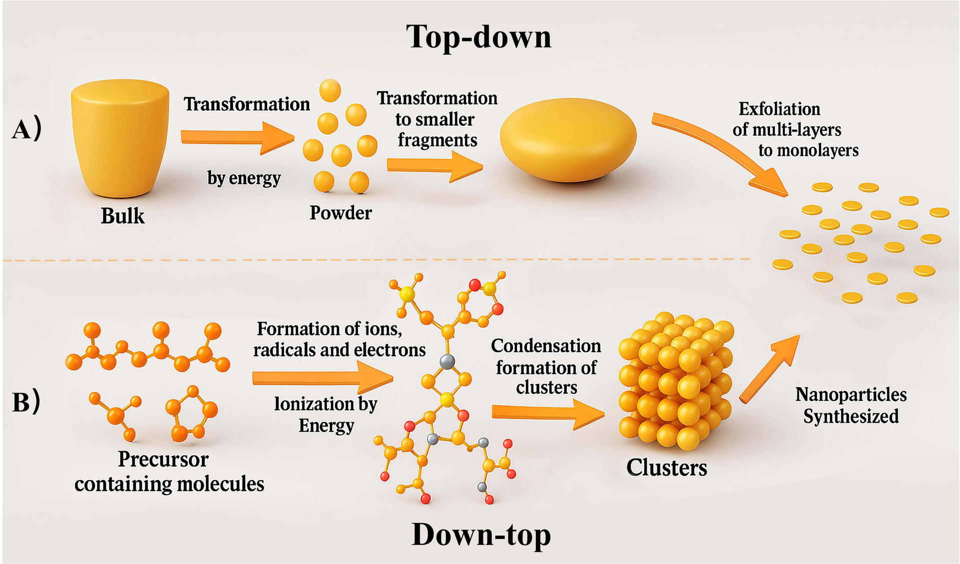


Figure 2 The two strategies for nanoparticle synthesis. (**A**) Top-down: breaking down large bulk materials into nanoscale particles through energy-driven decomposition. (**B**) Bottom-up: assembling nanoscale structures by reacting and polymerizing precursor molecules.

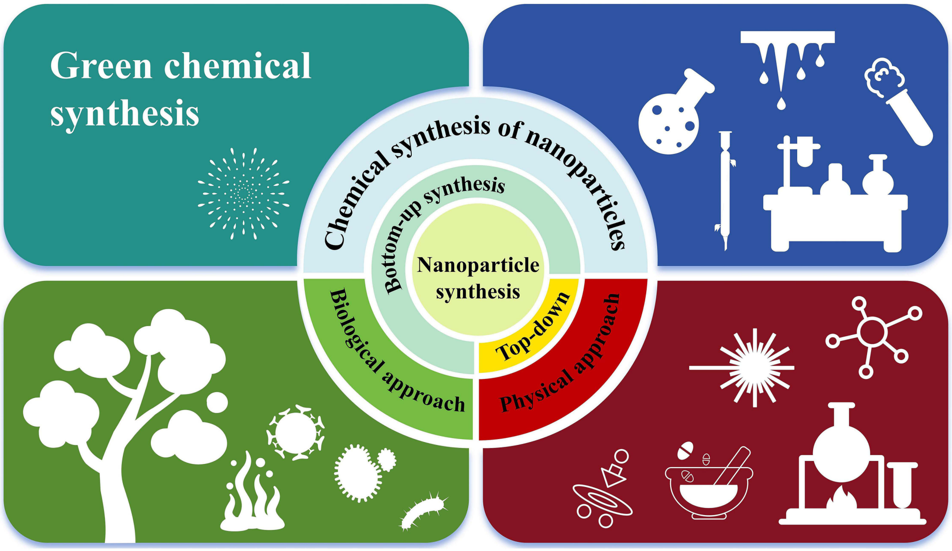


Figure 3 Schematic of the nanoparticle synthesis pathways. Top left: green chemical synthesis. Top right: gas-phase chemistry reaction, precipitation, hydrothermal synthesis, spray pyrolysis, and sol-gel method. Bottom left: actinomycetes, fungus, algae, bacteria, plants. Bottom right: laser ablation, lithography, thermal decomposition, milling, and etching.

storage.[22] In addition to biosynthesis, chemical synthesis is an alternative bottom-up technique for nanoparticle production. However, chemical methods often involve or produce toxic and hazardous substances, limiting their utility in biomedical applications.

Plants and Their Endophytic Fungi-Mediated Nanoparticles

Plant Green Biosynthetic Nanoparticles

The ability of plants to reduce metal ions was demonstrated in the early 20th century.[23] However, to date, research on the identity of these reducing agents remains limited.[24] Different synthetic schemes apply different principles. Synthesizing metal nanoparticles using entire plants involves absorption of metals from the environment, followed by their reduction and cellular accumulation in the form of nanoparticles.[11] Extracts from different plant parts, including the roots, stems, bark, leaves, flowers, fruits, and seeds, can be used to synthesize metal nanoparticles.[25] During the synthesis process, metal ions are first reduced to metal atoms, which then undergo nucleation to form the smallest nanoparticles before growing into larger nanoparticles. The compounds involved in the reduction of metal ions include hydroxyl, carbonyl, amino, and methoxy functional groups. These compounds interact electrostatically with metal ions and then undergo reduction reactions.[26] Plant secondary metabolites, alkaloids, cofactors, enzymes, flavonoids, and polyphenols also play a crucial role in the reduction process.[27] Over the last three decades, using plant extracts or tissue organs to reduce metal salts into nanoparticles has gained considerable attention owing to its efficiency and convenience.[28]

The Potential of Plant Endophytic Fungi in Green Nanoparticle Synthesis

Fungi are invaluable sources of natural products, exemplified by the discovery of penicillin, which sparked increased exploration and utilization of fungal resources. The use of microorganisms for nanoparticle synthesis is rooted in their metal resistance mechanisms.[29] Among the fungi that can produce nanoparticles, genera such as *Fusarium, Aspergillus, Trichoderma, Verticillium, Rhizopus*, and *Penicillium* are primarily used in research on nanoparticle biosynthesis. Silver and gold nanoparticles are the most commonly biosynthesized nanoparticles produced by fungi. These nanoparticles have been widely applied in various fields, including industry, medicine, and agriculture (Figure 4).[30]

The term "endophyte" was initially coined by Bary in 1866.[31] Plant endophytes are microorganisms that inhabit within the intercellular and/or intracellular spaces of their host plant throughout the entirety or a portion of the life cycle of the plant, generally without eliciting disease symptoms.[32] Using microorganisms for the biosynthesis of high-value secondary metabolites is a simple and economical approach, enhancing product availability and contributing to the reduction of market prices.[33] Since the isolation of the paclitaxel-producing endophytic fungus *Taxomyces andreanae* from the yew tree in 1993,[34] plant endophytic fungi have been recognized as a key source of natural bioactive compounds. With nearly 300,000 plant species globally, each harboring a diverse array of endophytes,[35] it is estimated

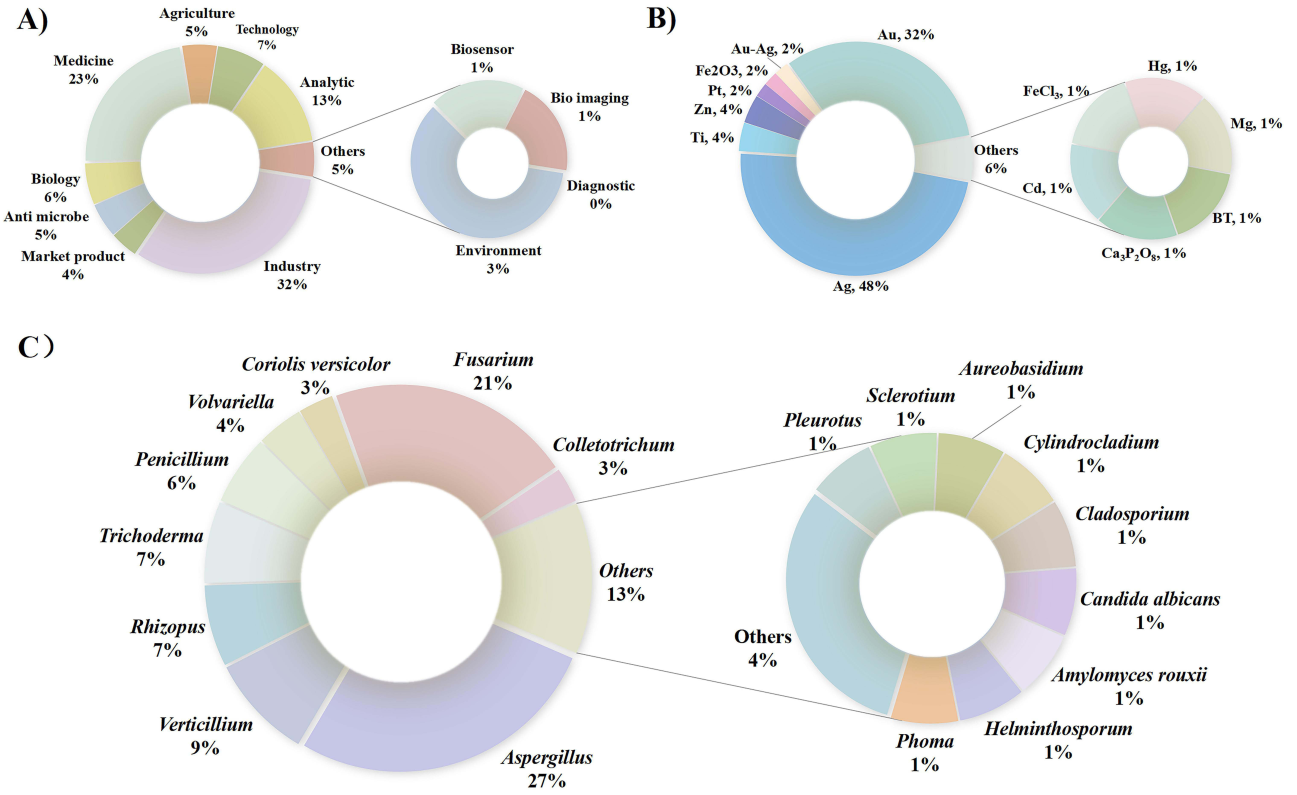


Figure 4 Overview of nanoparticle synthesis by fungi. (**A**) Different applications of fungal-based nanoparticles. (**B**) Application of different metals in the biosynthesis of nanoparticles by fungi. (**C**) Frequency of use of different fungal species for nanoparticles biosynthesis.

that over one million species of endophytic fungi exist in nature.[36] Despite numerous reports on the bioactive compounds of endophytic fungi, this field remains in its nascent stages.

Nanoparticle production by plants is typically facilitated by their enzymes, proteins, and amino acids.[37] For example, the reduction of silver ions to nanoparticles from *Dendranthema morifolium* extract is attributed to the presence of H^+, NAD^+, and ascorbic acid.[38] The alkaloids, proteins, enzymes, amino acids, alcohol compounds, and polysaccharides present in *Datura stramonium* leaf extract reduce silver ions and synthesize highly stable silver nanoparticles (AgNPs).[39] Similar compounds produced by plant endophytic fungi can also facilitate the reduction of metal ions and the synthesis of metal nanoparticles, both intracellularly and extracellularly. Their ability to produce nanoparticles is closely related to their metal ion tolerance and bioaccumulation capacities.[40] A strain of endophytic fungus *Aspergillus* sp. SA17 isolated from seagrass can synthesize spherical zinc oxide nanoparticles with an average size of 7.2 nm.[41] Nanosilver particles synthesized by *Penicillium polonicum* PG21, isolated from *Rehmannia glutinosa*, exhibit antibacterial activity against plant pathogens and significantly promote the growth of safflower (*Carthamus tinctorius*).[42] The endophytic fungus *Chaetomium globosum*, isolated from *Panax notoginseng*, biosynthesizes silver nanoparticles that can protect tomatoes from gray mold.[43]

Endophytic Fungi and Metal Nanoparticle Synthesis

Isolating endophytic fungi is a complex procedure that requires stringent aseptic conditions and depends on various factors, including the host plant species, tissue or organ of the plant, sampling season, endophytic fungi type targeted for isolation, and culture conditions.[44] The initial step involves selecting suitable plants and their corresponding tissue parts, with preference given to those known to successfully synthesize nanoparticles. It is advisable to collect plants that thrive in heavy metal-contaminated environments, as they are likely to harbor endophytic fungi capable of synthesizing nanoparticles.[45] After collection, the surfaces of the plant tissue samples must be sterilized to eliminate surface microorganisms. The sterilized tissue samples are then cut into uniform pieces of a given size, and their outer layers are disrupted to facilitate the growth of endophytic fungi. These tissue pieces are then placed onto culture medium plates for incubation at a constant temperature (Figure 5).[46] Alternatively, plant tissues can be ground under sterile conditions, serially diluted with sterile water, and plated onto isolation media for incubation at a constant temperature to isolate endophytic fungi.[47]

Although isolating endophytic fungi and metal nanoparticle synthesis are two distinct processes, they may be interrelated. Certain endophytic fungi can synthesize specific metal nanoparticles, which may exert beneficial influences on plant growth and development or exhibit other biological activities. A concise overview of the techniques for synthesizing metal nanoparticles using plant endophytic fungi is provided in Figure 5. The procedure is as follows: (1) Endophytic fungi are cultivated in an appropriate medium under controlled temperature conditions with agitation. Centrifugation or filtration is then applied to isolate endophytic fungal cells and extracellular fluid for nanoparticle synthesis. In intracellular synthesis, nanoparticles are formed within the hyphae. In extracellular synthesis, nanoparticles are produced by the cell-free filtrate derived from the fungi.[48] (2) Metal salt solutions of varying volumes are combined with endophytic fungal cells or extracellular fluid of different volumes to facilitate metal nanoparticle synthesis. The formation of certain metal nanoparticles can be preliminarily assessed through observable color changes and subsequently verified using nanoparticle characterization methods, such as spectral scanning.[49]

Optimization of Synthesis Conditions

The physicochemical properties of nanoparticles depend on their size and morphological structure, with both their dimensions and shape significantly influencing their characteristics and functionalities.[50] For instance, the surface area of nanosilver is closely correlated with its inhibitory activity against *Staphylococcus aureus* and *Escherichia coli*. Plate-like nanoparticles possess a larger surface area than rod-shaped configurations, resulting in superior antibacterial efficacy.[51] Moreover, at a size of 12 nm, zinc oxide nanoparticles can effectively inhibit the growth of pathogenic bacteria.[52] Therefore, during the fungal synthesis of nanoparticles, it is crucial to optimize various physical parameters, such as temperature, reaction duration, pH level, and metal ion concentration, to achieve effective nanoparticle morphology, size distribution, and yield efficiency (Table 1 and Figure 6).

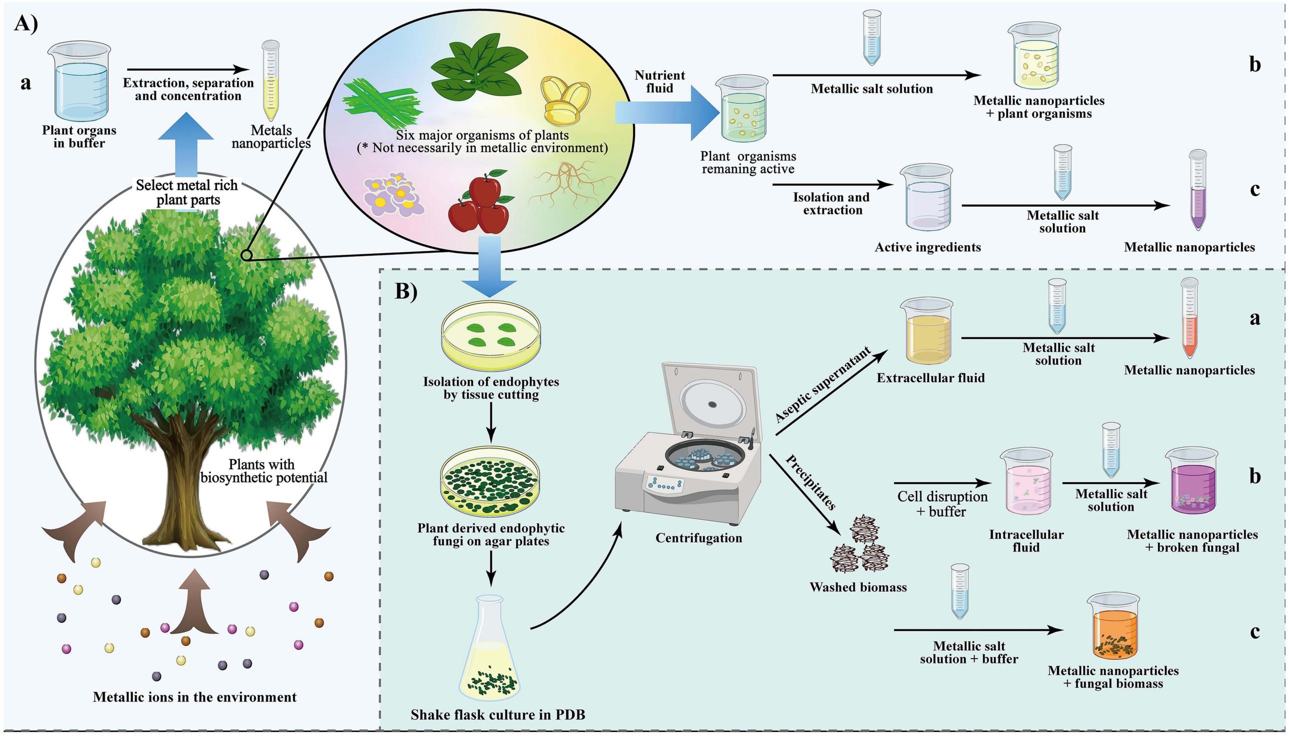


Figure 5 Schematic diagram illustrating the extraction of endophytic fungi from plants and metal nanoparticle synthesis. (**A**) Plant nanoparticle synthesis pathways: a, Extraction of metal nanoparticles absorbed and converted by plants from the environment; b, Nanoparticle synthesis directly within plant organs; c, Nanoparticle synthesis using active products derived from plants. (**B**) Pathways by which plant fungus endophytes synthesize nanoparticles. a, Nanoparticle synthesis from extracellular active products; b, Nanoparticle synthesis from intracellular actives; c, Metabolic synthesis of nanoparticles using fungal biomass. *: Explanation: The biosynthetic capacity of plant organisms is not necessarily related to whether they originate from a heavy metal-rich environment.

Mechanisms by Which Endophytic Fungi Synthesize Nanoparticles

The capacity of plants to synthesize nanoparticles arises from their diverse mechanisms designed to mitigate the detrimental effects of excessive metal accumulation.[11] Compounds with antioxidant properties play a crucial role in these protective mechanisms, as many metals produce reactive oxygen species (ROS) that can lead to significant cellular damage.[76] For example, phenolic compounds can enhance the antioxidant capacity of plants. The accumulation, reduction, and stabilization of metals within plant tissues have been confirmed in bioremediation processes, where metals are deposited as nanoparticles within the plant.[77]

Endophytic fungi play a crucial role in maintaining and supporting the normal functions of their host plants.[78] Notably, these fungi can produce metabolites that are either identical or functionally analogous to those produced by their host plants.[79] Given the synthetic capabilities of both plants and endophytic fungi, the demonstrated advantages of fungi in nanoparticle synthesis, their symbiotic relationship with host plants, and established successful synthesis protocols (Table 1), we propose the common mechanisms involved in the synthesis of fungal nanoparticles.[80] First, the polymers present in the cell wall function as electron carriers in reduction reactions catalyzed by nitrate-dependent reductases and pH-sensitive oxidoreductases. Second, the transfer of electrons from the external environment into the intracellular space can occur through metal reduction, facilitated by low-molecular-weight redox molecules such as nicotinamide adenine dinucleotide (NADH) or flavin dehydrogenase, as well as through direct interaction with cytochrome C oxidoreductase proteins. This process promotes the complex reduction of target metal ions into their corresponding nanoparticles.[81] Finally, metal precursors are subjected to oxidation and reduction reactions catalyzed by quinone derivatives derived from naphthoquinone and anthraquinone. These metal precursors are subsequently stabilized through the activity of fungal proteins and chelatins.

Table 1 Characteristics of Nanoparticles Synthesized by Plant-Derived Endophytic Fungi

Host Plant	Fungi	NPs	Metal Solutions	SM	pH	Tm	Time	Shape	Size (nm)	Biological Activity	Color Change	Λ_{max} (nm)	Ref
Oroxylum indicum	*Colletotrichum gloeosporioides*	AgNPs	$AgNO_3$	a	–	40±4°C	24 h	Sphere	9-29	Anti-breast cancer	Pale yellow to brown	400-450	[53]
Berberis aristata	*Colletotrichum gloeosporioides*	AgNPs	$AgNO_3$	a	-	room	12 h	-	Average 13	Antibacterial, antimalarial	Clear to brown to reddish brown	-	[54]
Lycium shawii	*Aspergillus flavipes*	AgNPs	$AgNO_3$	a	7	30°C	5 d	Sphere	Average 6.9232	Antibacterial	Colorless to yellow-brown	420	[55]
Ziziphus spinachristi	*Amesia atrobrunnea*	AgNPs	$AgNO_3$	a	7	25-30°C	73 h	Sphere	Average 10.64	Antifungal	Pale yellow to honey brown	435	[56]
Allium sativum	*Aspergillus terreus*	CuONPs	$Cu(CH_3COO)_2.H_2O$	a	8	-	1 h	Sphere	15-55	Antibacterial	Colorless to green	280	[57]
Blumea axillaris Linn.	*Xylaria arbuscula*	ZnONPs	$Zn(CH_3COO)_2.2H_2O$	a	9	28°C	72 h	CBH	Average 21	Antibacterial, antioxidant, antidiabetic, anti-inflammatory, dye-degrading	Colorless to white	370	[58]
Amoora rohituka	*Penicillium oxalicum*	AgNPs	$AgNO_3$	a	-	28±4°C	24 h	Sphere	5-23	Antibacterial, antifungal, antioxidant, anticancer	Pale yellow to brown	420	[59]
Acalypha hispida Burm	*Aspergillus niger*	ZnONPs	$Zn(CH_3COO)_2$	a	11	Water bath	30 min	Sphere	Average 23.97	Antibacterial	White	380	[60]
Datura metel	*Aspergillus terreus*	AuNPs	$HAuCl_4.3H_2O$	a	8	40°C	24 h	Sphere	10-16	Antibacterial	Light yellow to pink ruby red	536	[61]
Prunus persica	*Phoma sp.*	AuNPs	$HAuCl_4$	a	-	28°C	48 h	Sphere	10-100	Antifungal, antibacterial	Red	526	[62]
Cymbopogon citratus	*Fusarium proliferatum*	FeNPs	$FeCl_3$ and $FeSO_4$	a	7	35±2°C	24 h	Sphere	20-50	Removal of triphenylmethane dyes	Greenish-brown/black to orange/brown	260-270	[63]
Citrus pseudolimon	*Colletotrichum plurivorum*	Ag_2ONPs	$AgNO_3$	b	-	-	24 h	Cubes	Length 200–250, width 80-150	Antibacterial	Pale yellow to dark yellow and to orange	560	[64]
Aegle marmelosa	*Aspergillus terreus*	CuONPs	$CuSO_4$	a	7.4	-	36-48 h	-	<100	Antibacterial, antioxidant, anticancer	Brown	551	[65]
Origanum majorana	*Aspergillus terreus*	Co_3O_4NPs	$CoSO_4 \cdot 7H_2O$	a	6	-	2 h	Sphere	10.35	Antioxidant, antibacterial	Pink to dark	230	[66]
		CuONPs	$CuSO_4 \cdot 5H_2O$	a	6	-	2 h	Sphere	18.95		Blue to green	256	
		Fe_3O_4NPs	$Fe(NO_3)_3 \cdot 9H_2O$	a	6	-	2 h	Sphere	32.41		Yellow to deep black	285	
		NiONPs	NiSO4 $\cdot 6H_2O$	a	6	-	2 h	Sphere	42.51		Green to brown	330	
		ZnONPs	$ZnC_4H_6O_4 \cdot 7H_2O$	a	6	-	2 h	Irregular sphere	30.45		Colourless to cloudy white	370	
Commiphora wightii	*Cladosporium sp.*	AuNPs	$HAuCl_4$	a	-	37°C	-	Sphere	5-10	Anticancer, degradable fuels	Yellow to burgundy	524	[67]
Chonemorpha fragrans	*Fusarium solani*	AuNPs	$HAuCl_4$	a	8.5	-	48 h	-	40-45	Anticancer	Changes to pink-fuchsia	510-560	[68]
Datura metel	*Colletotrichum incarnatum*	AgNPs	$AgNO_3$	-	7	-	-	Sphere	5-25	Antibacterial, anticancer	Yellow to dark brown	420	[69]
Pinus densiflora	*Talaromyces purpureogenus*	AgNPs	$AgNO_3$	a	-	27°C	96 h	Circles and triangles	25	Anticancer, antibacterial	White to dark brown	418	[70]
Catharanthus roseus	*Botryosphaeria rhodina*	AgNPs	$AgNO_3$	a	-	Room	24 h	Sphere	2-50	Anticancer	Light brown to dark brown	450	[71]

Note: Synthesis: a extracellular solution; b intracellular extract; SM, synthesis method; NPs, nanoparticles; Tm, temperature; CBH, cylindrical bar and hexagonal; λ_{max}, maximum absorption peak wavelength;

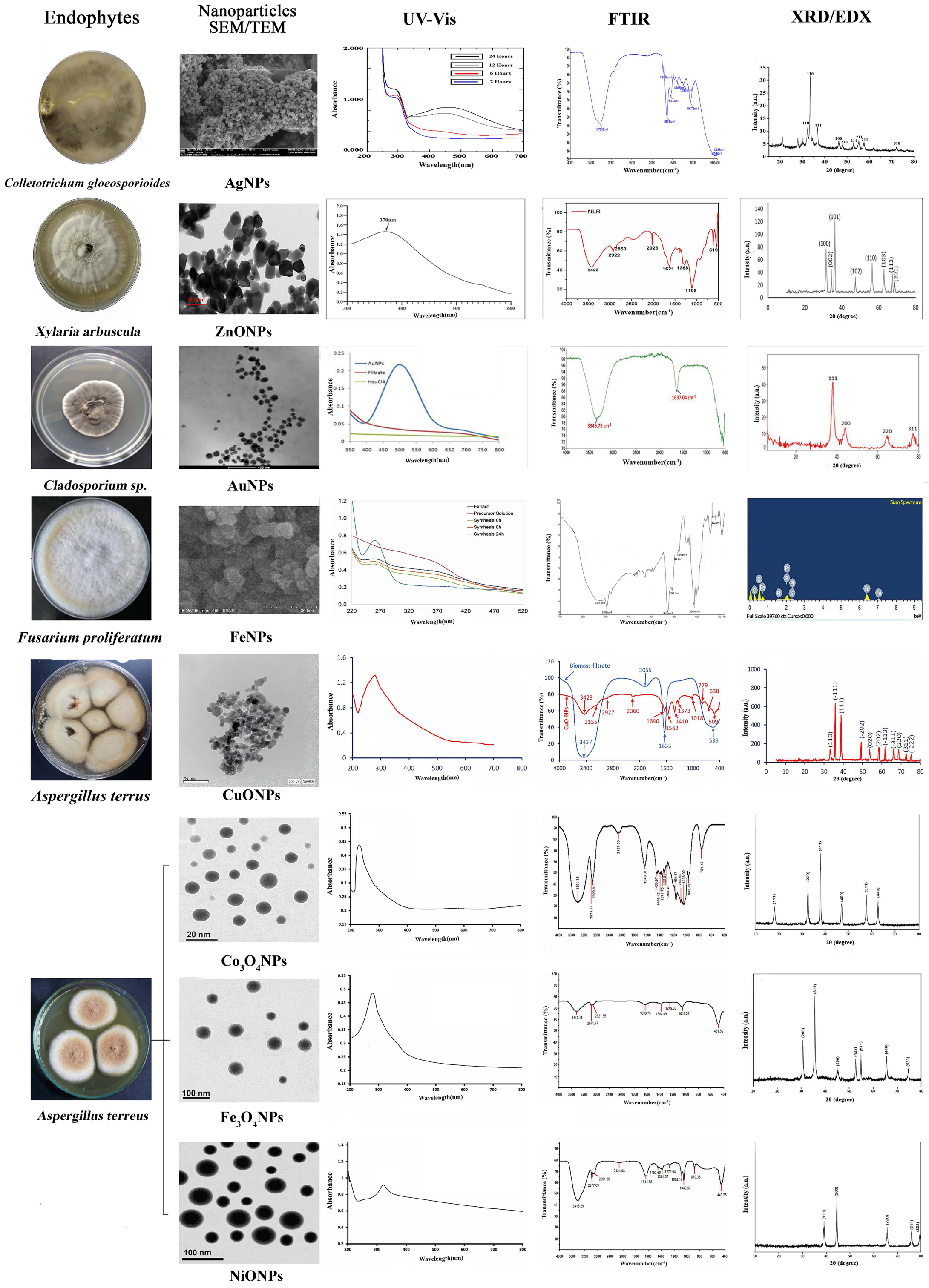


Figure 6 Characterization of nanoparticles synthesized by endogenous fungi under optimized conditions. The image of *Colletotrichum gloeosporioides* is reproduced with permission from Ref.[72] and the copyright 2022 Public Library of Science. The characterization images of AgNPs are reproduced with permission from Ref.,[53] © 2024 Elsevier B.V. The image of *Xylaria arbuscula* is reproduced with permission from Ref.,[73] © 2024 MDPI (Basel, Switzerland). The characterization images of ZnONPs are reproduced with permission from Ref.,[58] © 2023 Informa Healthcare. The image of *Cladosporium*. sp and the characterization images of AuNPs are reproduced with permission from Ref.,[67] © 2020 Elsevier B.V. The image of *Fusarium proliferatum* is reproduced with permission from Ref.,[74] © 2023 Springer Nature. The characterization images of FeNPs are reproduced with permission from Ref.,[63] © 2022 Taylor & Francis. The image of *Aspergillus terreus* is reproduced with permission from Ref.,[75] ©2019 MDPI (Basel, Switzerland). The characterization images of CuONPs are reproduced with permission from Ref.,[57] © 2023 BMC. The image of *A. terreus* and the characterization images of Co_3O_4NPs, Fe_3O_4NPs, and NiONPs are reproduced with permission from Ref.[66] © 2021 Springer Berlin Heidelberg.

Intracellular and Extracellular Synthesis Pathways

Microbiologically mediated nanoparticle synthesis encompasses both extracellular and intracellular methods, using cell-free supernatants and cell lysates or extracts, respectively.[82] There are notable differences between these two methods (Figure 7). For example, *Fusarium oxysporum* produces two distinct forms of nanoparticles: extracellularly secreted and intracellularly synthesized nanoparticles.[83] In the intracellular synthesis pathway, *F. oxysporum* is cultivated under optimal growth conditions to yield sufficient biomass. The harvested mycelium undergoes washing with sterile water, followed by incubation with an appropriate concentration of metal salts. The electromotive force facilitates the attraction and rapid absorption of cations, resulting in the adhesion of metal ions (M^+) to lysine residues on the fungal cell wall. This process is further supported by electrostatic interactions with the negatively charged surface of *F. oxysporum*. Subsequently, M^+ is reduced and precipitated by enzymes located within the cytoplasmic membrane, such as ATPase and hydrogenase, as well as those in the cell wall. This process results in nanoparticle production, followed by vesicle

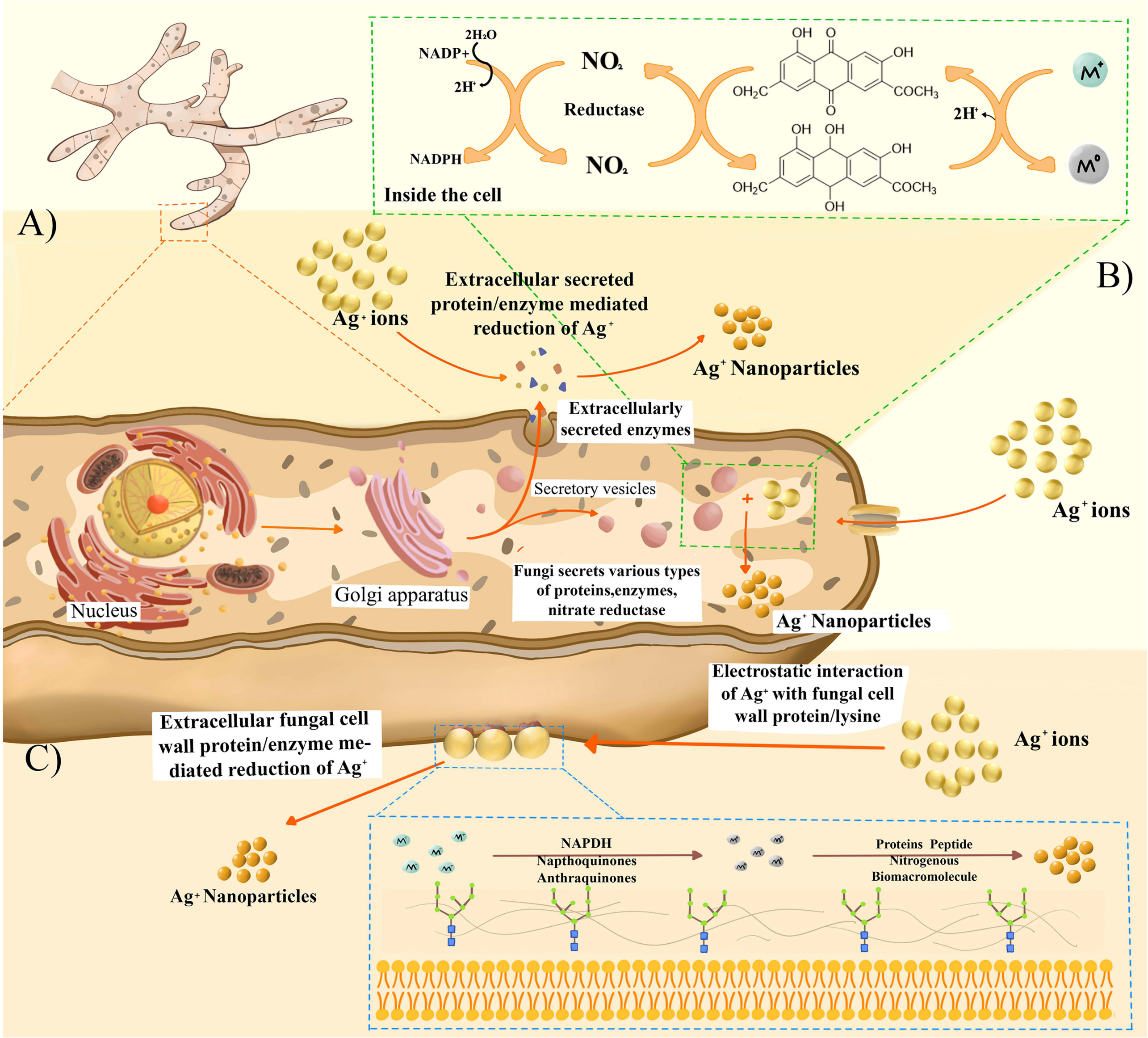


Figure 7 Schematic illustration of the mechanisms underlying fungi-mediated nanoparticle synthesis, specifically that of silver nanoparticles. **(A)** Extracellular fungal products reduce silver ions to form nanoparticles. **(B)** Intracellular substances within the fungus convert absorbed silver ions into nanoparticles. **(C)** Fungal cell wall proteins, enzymes, and polymers, along with electron shuttles such as naphthoquinones and anthraquinones, catalyze the reduction process through NADPH-dependent nitrate reductase. Subsequently, fungal proteins stabilize the nanoparticles.

aggregation and extracellular secretion.[80] Conversely, during extracellular synthesis, fungal enzymes present in the supernatant following liquid culture, including cytochrome b5 reductase, oxidoreductase, FAD-dependent glutathione reductase, and NADH-dependent nitrate reductase, are incubated with an aqueous solution of metal salts to facilitate nanoparticle generation. These nanoparticles are stabilized by nitrogen-containing biomacromolecules or proteins present in the supernatant.[59]

Roles of Fungal Enzymes in Nanoparticle Synthesis

Regardless of whether the synthesis of nanoparticles occurs intracellularly or extracellularly, the cellular constituents of fungi serve as crucial electron donors, playing a crucial role in nanoparticle synthesis through their catalytic activities.[84] Fungal constituents include cell walls, membrane-associated molecules, enzymes, cationic proteins, alkaloids, flavonoids, polysaccharides, phenolics, and other organic biomolecules. Fungi can degrade or hydrolyze intricate polymeric substrates through the action of extracellular enzymes, enabling them to assimilate and metabolize these substrates. Compared to other microorganisms, fungi consistently produce enzymes in substantial quantities. Owing to their cost-effective cultivation methods, reliable genetic manipulation techniques, and efficient downstream processing procedures, fungi have received considerable attention across various enzyme-based industries.[85]

In the green biosynthesis of nanoparticles, enzymes, cofactors, and biomolecules involved in the reduction of metal ions to metal nanoparticles, along with their respective mechanisms of action, are integral components of the process.[86] For example, nitrate reductase (NR), a ubiquitous enzyme, functions as a soluble NADPH-dependent assimilatory enzyme in bacteria, fungi, and plants. It facilitates the conversion of nitrate into nitrite, which is then reduced to ammonia by nitrite reductase.[87] Notably, NR has been identified as a crucial participant in nanoparticle biosynthesis, making it a focal point in studies investigating the synthesis mechanism. In 2006, Kumar et al used an α-NADPH-dependent NR derived from the fungus *F. oxysporum*, along with phytochelatin, to successfully synthesize AgNPs in vitro. Under the catalytic action of NR, Ag^+ was reduced to form stable silver sols with diameters of 10–25 nm, which were stabilized through the capping peptides.[88] Additionally, sulfite reductase (SR) is a key enzyme in the assimilation of sulfur and the dissimilation of oxygen anions such as sulfate and sulfite.[89] Sastry et al reported that *F. oxysporum* secretes SR, converting sulfate ions into sulfide ions. These sulfide ions subsequently react with aqueous Cd^{2+} to form highly stable cadmium sulfide nanoparticles with sizes of 5–20 nm.[90]

Proteases constitute a substantial class of enzymes, categorized into six primary categories based on substrate specificity, catalytic mechanism, active site attributes, optimal operational parameters, and thermal stability. These categories include serine proteases, serine carboxypeptidases, cysteine proteases, aspartic proteases, metalloproteases, and metal carboxypeptidases.[91] Despite the scarcity of current reports on fungal proteases, bacterial proteases have been successfully used to synthesize nanoparticles, providing insights for investigating nanoparticle synthesis associated with endophytic fungi. For example, Muzikar used purified and overexpressed *Escherichia coli* harboring the glutathione reductase (GR) gene to synthesize gold nanoparticles (AuNPs), demonstrating that GR can catalyze NADPH-dependent gold reduction. This process resulted in the formation of AuNPs that can bind to the active site, with their size precisely controllable over a broad range.[92]

Characterization Methods

Structurally, nanoparticles can be classified into decahedra, icosahedra, face-centered cubic, and hexagonal close-packed structures.[93] One of the most notable characteristics of nanomaterials is their minuscule size.[94] Nanomaterials are composed of minute molecular or atomic units, conferring them with physical or chemical properties that distinguish them from bulk materials consisting of the same chemical elements. These distinctive mechanical, electrical, magnetic, and thermal properties have been widely leveraged in rapidly evolving technological fields.[95] Determining the success of nanoparticle synthesis and assessing the quality of the synthesized nanoparticles are crucial steps in advancing nanotechnology. Nanoparticles are characterized by attributes such as size, shape, surface area, and dispersibility,[96, 97] and the uniformity of these characteristics is crucial across many applications. Common methods used for characterizing nanoparticles include ultraviolet-visible spectroscopy, dynamic light scattering, scanning electron microscopy, transmission electron microscopy, Fourier transform infrared spectroscopy, powder X-ray diffraction, and energy-dispersive spectroscopy. Each of these techniques has certain advantages in the characterization of nanoparticles, as outlined in Table 2.

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Table 2 Various Techniques to Characterize Nanoparticles Along with Their Respective Merits and Demerits

Techniques	Principle	Key parameters	Advantages	Limits	Ref
UV-Vis	Beer-Lambert's law light absorption in a sample is proportional to its path length and concentration.	Size, shape, concentration, agglomeration, refractive index.	Simple to operate, easy to sort.	The separation of absorption peaks among nanoparticles of varying sizes is inadequate, and lacks a highly specific spectrum for certain molecules.	[98]
DLS	Brownian motion of dispersed particles with solvent molecules, causing energy transfer and particle motion.	Changes in particle size and stability with suspension time at different pH and temperature.	Capable of measuring small particles, accurate and repeatable data for 2 nm and larger particles.	Multiple particles scatter multiple times before reaching the detector, affecting the accurate calculation of particle size in concentrated samples	[99]
AFM	Weak electrostatic attraction or repulsion between the probe and the sample surface.	3D visualisation for shape, size and distribution; nanoparticle count.	Accurate maps of surface features; without sample handling or vacuum requirements	Single-scan image size (150 μm × 150 μm); thermal drift due to relatively slow scan time.	[100]
TEM	Imaging nanoparticles using electron beam.	Particle size, morphological information, crystallographic data, chemical composition, plane type, phase type and distribution.	Powerful magnification for high quality and detailed images; dynamic crystallisation with high angle grain boundary formation	Large volume of sample preparation, costly and laborious work; professional data interpretation training prior to operation.	[101]
SEM	Fine medium energy electron beam to scan the sample under generating secondary electrons.	Particle size distribution, standardised measurements for "in-depth" observation.	The simultaneous measurement of numerous samples ensures high statistical reliability and efficiency in assessing nanoparticle size and shape distribution.	Expensive, bulky, and need an environment free from any potential electrical, magnetic or vibration interference.	[102]
XRD	Structural interference of monochromatic X-rays and crystalline samples	Phase identification, sample purity, crystalline size, and morphology	Strong and fast technology.	Homogenous sample; need to obtain standard reference data.	[95]
FT-IR	Absorption of infrared radiation by samples.	Surface adsorption of functional groups on nanoparticles.	Higher signal-to-noise ratio; high accuracy, good quality, high energy throughput and stability.	Large background noise and low resolution at higher wavelengths.	[103]

Abbreviations: UV-Vis, Ultraviolet–visible spectroscopy; DLS, Dynamic light scattering; AFM, Atomic force microscope; TEM, Transmission electron microscope; SEM, Scanning electron microscope; XRD, X-ray diffraction; FT-IR, Fourier transform infrared spectroscopy.

Application of Biosynthetic Metal Nanoparticles in Cancer Treatment

Cancer poses a significant threat to human life and health, presenting a considerable challenge for the medical community in developing definitive cures. Current clinical treatments for cancer include surgery, chemotherapy, immunotherapy, and radiation therapy.[104] Notably, advancements in nanotechnology and nanoparticle biosynthesis using endophytic fungi have driven significant progress in the application of biosynthesized nanomaterials to cancer research and treatment.[105] Nanotechnology represents an innovative and promising field that offers exceptional tools for cancer detection and management.[106] The applications of nanoparticles in anticancer research (Figure 8) are extensive:[107] (1) They provide novel imaging agents that enhance imaging efficacy and seamlessly integrate with existing detection instruments, thereby advancing cancer diagnosis and treatment while minimizing toxic side effects.[108] (2) Nanoparticles help overcome biological barriers to directly deliver therapeutic drugs to cancer tissues, making personalized medicine increasingly feasible in routine clinical practice.[109] Metal nanoparticles represent a diverse range of nanoscale materials containing various metal ions, such as iron, copper, zinc, gold, silver, and titanium, which can be combined with other organic or inorganic components.[110] This combination enhances their pharmacological functions. Moreover, these metal-derived nanocomposites, including antibodies and peptides, can target cancer cells or prolong their circulation time in

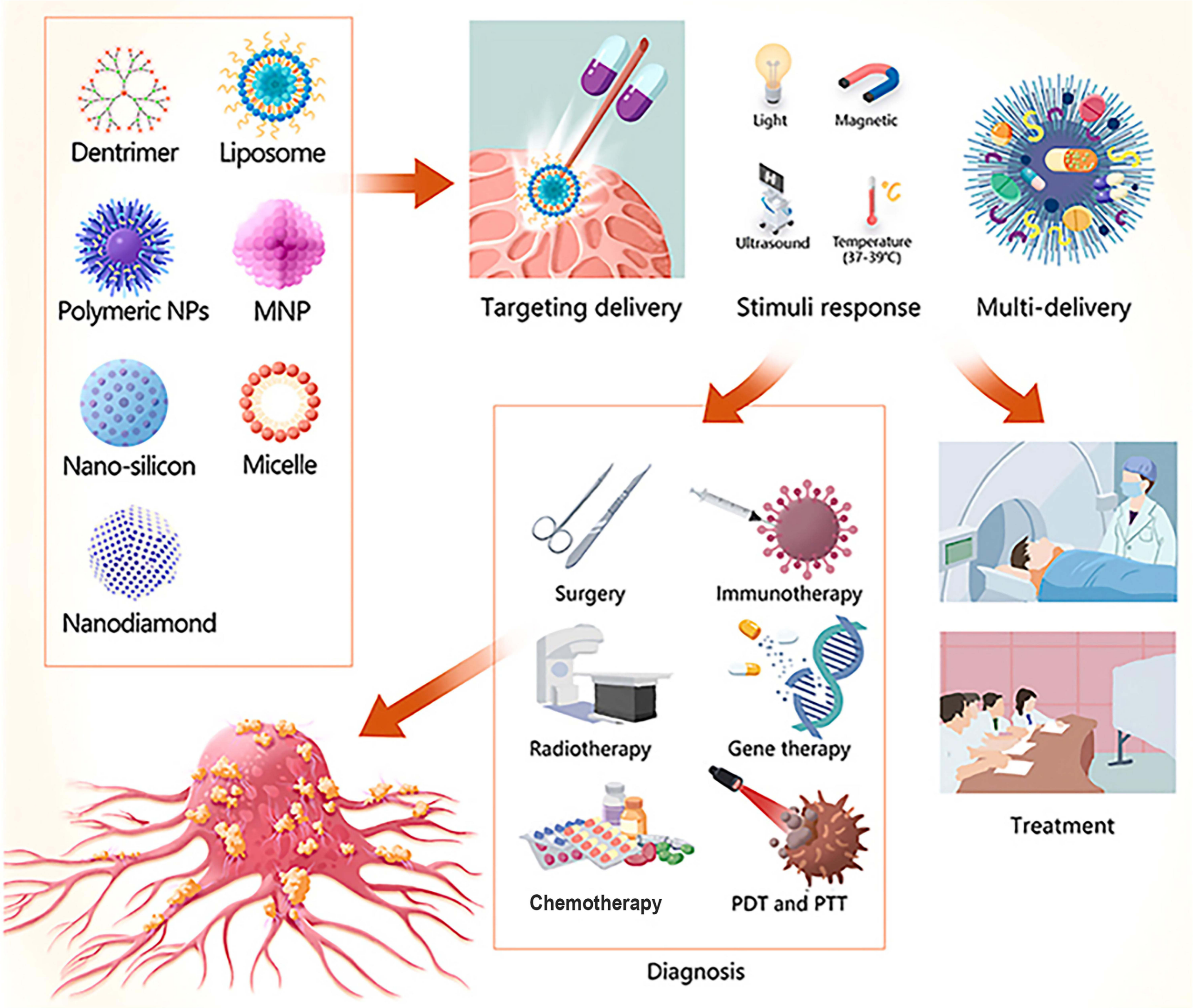

Figure 8 An example of the application of nanobiomaterials to the diagnosis and treatment of head and neck cancers (HNCs). Nanomaterials can serve as carriers to encapsulate various agents, including imaging agents, drugs, genes, vaccines, radiosensitizers, and photosensitizers. These nanocarriers enable targeted delivery, stimulus response, and multi-delivery, potentially enhancing the efficiency of HNC diagnosis and treatment. Reproduced with permission from Ref.[113] © 2023 Elsevier B.V.

conjunction with biocompatible polymers for therapeutic purposes.[111] (3) Nanoparticles enable tumor visualization and targeted drug delivery, indirectly contributing to cancer diagnosis and treatment. Furthermore, biomedical metal nanoparticles may exhibit direct anticancer properties and serve as pivotal agents in cancer therapy. In this process, metal ions within the nanoparticles can generate ROS and induce oxidative stress, leading to the death of malignant cells.[112]

Cancer Detection and Diagnosis

Traditionally, tumor diagnosis often involves surgical excision for tissue sampling. However, this approach has several limitations, including biodegradation, limited specificity, and potential inaccuracies in results. Subsequent therapeutic interventions are often hindered by short drug retention periods and inadequate targeting capabilities.[114] The application of nanotechnology in molecular diagnostics, known as nanodiagnostics,[115] involves integrating nanodevices with existing diagnostic methods to enable more precise in vivo and in vitro detection of cancerous lesions (Figure 9A).[116] This integration significantly enhances detection sensitivity, facilitating early diagnosis and treatment.[117] In terms of imaging modalities, computed tomography (CT) is effective at detecting differences in electronic density between tumors and

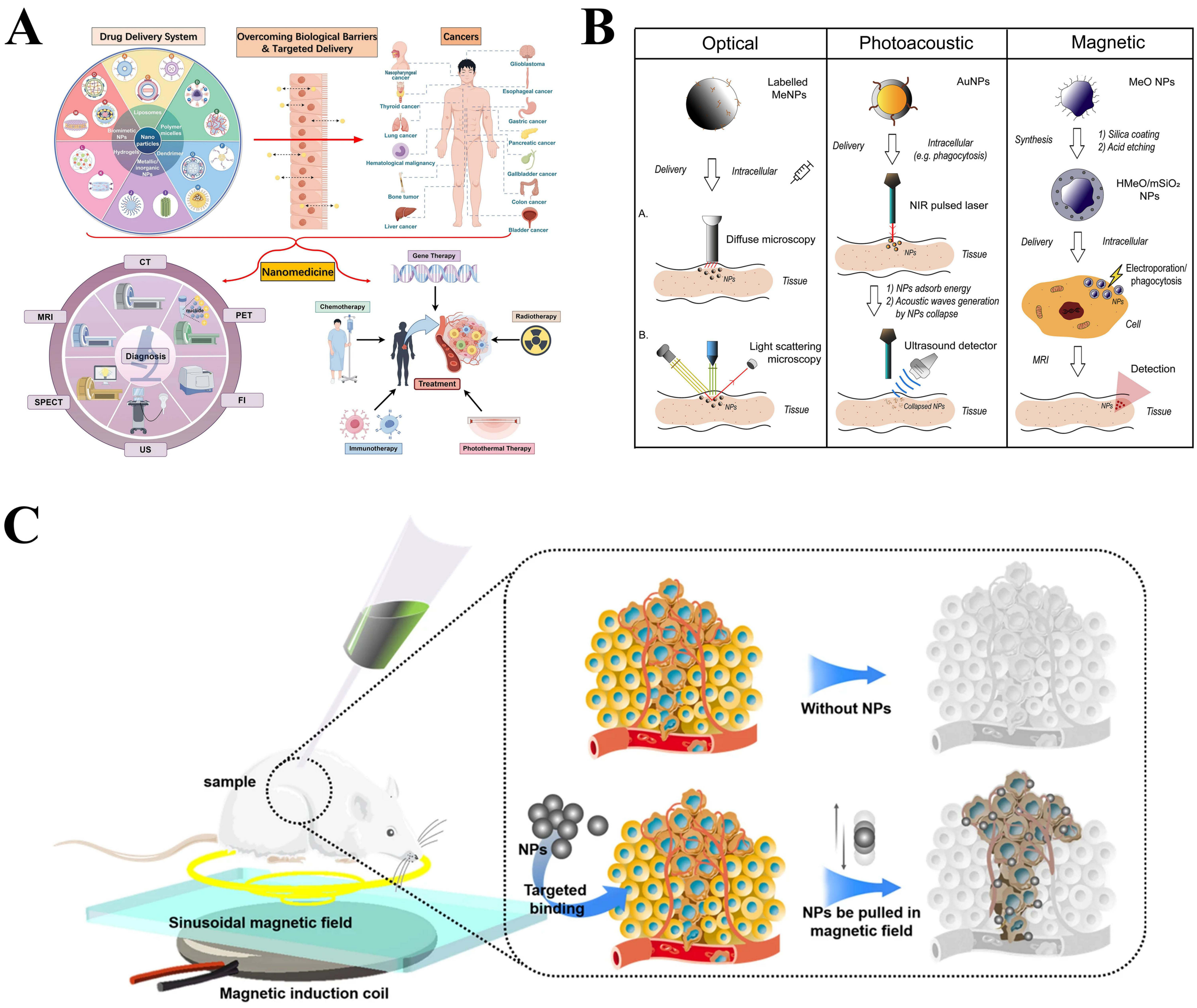

Figure 9 Application of nanoparticles to cancer diagnostics. (**A**) Summary of the diagnostic techniques used in nanomedicine during the therapeutic process. Reproduced with permission from Ref.,[106] © 2024 Springer Nature. (**B**) Metal and metal oxide nanoparticles used in tumor imaging. Reproduced with permission from Ref.,[110] © 2020 Elsevier B.V. (**C**) A schematic illustrating mice undergoing nanoparticle-enhanced diagnostic imaging. Reproduced with permission from Ref.,[122] © 2021 Springer US.

surrounding tissues, making it a commonly used tool for identifying cancer cells. CT provides comprehensive information about tumors, including their size and precise location.[118] However, its sensitivity is often compromised in soft tissues,[119] and its application alone is insufficient for effectively detecting potential tumors. Notably, this limitation can be addressed by incorporating contrast agents, such as nanoparticles (Figure 9B).[120] Currently, CT utilizes folic acid-cysteine-AuNPs to improve the detection of small and indistinguishable head and neck tumors.[113] Magnetic resonance imaging (MRI) is also used for tumor detection, where magnetic nanoparticles or iron oxide nanoparticles serve as contrast agents targeting cancer cells.[121] These agents enable the quantification of the magnetization of hydrogen molecules (Figure 9C),[122] enhancing the visibility and quantification of images.[123] Although magnetic nanoparticles cannot penetrate cancer cells, they can be taken up by healthy Kupffer cells in the liver, resulting in distinct MRI images that differentiate healthy from cancerous cells. Cancer cells appear in high-signal images, whereas healthy cells generate low-signal images.[124] This capability has greatly advanced liver imaging, meeting the medical needs of patients with cancerous lesions and those with significant liver and kidney impairments. In addition to standard paramagnetic nanoparticles, the versatility of nanoparticles can be leveraged by embedding tumor-specific markers within them, leading to differentiated images for various cancer types. Such combinations may play a crucial role in the diagnosis and treatment of tumors.[125] However, the current availability of biosynthesized nanoparticles for research and application in this field remains limited, highlighting a potential direction for future investigation.

Synergistic Effects of Nanoparticles in Combination with Anticancer Drugs

When combined with existing therapeutic compounds or drugs, nanomaterials can enhance efficacy, particularly by reducing drug side effects and improving treatment safety and stability. Utilizing the synergistic interaction between nanoparticles and drugs represents an effective strategy for increasing the activity of anticancer drugs and enhancing their bioavailability (Figure 10). Specifically, nanoparticles can target cancer cells either passively or actively, exhibiting promise as drug delivery systems.[126] Tumors often have large interstitial gaps of approximately 100 to 800 nm, which create defective, barrier-like blood vessels. These vessels allow only small nanoparticles to traverse and accumulate near the tumor. This selective accumulation minimizes interactions between nanoparticles and normal cells, minimizing adverse effects on healthy tissue and enhancing drug efficacy through targeted delivery.[126] In addition to passive targeting, which relies on the physical attributes of nanoparticles, the particle surface can be further modified by attaching specific targeting molecules or applying biocompatible molecules and biodegradable polymers.[127] However, not all combinations yield synergistic outcomes, as effective nanocarriers for the targeted delivery of anticancer drugs must meet the following prerequisites: (1) possess a strong affinity for anticancer drugs and enable conjugation; (2) ensure complete drug release the intended target site; (3) maintain stability of the drug–nanoparticle complex in serum; and (4) their degradation must pose no risk to the organism.[128]

The synergistic properties of nanoparticles have been effectively utilized to enhance the efficacy of conventional pharmaceuticals. For example, NGO-AgNPs-PEG, a PEGylated silver-decorated graphene nanocomposite material synthesized using the aqueous extract of *Azadirachta indica* leaves as a reducing agent and loaded with doxorubicin (DOX), demonstrates significantly improved loading efficiency. Compared to free DOX, NGO-AgNPs-PEG loaded with DOX causes reduced damage to normal cells while exhibiting increased toxicity to HeLa cells.[129] Moreover, imatinib-loaded silver nanoparticles (IMAB-AgNPs) exhibited a dose-dependent cytotoxic effect on MCF-7 cells, with half maximal inhibitory concentration (IC50) values of 1.69, 3.02, and 9.63 μM for IMAB-AgNPs, IMAB, and AgNPs, respectively. IMAB-AgNPs also induce the expression of apoptotic proteins.[130] In another study, AgNPs, biosynthesized using the water extract of *Setaria verticillata* seeds, were loaded with the hydrophilic anticancer drugs daunorubicin (DNR) and DOX. Notably, the cytotoxicity of these AgNPs increased with the concentration of seed extract, and the loading efficiency of DNR-AgNPs was 40.25%, whereas that of DOX-AgNPs was 80.50%.[131]

Direct Intervention Effects of Nanoparticles

To date, relatively few studies have explored the use of biosynthesized nanoparticles in oncological diagnostics. In contrast, bio-sourced nanoparticles have been widely investigated as adjuncts to clinically validated drugs for therapeutic applications. Most research on cancer nanotherapeutics has primarily focused on the effects of nanoparticles on cancer

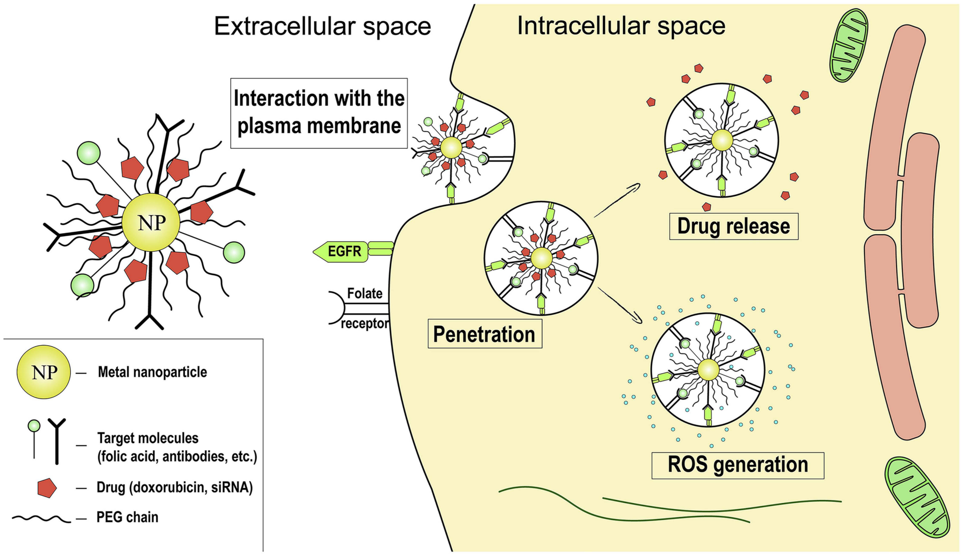

Figure 10 Application of metal nanoparticles in chemotherapy. Nanoparticles (NPs) can carry antibodies targeting tumor-specific receptors, directing them to the tumor site. They penetrate the plasma membrane to release chemotherapeutic agents. They exhibit antitumor potential by generating reactive oxygen species (ROS) and inducing tumor cell death. Reproduced with permission from Ref.,[110] © 2020 Elsevier B.V.

cells. The most direct effects of nanoparticles on these cells include the induction of cell death mechanisms such as apoptosis, cell cycle arrest, and ferroptosis. Moreover, the progression of tumors to advanced stages is largely attributed to the proliferation and spread of cancer cells. Certain nanoparticles exhibit anti-angiogenic and anti-metastatic properties, significantly slowing disease progression. Additionally, Virchow's hypothesis,[132] which suggests a link between lymphoreticular infiltration and cancer development at sites of chronic inflammation, underscores the crucial role of inflammatory processes in regulating cancer progression through inflammatory factors, cytokines, and chemokines within the tumor microenvironment.[133] Notably, metal nanoparticles often exert robust anti-inflammatory effects and can be used to inhibit tumor growth and metastatic dissemination associated with chronic inflammation.[134]

Direct Impacts on Cancer Cells

Inducing apoptosis in tumor cells is a crucial strategy in the development of anticancer drugs.[135] When cells are exposed to external, non-receptor-mediated stimuli, the mitochondrial membrane potential becomes disrupted, triggering the apoptotic process.[136] In the extrinsic signaling pathway, apoptosis is triggered by the activation of a transmembrane receptor, facilitating the transduction of extracellular signals into the cytoplasm. Importantly, metal nanoparticles can stimulate apoptosis in various cancer cells, including breast, lung, liver, colorectal, bladder, ovarian, and cervical cancer cells (Figure 11A).[137]

In gastrointestinal digestion, AgNPs can induce apoptosis by upregulating nicotinamide adenine dinucleotide oxidase (4-NOX4), thereby stimulating mitochondrial oxidative stress. When colon cancer cells (HCT116) are treated with AgNPs, pre-treatment with diphenyleneiodonium chloride (DPI) or 4-phenylbutyric acid inhibits several key responses, including the generation of mitochondrial ROS, apoptosis, endoplasmic reticulum stress response, NOX4 expression, and mitochondrial dysfunction.[138]

Nanoparticle synthesis using plant extracts has witnessed advancements. For example, the reduction of $AgNO_3$ using an extract from Chinese cabbage leaves (*Brassica rapa* var. *japonica*) acts as both a reductant and stabilizer, resulting in the production of spherical AgNPs with a size range of 15–30 nm. These nanoparticles exhibit potent growth inhibitory effects against certain bacteria and cause the downregulation of the NF-κB/Akt/mTOR signaling pathways in colorectal cancer (Caco-2) cells, leading to apoptosis and DNA damage.[139] Moreover, the endophytic fungus *F. chlamydosporum* MW341592.1, isolated from healthy leaves of *Eucalyptus sideroxylon*, can biosynthesize both zinc oxide nanoparticles (ZnONPs) and AuNPs. These nanoparticles can reduce the number of HCT116 human colon cancer cells and Caco-2 human intestinal cancer cells.[140] In human breast cancer cells (MCF-7), bismuth(III) oxide nanoparticles demonstrate dose- and time-dependent apoptotic effects by

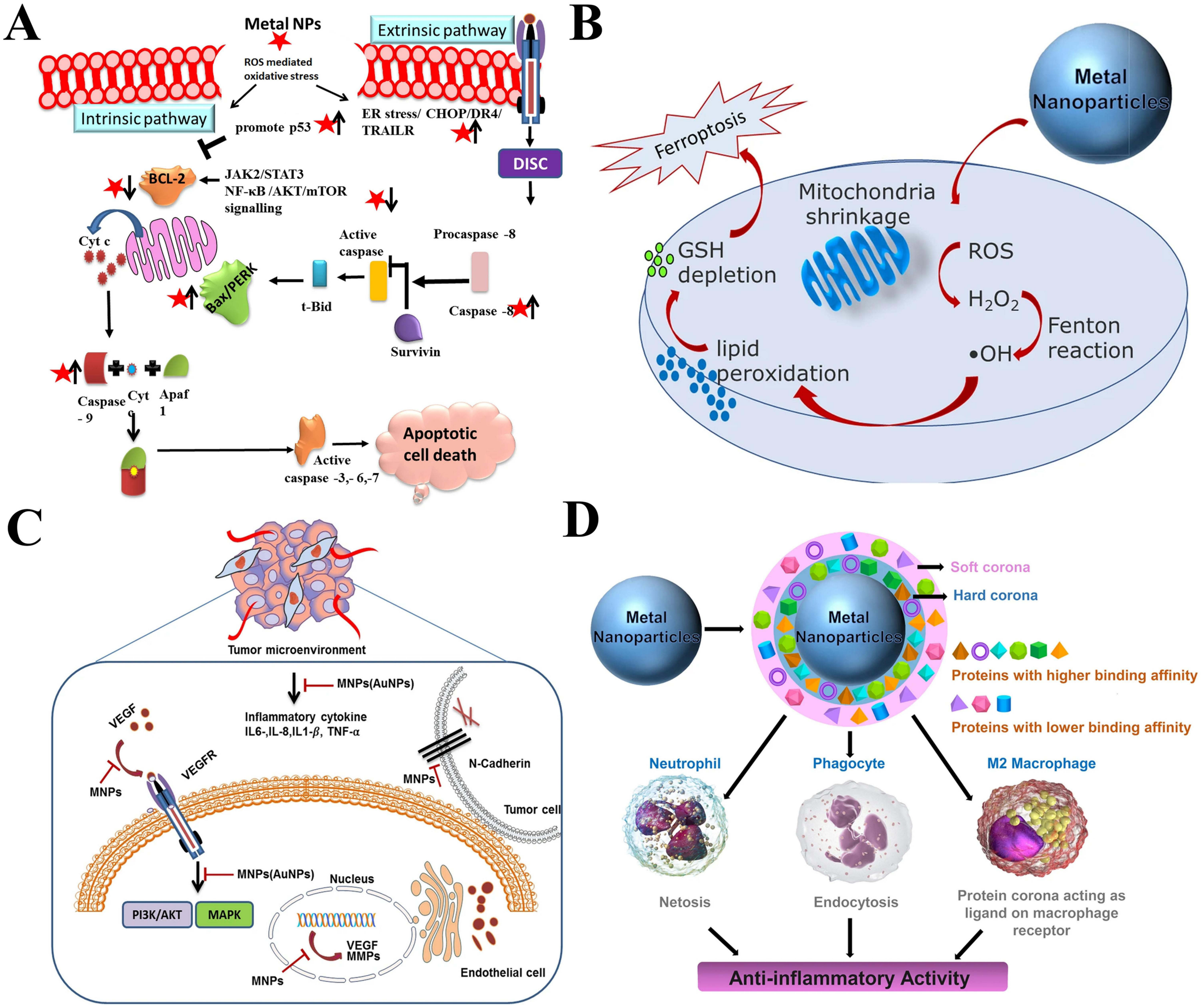

Figure 11 Direct intervention role of nanoparticles. (**A**) A representative scheme of intrinsic and extrinsic signaling pathways governed by metal nanoparticles (NPs), leading to apoptotic death in cancer cells. Ag, Zn, and Au NPs are the most widely investigated nanoparticles, owing to their ability to induce apoptosis in cancer cells by generating cytotoxic reactive oxygen species (ROS). (**B**) Metal NPs (Fe and Mn) mediate the induction of ferroptosis in cancer cells via the Fenton reaction. (**C**) Molecular mechanisms involved in the anti-angiogenic and anti-metastatic actions of metal nanoparticles. (**D**) Anti-inflammatory activity of metal nanoparticles. Reproduced with permission from Ref.,[107] © 2022 Springer Berlin Heidelberg.

inhibiting the mitochondrial membrane potential and activating caspase-3.[141] Moreover, AgNPs biosynthesized by *Chaetomorpha linum* can downregulate the expression of anti-apoptotic proteins, such as Bcl-2 and Bcl-xl, in MCF-7 cells.[142] AgNPs synthesized using a water extract of *Bergenia ligulata* as a reducing agent can induce apoptosis by upregulating P53-dependent pro-apoptotic markers, including Bax and caspase-3.[143] In MCF-7 and mouse breast cancer cells, a significant negative correlation has been observed between the concentration of ZnONPs produced using *Cucumis melo* extract and cell viability, with ZnONPs including apoptosis by upregulating the expression of *caspases 3* and *8*.[144] Moreover, selenium nanoparticles (SeNPs) have been successfully synthesized using four endophytic fungi present in garlic roots (*Allium sativum*). These SeNPs exert anticancer activity against PC3 and MCF7 cells, with IC50 values of 225.7 ± 3.6 and 283.8 ± 7.5 µg/mL, respectively, while maintaining biocompatibility with normal WI38 and Vero cells.[145] In human ovarian cells, treatment with ZnONPs resulted in the upregulation of the expression of caspase-9, Rad51, γ-H2AX, p53, and LC3, and the downregulation of Bcl-2 expression, leading to significant cytotoxicity, apoptosis, and autophagy.[146] In HeLa cells, AuNPs synthesized by *Catharanthus roseus* induce apoptosis by increasing Bax expression and decreasing that of anti-apoptotic proteins such as Bcl-2 and Bid.[147]

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In addition to their importance in the digestive tract and gynecological health, metal nanoparticles also have applications in other fields. In studies on the treatment of human epidermoid carcinoma cells, zinc oxide nanoparticles, synthesized through the sol-gel method using zinc acetate dihydrate, ethylene glycol, and 2-propanol, induced apoptotic cell death by generating ROS and causing DNA damage.[148] Wang et al biosynthesized ZnONPs using *Marsdenia tenacissima* and demonstrated their role in promoting cell apoptosis in laryngeal cancer cells (Hep-2) by upregulating the expression of Bax and Caspases 3 and 9.[149] In human lung epithelial carcinoma (BEAS-2B) cells, titanium dioxide nanoparticles (TiNPs) induce apoptotic death through the mitochondrial apoptosis pathway by increasing the expression of cytochrome C, p53, and caspase 9.[150] In human liver cancer, cerium dioxide nanoparticles reduce cell viability and induce apoptotic death by generating ROS and phosphorylating ERK1/2, JNK, and p38 MAPK.[151]

Additional effects and actions of metal nanoparticles synthesized using endophytic fungi on cancer cells are presented in Table 3. Metal nanoparticles can induce apoptotic cell death and cell cycle arrest. For example, AgNPs biosynthesized using papaya leaf extract downregulate cyclin D1 and upregulate tumor suppressor protein expression, including cip1/p21 and kip1/p27. This results in cell cycle arrest at the G1-S phase, exhibiting cytotoxic activity against human prostate cancer cells (DU145).[152] Similarly, spherical AgNPs measuring 12.96 nm in diameter, biosynthesized using *Juniperus chinensis* extract, decrease the expression level of cyclin D1 protein, leading to cell cycle arrest at the G0/G1 phase in A549 lung cancer cells in vitro.[153] AuNPs synthesized with monodisperse properties and high stability, using the water extract of *Sesuvium portulacastrum*, can induce cell cycle arrest at the G0/G2 phase in A549 cells, thereby inhibiting cell cycle progression.[154] Moreover, TiO_2NPs induce genotoxicity and cause G2/M cell cycle arrest in A549 cells by upregulating ATM, P53, and cd-2, while downregulating cyclin B1 expression.[155] In HCT116 cells, these nanoparticles exhibit cytotoxicity by inducing apoptosis and G1 cell cycle arrest.[156] In MCF-7 cells, 30 nm AuNPs significantly decrease overall cell viability and induce G2/M arrest. Compared to the control group, the treated cells exhibit an increased number of apoptotic cells, along with significant upregulation of CDH1 and downregulation of PALB2 expression.[157]

Ferroptosis is a novel, regulated form of cell death caused by an imbalance between oxidative damage and protective mechanisms, holding significant potential as a strategy for cancer treatment.[161] In cancer cells, hydrogen peroxide (H_2O_2) secreted by mitochondria interacts with iron ions, resulting in the generation of harmful free radicals that can induce cell death through iron-mediated toxicity. The primary mechanism underlying ferroptosis involves iron-dependent Fenton reactions that produce ROS.[162] Fe^{3+} ions enter the cell via glycoprotein transferrin receptors and are subsequently reduced and released from transferrin glycoproteins to form Fe^{2+}. The increased availability of Fe ions enhances the Fenton reaction between iron and H_2O_2, leading to ROS production. These ROS oxidize polyunsaturated fatty acids, resulting in the formation of toxic lipid radicals and ultimately cell death.[163] Based on the mechanism of the Fenton reaction, various nanocancer drugs that induce ferroptosis have been developed (Figure 11B). Among these, glutathione

Table 3 Anticancer Effects of Metal Nanoparticles Biosynthesised by Plant Endophytic Fungi

Host Plant	Endophytic Fungi	Nanoparticles	Cancer Cell	IC_{50} For Cancer Cell	Ref
Aegle marmelosa	*A. terreus*	CuONPs	HT-29	22 μg/mL	[65]
Allium sativum	*A. terreus*	CuONPs	MCF7, PC3	159.2, 116.2 μM	[57]
Amoora rohituka	*Penicillium oxalicum*	AgNPs	MDA-MB-231, MCF-7	20.080, 40.038 μg/mL	[59]
Catharanthus roseus	*Botryosphaeria rhodina*	AgNPs	A549	40μg/mL	[71]
Commiphora wightii	*Cladosporium sp.*	AuNPs	MCF-7	38.23 μg/mL	[67]
Datura metel	*C. incarnatum*	AgNPs	HeLa	50 μg/mL	[69]
Limonia acidissima	*P. oxalicum*	AgNPs	MDA-MB-231	91 μg/mL	[158]
Marine seagrass	*Aspergillus sp.*	ZnONPs	WI38, HCT-116, HepG-2	59.74, 43.21, 35.66 μM	[41]
Millingtonia hortensis	*Xylaria acuta*	ZnONPs	MDA-MB-134	6.589μg/mL	[159]
Oroxylum indicum	*Colletotrichum gloeosporioides*	AgNPs	MDA-MB-231, MCF-7	18.398, 38.587 μM	[53]
—	*Alternaria tenuissima*	ZnONPs	HFB-4, MCF-7, HepG-2	55.76, 18.02, 16.87 μg/mL	[160]

Abbreviations: NPs, Nanoparticles; WI38, human lung fibroblasts; HCT-116/HT-29, colorectal cancer colon cancer; MCF-7/MDA-MB, breast breast cancer; HepG-2, hepatocellular carcinoma; PC3, prostate cancer cells; A549, human lung cancer cells; HeLa, human cervical cancer cell line; HFB-4, human melanocytes; IC_{50}, *half* maximal inhibitory concentration.

peroxidase 4 (GPX4) utilizes glutathione to neutralize phospholipid peroxides, protecting cells from iron overload and serving as a crucial regulator in metal-induced ferroptosis mechanisms.[164] Cheng et al designed a manganese-deposited iron oxide nanoparticle platform (Pt-FMO) loaded with the prodrug cisplatin to initiate a series of intracellular reactions, generating ROS to enhance the effects of iron oxidation, and explored the mechanism underlying its induction of ferroptosis.[165] The ethanol extract of *Cirsium japonicum* biosynthesized novel AuNPs that elicit oxidative stress and iron-dependent ferroptosis in human gastric adenocarcinoma cells. These AuNPs achieve their effect by disrupting GPX4-dependent antioxidant defense, leading to the accumulation of mitochondrial ROS, Fe^{2+}, and lipid peroxides, as well as mitochondrial damage.[166] These nanotherapeutic agents initiate apoptotic cell death by upregulating the expression of the apoptosis-inducing factor.

Preventing Cancer Cell Metastasis Through Anti-Angiogenesis and Anti-Metastasis Effects

Angiogenesis is the formation of new blood vessels from existing ones.[167] This process is common and plays a crucial role in several physiological contexts, including ovulation, embryonic development, and wound healing.[168] It is also essential for cancer cells to acquire nutrients and oxygen,[169] making it a key factor in tumor proliferation and migration.[170] Metal nanoparticles have emerged as innovative and effective inhibitors of angiogenesis and metastasis.[171] Within the tumor microenvironment, gold-core silver-shell hybrid nanomaterials can reduce the supportive effects of cancer-associated fibroblasts on tumor cells. By influencing the gene expression and secretion profile of stromal fibroblasts, metal nanoparticles can modify their communication with malignant cells, thereby affecting the pro-cancerous activity within the tumor microenvironment (Figure 11C).[172] Katifelis et al investigated the effects of $Ag_3 Au_1Trp_{1:2}$ nanoparticles on tumor growth, metastasis, and the underlying molecular mechanisms using a server combined immune-deficiency mouse tumor model. These nanoparticles accumulate at the tumor site owing to their enhanced permeability and retention effects and selectively induce apoptosis in cancer cells via a Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand-dependent extrinsic pathway. In terms of mechanism action and signal transduction, the vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR)-mediated signaling pathway is a key molecular target for assessing anti-angiogenic efficacy.[173] AuNPs can bind to vascular permeability factor/VEGF-165 and basic fibroblast growth factor (bFGF), both of which are mitogens and angiogenic mediators for endothelial cells. This binding inhibits the proliferation of endothelial cells and fibroblasts in vitro, as well as VEGF-induced permeability and angiogenesis in vivo.[174] Arvizo et al postulated that the anti-angiogenic effect of AuNPs is attributed to their capacity to inhibit VEGF165 and bFGF, thereby enhancing the functionality of heparin-binding growth factors (HB-GFs). They demonstrated that the inhibitory action of AuNPs is due to the nanoparticles altering the conformation/configuration (denaturation) of HB-GFs.[175] Moreover, silver oxide nanoparticles synthesized by the endophytic fungus *Aspergillus terreus*, isolated from the medicinal plant *Aegle marmelos*, can inhibit or prevent angiogenesis and suppress the formation of new blood vessels in a dose-dependent manner across various culture stages.[176] Similarly, two strains of endophytic fungi, *Aspergillus sydowi* and *Aspergillus versicolor*, isolated from *Azadirachta indic*a, are also capable of synthesizing ZnO nanoparticles with notable anti-angiogenic activity.[177]

Anti-Inflammatory Effects of Metal Nanoparticles

Cancer progression is linked to chronic inflammation, which is estimated to contribute to approximately 20% of all cancer cases.[178] Within the inflammatory microenvironment, elevated levels of nuclear factor-κB (NF-κB), cytokines, prostaglandins, and microRNAs lead to changes in cell proliferation, senescence, and apoptosis, as well as aberrant DNA mutations, DNA methylation, and angiogenesis.[179] Soluble mediators, such as chemokines and cytokines, are integral to the inflammatory process and can regulate both healthy and tumorigenic cells. Pro-inflammatory mediators, including proteases, cytokines, chemokines, and other inflammatory factors, are abundant in the tumor microenvironment. A diverse array of cytokines, including TNF-α, Interleukin (IL)-6, IL-17, IL-12, IL-23, IL-10, and transforming growth factor-β, collectively shape the tumor microenvironment, often promoting tumor growth.[180] Notably, metal nanoparticles can inhibit these inflammatory responses in cancer and modulate the interaction between systemic inflammation and local immune responses (Figure 11D).[181] For example, AuNPs can reduce lipopolysaccharide-induced cytokine production, including IL-1, IL-17, and TNF-α, as well as ROS generation, by regulating the mitogen-activated protein kinase and phosphatidylinositol 3-kinase pathways.[182] Conversely, AgNPs exert their anti-inflammatory effects by suppressing the expression of vascular endothelial growth factor, hypoxia-inducible factor 1, cyclooxygenase-2, IL-13, and TNF-α.[183] Numerous biosynthesized metal and metal oxide nanoparticles exhibit anti-inflammatory properties.[184] AgNPs synthesized from extracts of *Viburnum opulus, Calophyllum tomentosum*, and *Centratherum punctatum*;[185] AuNPs synthesized from extracts of *Litchi chinensis, Prunus domestica, P. serrulata*, and *Rubia cordifolia*; and zinc oxide nanoparticles synthesized from extracts of *Polygala tenuifolia* and *Andrographis paniculate*,[186] all exhibit anti-inflammatory effects.[184]

Conclusion and Outlook

Owing to increasing industrial demand and a societal focus on environmental sustainability, the application fields for nanoparticles and nanomaterials are continually expanding, highlighting the urgent need for green synthesis methods for nanoparticles. Plant endophytic fungi, which exhibit a symbiotic relationship with their plant hosts, may produce metabolites similar to those of plants and participate in similar production processes, exhibiting great potential for the green synthesis of metal nanoparticles. Moreover, metal nanoparticles can support cancer treatment in several ways, including enhancing the effectiveness of contrast agents and reducing their toxicity, boosting the effect of chemotherapy drugs, directly producing ROS, and inducing oxidative stress, leading to the death of malignant cells.

The present review provides a comprehensive overview, from the discovery of potential plant endophytic fungi to the synthesis and characterization of metal nanoparticles, and finally to the role of metal nanoparticles in cancer treatment. We comprehensively reviewed the application of metal nanoparticles synthesized by plant endophytic fungi in the field of cancer treatment, providing new perspectives for research on the synthesis of anticancer nanoparticles. In this synthesis process, plant endophytic fungi have demonstrated their advantages: abundant resources, as many studies have reported endophytic fungi with synthetic capabilities; green and environmentally friendly, as plant endophytic fungi can reduce the use of forestry resources and harmful reagents; mild and efficient, given the rapid expansion of plant endophytic fungi fermentation and synthesis reactions under mild conditions; and cost-effective, as their use reduces the amount of chemical reagents used and energy costs owing to the mild conditions. These advantages demonstrate that the biosynthesis of metal nanoparticles by plant endophytic fungi is a promising area of research that warrants further development.

However, we must also recognize that current research is extremely limited. Most of the current research has only focused on the biosynthesis of metal nanoparticles, with limited studies exploring the detailed mechanisms by which endophytes produce these metal nanoparticles. There is also insufficient investigation into the efficacy and safety of bio-sourced metal nanoparticles for cancer treatment, which hinders their clinical application. Additionally, many challenges remain before the widespread adoption of biosynthesis technology. These include the establishment of management systems for microbial resources and toxicity control issues, and the exploration of the controllability and scalability of biosynthetic metal nanoparticles. Moreover, regulatory frameworks must be further refined to ensure the quality of nanoparticle products. However, with the increasing basic research and advancements in biotechnology, we believe that the production and application scenarios of bio-sourced metal nanoparticles will also increase, enabling their improved application in clinical treatment of cancer. In the future, it is important to identify the key secondary metabolic synthesis gene clusters involved in the synthesis process of endophytic fungi, main products involved during the synthesis, and important synthesis conditions that affect the performance of nanoparticles. Moreover, developing a safe and controllable biosynthesis plan using plant endophytic fungi, combined with mature cancer treatment methods, is expected to pave the way for new green and environmentally friendly treatment models.

Data Sharing Statement

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Disclosure

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