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# Biosynthesis of Nanoparticles Using Endophytes: A Novel Approach for Enhancing Plant Growth and Sustainable Agriculture

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**Abstract:** Current strategies for increasing food production rely heavily on the use of agrichemicals to improve plant growth and resistance to disease. However, many of these chemicals have been shown to have negative impacts on human health and the environment. Nanotechnology presents itself as one of the promising technologies that can be employed to overcome these challenges, but, in the same way that agrichemicals can be harmful, so too can nanotechnology production lines cause harm. In an effort to produce nanoparticles (NPs) in an environmentally friendly and sustainable manner, biological synthesis pathways using microbes and plants are being explored and developed. Synthesis of NPs using endophytic microbiomes is one of the biological approaches showing great potential, offering environmentally friendly alternatives to current production lines and adding value to agricultural systems. This review presents the current potential of NPs synthesized using endophytic microbiomes (primarily bacteria and fungi) to enhance plant growth and improve disease resistance, ultimately making agriculture more sustainable. The future focus on the exploration of this important technique is advocated.

**Keywords:** biogenic methods; endophytes; fungi and bacteria; food availability; nanotechnology

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## 1. Introduction

Nanotechnology has found wide applications as biomarkers, diagnostics, and, most importantly, as promising agents for biological imaging, nanodrugs, antimicrobial agents, and acting as drug delivery systems [1,2]. However, one of the latest advancements in the utilization of nanotechnology is in the agricultural and food sectors [3,4]. Nanotechnology has played a major role not only in monitoring the development and growth of plants but also in the protection of plants, alongside contributing to considerable improvements in food production and quality [5,6]. In a bid to strengthen the utilization of nanoparticles (NPs), experts are now concentrating on the synthesis of NPs through non-toxic, environmentally friendly, and reliable methods, such as the use of biological systems.

The adoption of biological systems for NP synthesis is being given preference over traditional chemical techniques, which can be harmful to the environment [7,8]. These biological systems can be referred to as forms of "green chemistry", combining methodologies derived from microbial biotechnology and nanotechnology to synthesize NPs. A shift away from the traditional technologies used for NP production towards more environmentally friendly systems will ultimately contribute to making agriculture and food production systems more sustainable.

Microorganisms (fungi, viruses, bacteria, yeast, and actinomycetes) can be referred to as biological nanofactories, assimilating metal ions from the environment and converting these ions into elemental compounds. These processes can occur as either intracellular or extracellular events, and NPs synthesized by microorganisms are thus classed accordingly as either intra- or extracellular NPs [9]. Microorganisms have been used for the biosynthesis of the following NPs: Selenium, silver, tellurium, gold, silica, platinum, titania, uraninite, palladium, and quantum dots (QDs), zirconia, and magnetite nanoparticles [10]. Microorganisms are highly diverse, multiply rapidly, and are adaptable to a variety of environments, making them ideal systems for biological production processes, especially when compared to larger organisms, such as plants [11]. In addition, microorganisms can biosynthesize nanomaterials in solution, which is a cheaper and more efficient approach, allowing the NPs to be filtered and separated easily and efficiently [12].

Endophytes are microorganisms that inhabit plant tissues without causing any harm to the plants, although recent studies have shown that some can change life modes and become pathogenic [13–15]. Endophytic organisms include archaea, bacteria, fungi, yeast, and viruses, and are capable of producing a wide range of secondary metabolites, making them ideal agents for NPs production [14,16,17]. Numerous plant endophytes, such as bacteria (*Colletotrichum* sp., *Bacillus cereus*, *Penicillium citrinum*, *Pseudomonas veronii*) and fungi (*Aspergillus fumigatus*, and *Saccharomonospora* sp.), have been reported to have the potential to synthesize NPs [17–22]. This brief review summarizes the biosynthesis process and discusses the current applications of NPs synthesized from endophytic microbiomes (primarily bacteria and fungi), with emphasis on their prospect of enhancing plant growth and ultimately contributing to sustainable agriculture.

## 2. Biosynthesis of Nanoparticles: Endophytic Microbiomes as Biological Factories

A variety of biological, physical, hybrid, and chemical approaches are employed in NP production, however, only the biosynthetic approaches are environmentally friendly and devoid of toxic chemicals. The toxic chemicals used in synthetic production processes limit the scope of application for the final NP products, especially in biomedical, clinical, and food-based industries [23,24]. A variety of mechanisms (intracellular and extracellular) for the biosynthesis of nanomaterials exist in nature, however, this area of research has yet to be fully explored [25]. The development of non-toxic, clean, and environmentally friendly techniques for NPs production would be the outcome of harnessing these natural production systems with the aid of organisms, such as plants, fungi, and bacteria [23,26] (Figure 1).

Metal-based NPs are synthesized by microorganisms via both extracellular and intracellular mechanisms [27]. In all, an electrostatic contact occurs between negative and positive charges of metallic ions of the cell wall of the microorganism during intracellular production, followed by the reduction of the metal ion ($M^+$) back to its metallic form (Mo). Microbial reductases and reductases reliant on the cofactors nicotinamide adenine dinucleotide phosphate (NADPH) and nicotinamide adenine dinucleotide (NADH), which function as electron carriers in oxidation-reduction processes, catalyze this activity. As a result, proteins in the periplasmic space or cytoplasm cap the NPs, stabilizing them. To obtain pure NPs, however, cell disruption is an intrinsic requirement [28]. The culture supernatant, cell-free extract, or biomass is combined with the solution of metals during extracellular synthesis, while the NPs are formed outside the cell of the microorganisms. Reductases generated and released into the culture medium by cofactors, and microbial cells carry out this activity. The synthesized NPs are additionally stabilized by capping agents once nucleation and bio-reduction have been carried out [12].

Fungal and bacterial endophytes have been proposed as biofactories for the production of metal-based NPs with agricultural and therapeutic applications [10,29]. These microbes colonize plant intra- and/or intercellular tissues, forming a symbiotic connection [16,30]. The endophytes may benefit plant health and development through a variety of mechanisms, including the secretion of antimicrobial compounds and the production of growth-enhancing metabolites [14] (Figure 1).

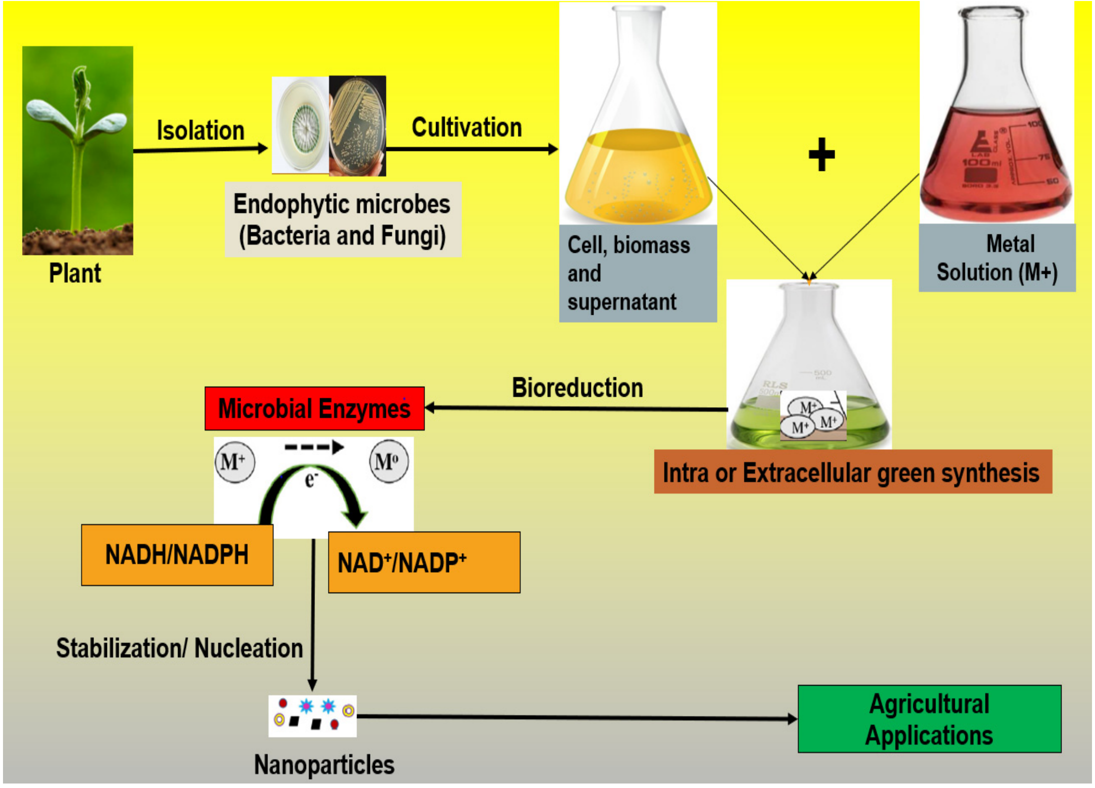

**Figure 1.** Diagrammatic representation of overall steps involved in the biosynthesis of nanoparticles using endophytic microorganisms. Modified from [10].

Endophytic bacteria and fungi residing inside plant tissues can produce nanoparticles, which can subsequently benefit the host plant by improving growth or reducing the incidence of disease. Endophytes may withstand and/or collect metals in the environment to relieve toxicity and stress in the host plant, alongside promoting their competitive advantage and adaption over other niche microbes [10,31]. The capacity of endophytes to detoxify metals can be used to synthesize metal-based NPs through extracellular and intracellular mechanisms. Some examples of this process include the production of AgNPs, with a mean size of 22 to 45 nanometers and a spherical shape, which were synthesized intracellularly using the supernatant of Ag-resistant *B. safensis* TEN12 [32]. Stable and quasispherical ZnONPs, sized 2–9 nm, were synthesized extracellularly by the zinc-tolerant endophyte *C. geniculatus* [33]. Additionally, cobalt oxide nanoparticles (CoONPs), spherical in shape, with 20 nm in diameter, were also synthesized extracellularly by the CoO-tolerant *A. nidulans* [33]. The zinc-tolerant endophyte *Cochliobolus geniculatus* generated quasispherical and stable ZnONPs with sizes of 2–9 nm, again, through an extracellular mechanism [33]. Similarly, the CoO-tolerant endophytic *Aspergillus nidulans* generated spherical CoONPs with a diameter of 20 nm via an extracellular pathway [33].

Endophytic microbes can secrete several bioactive metabolites with a wide range of structural diversity and biological activity, which can be used to investigate human health and are also important in enhancing agricultural sustainability [14,34–36]. As a result, fungi and bacteria isolated from various sections of plants may be readily cultivated in the laboratory under optimal growth conditions to produce NPs with the required activities and properties for biomedical or agricultural applications [37].

The application of nanotechnology in agriculture is an emerging field although there are numerous existing applications (Figure 2), the true potential is yet to be fully appreciated. Most inorganic NPs, especially gold and silver, are gaining relevance due to their wide application. However, only a few studies exist on NPs synthesis from the endophytic microbiome, highlighting the need for further research in this field.

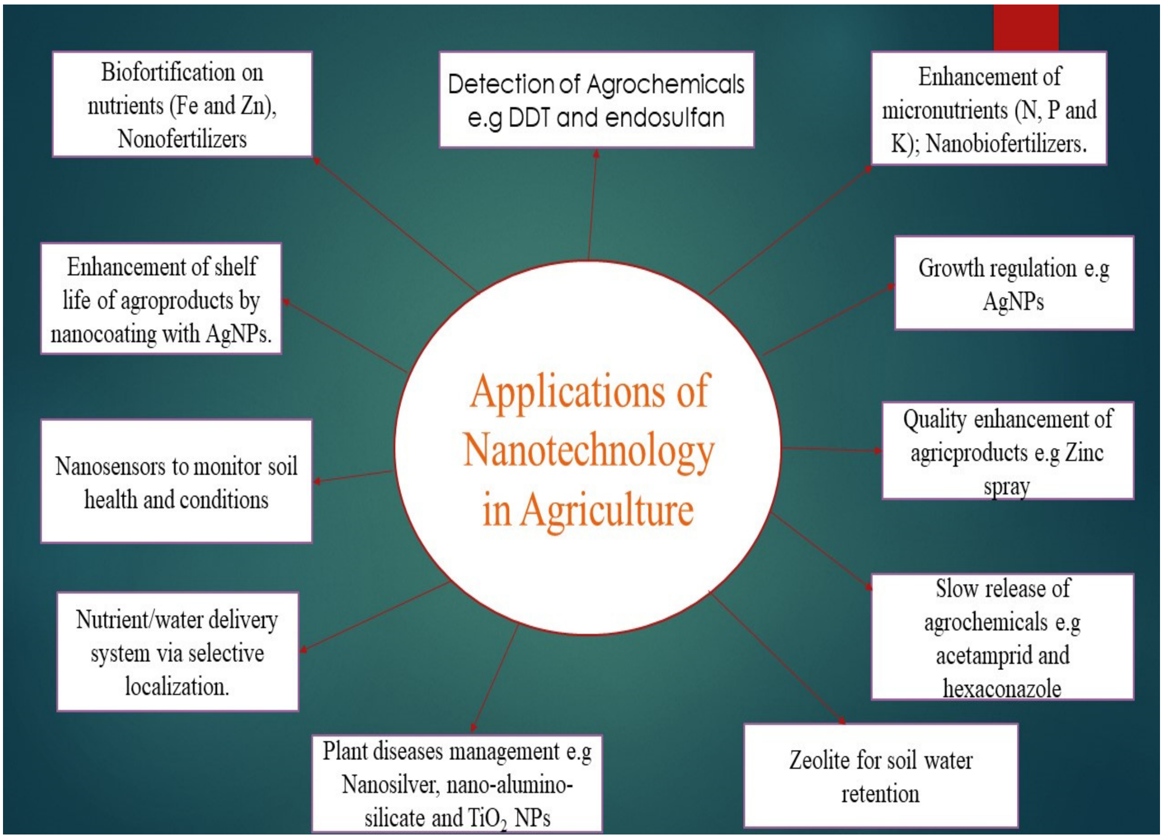

**Figure 2.** Current applications of nanotechnology in agriculture.

## 3. Endophytic Microbes in the Biosynthesis of Nanostructural Materials

In comparison to microstructured materials, nanoparticulate materials offer significant benefits, such as enhancement of food safety and quality, reduction of agricultural inputs, and enriching of absorbable soil nutrients. However, several parameters (shape, size, and chemical composition) need to be taken into consideration when assessing the use or potential application of NPs in the agricultural sector. The microorganisms involved in the biosynthetic pathways, and the typical synthesis process, are the defining variables that will dictate the production process, and thus, the end products. These metal reduction activities usually take place via the NADPH and NADH-dependent reductases found in endophytic bacteria and fungi [10].

The detection, identification, and isolation of the targeted endophyte is the initial step in the manufacture of nanomaterials from endophytic microbes. A basic outline of this approach is the selection and cleansing of plant material (leaf, root, seed, stem), and the placement of small pieces of plant material on a growth medium. This is then exposed to various growing conditions (nutritional supplements, temperature, $CO_2$ rate, culture medium, humidity) in order to determine which conditions are ideal for the specific endophyte in question [38]. Following the initial growth, a process of subculturing and formation of pure endophyte colonies will follow. For a thorough understanding of the process of selecting, isolating, identifying, and subculturing endophytes, see the works of Correa-Galeote et al. [39] and Zhou et al. [40].

To make NPs, the complete biomass of the microbes, the cell-free extract (which is made up of the metabolites produced by the microbes) or the cell extract (obtained by original biomass filtering) can be employed [41]. The NPs are created by using either the cell extract (obtained during the filtering of the original biomass), or a cell-free extract (which retains metabolites produced by the microorganisms). It is also vital to figure out which of the above forms of interactions will be employed because these living systems include inherent variables (such as enzymes and bioactive metabolites) that determine the type of nanoparticle produced. It is also worth noting that various microorganisms create different types of enzymes and metabolites in varying amounts. These substances can function as surfactants, even reducing agents or stabilizers, throughout the biosynthesis process [42].

A solution of the NPs metal precursor salt is applied to a cell extract/biomass/cell-free extract as a standard process for the creation of nanoparticulate materials. The most common compounds employed are transition metal chlorides, nitrates, acetates, and sulfates. The critical components to maximizing the interactions required for the production of the NPs are the reactional circumstances of pH, time, temperature, beginning reactants, and pressure. This makes it possible to regulate the shape, content, as well as size of the NPs that are produced. These NPs can be used to create a colloid after all these parameters have been established, or they can be washed and filtered to produce a powder as the end result.

### *3.1. Silver Nanoparticles*

Because of its anti-inflammatory and antimicrobial characteristics, silver has been recognized and utilized as a medicine since ancient times [43,44]. It is also the primary NP that is obtained using endophytic microbes' green biosynthesis. It is worth noting that all AgNPs produced by endophytes have a spheroidal form and use silver nitrate as the Ag+ ion source.

The utilization of endophytic microbes found in tropical plant roots might be a significant mechanism for AgNP production. The bacterial endophyte *Isoptericola* sp. SYSU 333,150 [45] and *Streptomyces laurentii* [29] were used to obtain spheroidal Ag NPs with diameters less than 40 nm. Similar studies show that cell-free extracts (proteins and metabolites secreted in culture) of fungal endophytes *Chaetomium* sp., *Alternaria* sp., *Aspergillus* sp., *Cladosporium* sp., *Guignardia* sp., *Colletotrichum* sp., *Penicillium* sp., *Curvularia* sp., *Pestalotia* sp., *Phomopsis* sp., and *Pestalotiopsis* sp., with 30 nm AgNPs were extracted from the leaves of *Azadirachta indica* [46] and *Raphanus sativus* [47].

The cell extract of endophytes provides a unique synthesis medium, enabling the bioreduction of Ag+ ions to form AgNPs. Extracts taken from the cells of *Aspergillus* sp., *Alternaria* sp., *Cladosporium* sp. and *Penicillium* sp. were isolated from *Calotropis procera* leaves [48], and *Bionectria ochroleuca* and *Aspergillus tubingensis* isolated from *Laguncularia race* and *Rhizophora magle* can all form AgNPs sized up to 45 nm. Using fungal cell extracts of *Exserohilum rostrata*, isolated from *Ocimum tenuiflorum* [49] and *Penicillium* sp. from *Tinospora cordifolia*, AgNPs smaller than 15 nm may be generated in the same way [50].

The AgNPs can also be obtained from the whole biomass of these microbes, such as *Colletotrichum incarnatum*, *Penicillium funiculosum* and *Alternaria solani* (from leaves of *Gloriosa superba* and *Datura metel*) [51], leading to the formation of particles as small as 40 nm in diameter [52]. The biomass of endophytic fungi found in tropical seaweeds may likewise be employed to make AgNPs. Hulikere and Joshi [53] extracted *Cladosporium cladosporioides* biomass from the *Sargassum wightii*, a seaweed, generating AgNPs with a 60 nm diameter. In a similar study, Neethu et al. [54] used a cell extract of *Penicillium polonicum*, derived from *Chaetomorpha antennina*, to synthesize AgNPs with a diameter of 15 nm.

### *3.2. Gold Nanoparticles*

The anti-inflammatory and antimicrobial activities of AuNPs, like those of AgNPs, are well documented [55]. Gold-derived NPs are formed with the aid of endophytes similarly to other NPs, such as AgNPs, using intra and extracellular mechanisms. However, the provision of Au ions as substrates for these NPs can be expensive. $HAuCl_4$ is the most utilized Au-based starting reagent in the synthesis of these NPs. The most common procedure for the endophytic production of AuNPs is to use biomass of the fungal endophyte *Cladosporium cladosporioides* taken from *Sargassum wightii*, which can produce AuNP spheres up to 60 nm in diameter [56].

Baker and Satish [17] reported that a novel bacterial endophyte isolated from *Annona squamosal* was capable of synthesizing AuNps, adding to the list of NPs generated by endophytic microbes. Furthermore, the cell extract derived from *Cladosporium* sp., found in the leaves of *Commiphora wightii*, was used to make AuNP spheres with a diameter of around 10 nm [57]. Cell extracts from *Alternaria* sp. and *Aspergillus* sp., discovered in the stem and roots of *Azadirachta indica* and *Rauvolfia tetraphylla*, respectively, were used to make AuNPs with triangular shapes [58]. The fungus *Fusarium solani*, which is found in *Cleistes fragrans* roots, was used to make AuNPs with a needle-like shape and a size of 45 nm [59]. A recent study by Bogas et al [10] has focused on the biosynthesis of AuNPs. The procedure was adjusted by considering the required particle sizes, synthesis time, and extract concentrations, utilizing *Paenibacillus terrae* and *Paenibacillus polymyxa* isolated from *Prunus* spp., [60] and Tabebuia spp. [61], respectively. This study highlights the necessary procedures involved in producing AuNPs using biosynthetic pathways and assessing the quality and function of the end products.

### 3.3. Copper-Based Nanoparticles

A less expensive option for both AuNPs and AgNPs is the production of CuNPs. It was reported that the fungus *Aspergillus terreus* isolated from *Origanum majorana* and *Aegle marmelosa* can produce spheroidal CuONPs from $CuSO_4$ [62]. In this case, the use of biomass and cell extract of the fungus led to the formation of CuONPs of numerous sizes. It was reported that CuNPs sized less than 100 nm can also be taken from marine actinomycetes, extracted from seaweeds [63], and *Streptomyces capillispiralis* isolated from the leaves of *Calendula arvensis* [64]. *Aspergillus terreus*, isolated from *Origanum majorana* and *Aegle marmelosa* [62] were able to produce spheroidal CuNPs using $CuSO_4$ as the reagent. Past studies have shown that it is possible to alter the shape of CuNPs by switching the source of $Cu^{2+}$ ions to $Cu(NO_3)_2$ and utilizing the *Phaeoacremonium* sp. to create nanorods with a diameter of roughly 97 nm [10].

### 3.4. Zinc-Based Nanoparticles

There has been commercial interest in Zn-based nanoparticles because they provide a new, clean way to create antimicrobial products with reduced cellular toxicity. Using $ZnSO_4$ as a starting reagent, ZnSNPs were obtained from the biomass of the fungus *A. flavus* [65], isolated from the leaves of *Nothapodytes foetida*, which produced 18 nm spheres. Uddandarao et al. [66] added Gd to ZnSNPs by adding $Gd(NO_3)_3$ to the cell extract. It has also been shown that starting reagents, such as $Zn(NO_3)_2$ and $ZnSO_4$, can be used to make rods (50 nm) and ZnO spheres, respectively [62].

### 3.5. Titanium-, Cobalt, Nickel, Iron-Based Nanoparticles

The fungal endophyte *Aspergillus terreus* may reduce Fe, Ni, and Co salts to produce spherical $Fe_3O_4$, NiO, and $Co_3O_4$ NPs with sizes of 60, 40, and 15 nm, respectively [62]. Spheroidal CoONPs have also been reported to be produced from the *A. nidulans* isolated from the leaves of *N. foetida* [33]. Using the biomass of the endophyte *Trichoderma citrinoviride*, isolated from *Sorghum bicolor* roots, nano- and microstructured $TiO_2$ particles of various forms, such as triangular, rodlike, spherical, and pentagonal have been generated [67].

## 4. Applications of NPs from Endophytic Microbiomes for Controlling Disease and Promoting Sustainable Agriculture

### 4.1. Antimicrobial/Disease Suppression Activities

Plant pathogens and the related diseases associated with pathogenic infections account for losses of up to 30% in the production of staple crops globally [68]. Traditional methods of treating plant disease rely heavily on pesticides which are harmful to the environment as well as to human health. Several emerging fields aim to provide environmentally friendly alternative practices for pest control. Examples include biological control agents and the use of NPs derived from endophytic microbiomes.

Kim et al. [69] gave the first report to establish that silver is effective in inactivating key enzymatic activities found in endophytic bacteria, thereby affecting the metabolic pathways of these organisms. This work highlights the role that AgNPs can play in the control of microbial plant infections. AgNPs synthesized from endophytic microorganisms have been reported to have strong antipathogenic properties against key strains of bacteria and fungi [9,70].

Although there have been numerous past studies on the mycosynthesis of AgNPs [20,71], few studies have explored the role of endophytes in the synthesis of AgNPs (Table 1). Verma et al. [72] revealed in their study that AgNPs synthesized from the endophytic fungus *A. clavatus* showed antifungal activity against *Candida albicans*. Moreover, Qian et al. [73] reported that silver nanoparticles synthesized from *Epicoccum nigrum*, an endophytic fungus, showed a broad antifungal spectrum against agricultural pathogenic fungi, such as *C. albicans*, *A. flavus*, *C. tropicalis*, *C. parapsilosis*, *F. solani*, *C. krusei*, *C. neoformans*, *S. schenckii*, and *A. fumigatus*. Netala et al. [74] also reported that silver nanoparticles synthesized from *A. versicolor* secreted strong antifungal compounds, which are active against the proliferation of *C. nonalbicans* and *C. albicans*.

AgNPs are believed to be extremely safe in controlling numerous phytopathogens when compared to chemical fungicides. AgNPs synthesized from *Pseudomonas rhodesiae* showed strong antibacterial activity against *Dickeya dadantii*, the causative against the bacterial root and stem rot disease of sweet potato [75]. Ibrahim et al. [76] also revealed that the silver nanoparticles synthesized from *Pseudomonas poae* an endophytic bacterium isolated from garlic, exhibited strong antifungal activity against *F. graminearum*, which is the causative agent of wheat Fusarium head blight in the wheat plant.

**Table 1.** Summary of antimicrobial activities of nanoparticles synthesized from endophytic microbes.

| Endophytic Species | Activity | Pathogens Active Against | References |
|---|---|---|---|
| **Silver nanoparticles** | | | |
| *Aspergillus niger* | Antibacterial | *K. pneumoniae* | Hemashekhar et al. [77] |
| *Epicoccum nigrum* | Antifungal | *C. tropicalis* | Qian et al. [73] |
| *Penicillium* sp. | Antibacterial | *K. pneumoniae* | Singh et al. [78] |
| *Bacillus cereus* | Antibacterial | *K. pneumoniae* | Sunkar and Nachiyar [18] |
| *Epicoccum nigrum* | Antifungal | *A. fumigatus* | Qian et al. [73] |
| *Nemania* sp. | Antibacterial | *P. aureginosa* | Farsi and Farokhi [79] |
| *Epicoccum nigrum* | Antifungal | *S. schenckii* | Qian et al. [73] |
| *Epicoccum. nigrum* | Antifungal | *C. neoformans* | Qian et al. [73],<br>Rana et al. [9] |
| *Penicillium polonicum* | Antibacterial | *A. baumanii* | Neethu et al. [54] |
| *Epicoccum nigrum* | Antifungal | *C. tropicalis* | Qian et al. [73] |
| *Lasiodiplodia theobromae* | Antibacterial | *P. aeruginosa* | Ranjani et al. [80] |
| *Penicillium* sp. | Antibacterial | *E. aerogenes* | Singh et al. [78] |
| *Penicillium oxalicum* | Antibacterial | *B. subtilis* | Balakumaran et al. [46] |
| *Epicoccum nigrum* | Antifungal | *A. flavus* | Qian et al. [73] |
| *Fusarium oxysporum* | Antibacterial | *C. cladosporioides* | Vijayan et al. [81] |
| *Pheidole pallidula* | Antibacterial | *P. mirabilis* | Muhsin and Hachim [82] |
| *Bacillus cereus* | Antibacterial | *P. aureginosa* | Sunkar and Nachiyar [18] |
| *Pestalotia* sp. | Antibacterial | *S. aureus* | Raheman et al. [70] |
| **Gold nanoparticles** | | | |
| *Cladosporium cladosporioides* | Antifungal | *A. niger* | Joshi et al. [56] |
| *Cladosporium cladosporioides* | Antibacterial | *P. aureginosa* | Joshi et al. [56] |
| **Copper nanoparticles** | | | |
| *Streptomyces capillispiralis* | Antibacterial | *P. aureginosa* | Hassan et al. [64] |
| *Streptomyces capillispiralis* | Antifungal | *A. brasiliensi* | Hassan et al. [64] |
| Actinobacteria | Antibacterial | *E. coli* | Rasool and Hemalatha [63] |
| *Streptomyces capillispiralis* | Antibacterial | *B. dimenuta* | Hassan et al. [64] |
| Actinobacteria | Antibacterial | *P. mirabilis* | Rasool and Hemalatha [63] |

### 4.2. Production of Nanopesticides

The number of patents and scientific publications on the plant protection properties of nanometals has increased remarkedly over the last decade. Most of the scientific publications on this topic have emanated from Asian scientists, while the highest number of patents are from Germany [83]. A survey by Kah and Hofmann [84] reported that nanopesticides were observed to be more efficient than commercially sold chemical pesticides. A study by Park et al. [85] reported the efficacy of an endophytic, silver-based nanopesticide in controlling fungal pathogens, such as *Botrytis cinerea*. The authors of this study reported that when the endophytic silver-based nanopesticide was sprayed at a concentration of 0.3 ppm on pumpkin leaves, this application successfully controlled powdery mildew disease after three days of application.

## 5. Toxicity Assessment of Endophytic Nanoparticles

Past studies have indicated that certain NPs can be a threat to animals and humans [86,87]. The interactions that nanoparticles have with cells and, consequently, their potential toxicity, are influenced by their physiochemical characteristics. The creation of safer nanoparticles may result from an understanding of these features. Recent research has started to pinpoint certain characteristics that differentiate some nanoparticles from others in terms of toxicity. According to theory, particle size is probably a factor in nanotoxicity. Smaller nanoparticles have greater accessible surface area to interact with biological components such nucleic acids, proteins, fatty acids, and carbohydrates as compared to bigger nanoparticles of the same mass due to their larger specific surface area (SSA) [88]. Due to its tiny size, it is also probably feasible to penetrate cells and harm them.

The cellular absorption of particles, as well as how they interact with organelles and proteins, may be influenced by the particle surface charge. Consequently, toxicity is influenced by particle surface charge. High particle absorption (i.e., higher bioavailability) corresponds with increased toxicity in accordance with mathematical likelihood and under the assumption that particles are hazardous. For instance, it was discovered that three similarly sized iron oxide particles were differentially lethal with varying charges on the human hepatoma cell line (BEL-7402) [89]. Surface charges for $Fe_3O_4$ coated with oleic acid, carbon, and Fe were 4.5, 23.7, and 14.5 mV, respectively. The nanoparticles' toxicity rose as the surface charge did. This implies that the larger the nanoparticle's positive charge, the more the electrostatic contacts and, thus, the greater the nanoparticle's endocytic uptake with the cell. Although the aforementioned research and other studies have helped us understand how and why a property of a nanoparticle mediates toxicity, a more systematic approach can help us learn even more about this topic.

Another illustration is that positively charged particles of the same size and shape as positively charged ZnO nanoparticles had less toxic effects on A549 cells [90]. The composition of cellular membranes can be used to partially explain the phenomena. There are several glycosaminoglycans on the surface of mammalian cells. Since these molecules have a negative charge, they are likely to interact electrostatically with nanoparticles that have a positive charge [91]. The likelihood of internalization of nanoparticles increases with the length and intensity of electrostatic interactions [92]. The same is true when negatively charged DNA interacts with positively charged nanoparticles, causing DNA damage. Although the aforementioned research and others have helped us understand how and why a property of a nanoparticle mediates toxicity, a more systematic approach can help us learn even more about this topic.

However, recent findings have shown biosynthesized nanoparticles, such as those from endophytes, are less toxic to humans and the environment as compared to metal-based nanoparticles. For instance, AgNPs synthesized using extracts of the fungal endophyte *L. theobromae* and tested against *P. aeruginosa*, and *P. aeruginosa* ATCC (27853), which were clinical isolates taken from hospital patients. The AgNPs used in this study reduced the antibiofilm that the pathogens produced while also significantly inhibiting the development of both strains as compared to the controls [93]. The endophytic bacteria *Waltheria indica* was isolated from *Pantoea anthophila* and used to synthesize AgNPs, which were assessed for their antimicrobial and antioxidant properties [87]. These authors found that numerous oxidative stress-related degenerative illnesses could be suppressed by the AgNPs used in their study.

Furthermore, the effects of nanomaterials on plants and the microorganisms inhabiting the soil have been widely studied [94], but only few studies exist on the toxic effects of endophytic nanoparticle on humans and the ecosystem [10]. A study was carried out by Lee et al. [95] to assess the impact of endophytic ZnONP on plant-soil interactions and found that the association reduced the toxicity of the nanoparticles on the population of rhizospheric bacteria. Lin and Xing [96] also studied the translocation of endophytic ZnONP in ryegrass and reported an increase in ryegrass biomass. Furthermore, a study carried out by Hong et al. [97] assessed the impact of endophytic synthesized nano$TiO_2$ on the photochemical activity of the chloroplasts of *Spinacia oleracea* and found that these NPs increased the chloroplastic activity of these plants. Moreover, a study by Lee et al. [98] analyzed the effects of AgNPs from endophytes on *Sorghum bicolor* and *Phaseolus radiates* and found no negative impact on the growth and yield parameters of the plants. The above studies show that it is necessary to assess the impacts of NPs on plants and that wide, indiscriminate use of NPs should not be encouraged before determining the full effect these particles may have on the host plants or the broader environment.

## 6. Challenges with the Biosynthesis of Nanoparticles Using Endophytic Microbiomes

NPs that are biocompatible, non-toxic, environmentally friendly, and economical would be best for agricultural use. A lot of research has been done on the potential advantages of metal-based NPs produced utilizing endophytes for agricultural applications [9,86]. However, the applications face a significant barrier due to the lack of understanding regarding their precise mechanisms of action, selectivity, and toxicity to people. Furthermore, the broad-spectrum effect on soil microorganisms and the environment, in general, has not been fully explored. Currently, a number of uncertainties remain regarding the effects and quantities of endophytic NPs that can be used for crop growth and health. There are no established procedures on the mode of application and carriers involved in the use of these NPs for agriculture.

Furthermore, there are still loopholes in the regulation regarding the use of NPs in agriculture. This situation highlights the incomplete understanding, by both practitioners and policy-makers, of the specific interactions of several nanomaterials with biological systems, as well as their ability to accumulate and potentially have hazardous environmental impacts [10]. With all the encouraging developments, there is still no unified regulatory advice across the many regulatory bodies. However, there is still a significant opportunity for the creation of new sustainable agriculture practices in the future through the green synthesis of nanoparticles employing endophytes and other microbes [99].

## 7. Future Perspectives

Undoubtedly, nanotechnology has made a significant impact on the agricultural and food sectors. However, despite the existing contributions already made and the potential for NPs in future applications, it is important to note that most of the knowledge we currently have is derived from laboratory tests. Understanding the practical use of NP technology without knowing how it affects environmental toxicity is not viable. In order to advance our current understanding and develop future NP technology platforms, it is necessary to carry out comprehensive trials.

The open government awareness initiative to inform the general public about agricultural and food nanotechnology and its uses by creating a sufficient database and supporting documentation to serve as logistical assistance for both farmers and the general public is very important. Moreover, trials assessing the dangers connected with the use of endophytic NP-based products in the agricultural sector are critical. It is critical to determine the lowest concentration dosage for NPs using soil-based concentration-dependent studies.

Furthermore, researchers must ensure a better understanding of the potential of NPs to bioaccumulate during field applications and how this affects nanotoxicity, as well as learn more about how trophic chain transmission affects the ecosystem. Research trials investigating the impact of NPs on soil microbial communities and the interaction of NPs with soil systems. Investigation of the value chain for the biosynthesis of NPs using endophytes and comparing this against traditional, industrialized methods of production is crucial alongside pilot tests being conducted in natural environments in order to demonstrate how endophytic NPs are influenced by their surroundings.

## 8. Conclusions

The synthesis of NPs using microorganisms is now being acknowledged as a cost-effective and environmentally friendly approach, providing a much-needed alternative to the traditional methods, which have been reported to produce hazardous and toxic by-products. Recent studies have shown that endophytic microbiomes, especially bacteria and fungi, can act as a warehouse of many bioactive metabolites which can be used for the synthesis of NPs. The size of the NPs most often dictates their application suitability in various fields, especially in the agricultural and biomedical fields. However, the breakthrough in the biosynthesis of nanopesticides has proven to be less harmful and effective in the control of many plant diseases. The synthesis of NPs from endophytic microorganisms is an interesting aspect of nanotechnology which needs to be further explored. Ideally, we hope to see biosynthesized NPs that can be used for targeted treatment of plant disease and the improvement of plant growth and performance. Furthermore, to have improved the shape and size of the NPs, future studies are required to investigate the molecular mechanisms involved in the biosynthesis by endophytic microbes. Future studies should also focus on better understanding the interactions between plants, different types of NPs, and the various plant pathogens that are affected by them.

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## References

1. Singh, R.; Nalwa, H.S. Medical applications of nanoparticles in biological imaging, cell labeling, antimicrobial agents, and anticancer nanodrugs. *J. Biomed. Nanotechnol.* **2011**, *7*, 489–503. [CrossRef] [PubMed]
2. Imade, E.E.; Ajiboye, T.O.; Fadiji, A.E.; Onwudiwe, D.C.; Babalola, O.O. Green synthesis of zinc oxide nanoparticles using plantain peel extracts and the evaluation of their antibacterial activity. *Sci. Afr.* **2022**, *16*, e01152. [CrossRef]
3. Ajilogba, C.F.; Babalola, O.O.; Nikoro, D.O. Nanotechnology as Vehicle for Biocontrol of Plant Diseases in Crop Production. In *Food Security and Safety: Africa's Perspective*; Babalola, O.O., Ed.; Springer: Cham, Switzerland, 2021; pp. 709–724, eBook; ISBN1 978-3-030-50672-8, Hardcover; ISBN2 978-3-030-50671-1. Available online: https://www.springer.com/gp/book/9783030506711 (accessed on 20 July 2022). [CrossRef]
4. Fadiji, A.E.; Mthiyane, D.M.N.; Onwudiwe, D.C.; Babalola, O.O. Harnessing the known and unknown impact of nanotechnology on enhancing food security and reducing postharvest losses: Constraints and future prospects. *Agronomy* **2022**, *12*, 1657. [CrossRef]
5. Locke, J.M.; Bryce, J.H.; Morris, P.C. Contrasting effects of ethylene perception and biosynthesis inhibitors on germination and seedling growth of barley (*Hordeum vulgare* L.). *J. Exp. Bot.* **2000**, *51*, 1843–1849. [CrossRef]
6. Elemike, E.E.; Uzoh, I.M.; Onwudiwe, D.C.; Babalola, O.O. The role of nanotechnology in the fortification of plant nutrients and improvement of crop production. *Appl. Sci.* **2019**, *9*, 499. [CrossRef]
7. Bhattacharya, R.; Mukherjee, P. Biological properties of "naked" metal nanoparticles. *Adv. Drug Deliv. Rev.* **2008**, *60*, 1289–1306. [CrossRef]
8. Ahmad, F.; Siddiqui, M.A.; Babalola, O.O.; Wu, H.-F. Biofunctionalization of nanoparticle assisted mass spectrometry as biosensors for rapid detection of plant associated bacteria. *Biosens. Bioelectron.* **2012**, *35*, 235–242. [CrossRef]

9. Rana, K.L.; Kour, D.; Yadav, N.; Yadav, A.N. *Endophytic Microbes in Nanotechnology: Current Development, and Potential Biotechnology Applications Eds by Ajay Kumar and Vipin Kumar Singh "in Microbial Endophytes"*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 231–262. [CrossRef]
10. Bogas, A.C.; Saulo, H.R.; Gonçalves, M.O.; De Assis, M.; Longo, E.; Paiva De Sousa, C. Endophytic microorganisms from the tropics as biofactories for the synthesis of metal-based nanoparticles: Healthcare applications. *Front. Nanotechnol.* **2022**, *4*, 823236. [CrossRef]
11. Azmath, P.; Baker, S.; Rakshith, D.; Satish, S. Mycosynthesis of silver nanoparticles bearing antibacterial activity. *Saudi Pharm. J.* **2016**, *24*, 140–146. [CrossRef]
12. Hulkoti, N.I.; Taranath, T. Biosynthesis of nanoparticles using microbes—A review. *Colloids Surf. B Biointerfaces* **2014**, *121*, 474–483. [CrossRef]
13. Brader, G.; Corretto, E.; Sessitsch, A. Metagenomics of plant microbiomes. In *Functional Metagenomics: Tools and Applications*; Charles, T., Liles, M., Sessitsch, A., Eds.; Springer: Cham, Switzerland, 2017; pp. 179–200.
14. Fadiji, A.E.; Babalola, O.O. Elucidating mechanisms of endophytes used in plant protection and other bioactivities with multifunctional prospects. *Front. Bioeng. Biotechnol.* **2020**, *8*, 467. [CrossRef] [PubMed]
15. Fadiji, A.E.; Babalola, O.O. Metagenomics methods for the study of plant-associated microbial communities: A review. *J. Microbiol. Methods* **2020**, *170*, 105860. [CrossRef]
16. Fadiji, A.E.; Babalola, O.O. Exploring the potentialities of beneficial endophytes for improved plant growth. *Saudi J. Biol. Sci.* **2020**, *27*, 3622–3633. [CrossRef] [PubMed]
17. Baker, S.; Satish, S. Biosynthesis of gold nanoparticles by *Pseudomonas veronii* AS41G inhabiting *Annona squamosa* L. *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* **2015**, *150*, 691–695. [CrossRef] [PubMed]
18. Sunkar, S.; Nachiyar, C.V. Biogenesis of antibacterial silver nanoparticles using the endophytic bacterium *Bacillus cereus* isolated from *Garcinia xanthochymus*. *Asian Pac. J. Trop. Biomed.* **2012**, *2*, 953–959. [CrossRef]
19. Alappat, C.; Kannan, K.; Vasanthi, N. Biosynthesis of Au nanoparticles using the endophytic fungi isolated from *Bauhinia variegata* L. *Eng. Sci. Technol. Int. J.* **2012**, *2*, 377–380.
20. Bala, M.; Arya, V. Biological synthesis of silver nanoparticles from aqueous extract of endophytic fungus *Aspergillus fumigatus* and its antibacterial action. *Int. J. Nanomater. Biostruct.* **2013**, *3*, 37–41.
21. Ahmad, A.; Senapati, S.; Khan, M.I.; Kumar, R.; Ramani, R.; Srinivas, V.; Sastry, M. Intracellular synthesis of gold nanoparticles by a novel alkalotolerant actinomycete, *Rhodococcus* species. *Nanotechnology* **2003**, *14*, 824. [CrossRef]
22. Verma, V.C.; Anand, S.; Ulrichs, C.; Singh, S.K. Biogenic gold nanotriangles from *Saccharomonospora* sp., an endophytic actinomycetes of *Azadirachta indica* A. Juss. *Int. Nano Lett.* **2013**, *3*, 21. [CrossRef]
23. Kaur, P. Biosynthesis of nanoparticles using eco-friendly factories and their role in plant pathogenicity: A review. *Biotechnol. Res. Innov.* **2018**, *2*, 63–73.
24. Sone, B.; Diallo, A.; Fuku, X.; Gurib-Fakim, A.; Maaza, M. Biosynthesized CuO nano-platelets: Physical properties and enhanced thermal conductivity nanofluidics. *Arab. J. Chem.* **2020**, *13*, 160–170. [CrossRef]
25. Bansal, P.; Duhan, J.S.; Gahlawat, S.K. Biogenesis of nanoparticles: A review. *Afr. J. Biotechnol.* **2014**, *13*, 2778–2785.
26. Konishi, Y.; Ohno, K.; Saitoh, N.; Nomura, T.; Nagamine, S.; Hishida, H.; Takahashi, Y.; Uruga, T. Bioreductive deposition of platinum nanoparticles on the bacterium Shewanella algae. *J. Biotechnol.* **2007**, *128*, 648–653. [CrossRef] [PubMed]
27. Ovais, M.; Khalil, A.T.; Ayaz, M.; Ahmad, I.; Nethi, S.K.; Mukherjee, S. Biosynthesis of metal nanoparticles via microbial enzymes: A mechanistic approach. *Int. J. Mol. Sci.* **2018**, *19*, 4100. [CrossRef]
28. Busi, S.; Rajkumari, J. Microbially synthesized nanoparticles as next generation antimicrobials: Scope and applications. In *Nanoparticles Pharmacotherapy*; Grumezescu, A.M., Ed.; Elsevier: Norwich, NY, USA, 2019; pp. 485–524. [CrossRef]
29. Eid, A.M.; Fouda, A.; Niedbała, G.; Hassan, S.E.-D.; Salem, S.S.; Abdo, A.M.; Hetta, H.F.; Shaheen, T.I. Endophytic Streptomyces laurentii mediated green synthesis of Ag-NPs with antibacterial and anticancer properties for developing functional textile fabric properties. *Antibiotics* **2020**, *9*, 641. [CrossRef]
30. Petrini, O. Fungal endophytes of tree leaves. In *Microbial Ecology of Leaves*; Brock/Springer Series in Contemporary Bioscience; Andrews, J.H., Hirano, S.S., Eds.; Springer: New York, NY, USA, 1991; pp. 179–197. [CrossRef]
31. Xu, R.; Li, T.; Cui, H.; Wang, J.; Yu, X.; Ding, Y.; Wang, C.; Yang, Z.; Zhao, Z. Diversity and characterization of Cd-tolerant dark septate endophytes (DSEs) associated with the roots of Nepal alder (*Alnus nepalensis*) in a metal mine tailing of southwest China. *Appl. Soil Ecol.* **2015**, *93*, 11–18. [CrossRef]
32. Ahmed, T.; Shahid, M.; Noman, M.; Niazi, M.B.K.; Zubair, M.; Almatroudi, A.; Khurshid, M.; Tariq, F.; Mumtaz, R.; Li, B. Bioprospecting a native silver-resistant Bacillus safensis strain for green synthesis and subsequent antibacterial and anticancer activities of silver nanoparticles. *J. Adv. Res.* **2020**, *24*, 475–483. [CrossRef]
33. Vijayanandan, A.S.; Balakrishnan, R.M. Biosynthesis of cobalt oxide nanoparticles using endophytic fungus *Aspergillus nidulans*. *J. Environ. Manag.* **2018**, *218*, 442–450. [CrossRef]
34. Gupta, M.; Shukla, K.K. Endophytic Fungi: A Treasure Trove ofNovel Bioactive Compounds. In *Bioactive Natural Products in Drug Discovery*; Singh, J., Meshram, V., Gupta, M., Eds.; Springer: Singapore, 2020; pp. 427–449. [CrossRef]
35. Fadiji, A.E.; Ayangbenro, A.S.; Babalola, O.O. Metagenomic profiling of the community structure, diversity, and nutrient pathways of bacterial endophytes in maize plant. *Antonie Leeuwenhoek* **2020**, *113*, 1559–1571. [CrossRef]

36. Fadiji, A.E.; Ayangbenro, A.S.; Babalola, O.O. Organic Farming enhances the diversity and community structure of endophytic archaea and fungi in maize plant: A shotgun approach. *J. Soil Sci. Plant. Nutr.* **2020**, *20*, 2587–2599. [CrossRef]
37. Messaoudi, O.; Bendahou, M. Biological Synthesis of Nanoparticles Using Endophytic Microorganisms: Current Development. In *"BiologicalSynthesis of Nanoparticles Using Endophytic Microorganisms: Current Development" in Nanotechnology and the Environment*; Sen, M., Ed.; IntechOpen: Rijeka, Croatia, 2020; pp. 1–19. [CrossRef]
38. Adeleke, B.S.; Babalola, O.O. Pharmacological potential of fungal endophytes associated with medicinal plants: A review. *J. Fungi* **2021**, *7*, 147. [CrossRef] [PubMed]
39. Correa-Galeote, D.; Bedmar, E.J.; Arone, G.J. Maize endophytic bacterial diversity as affected by soil cultivation history. *Front. Microbiol.* **2018**, *9*, 484. [CrossRef] [PubMed]
40. Zhou, X.R.; Dai, L.; Xu, G.F.; Wang, H.S. A strain of Phoma species improves drought tolerance of *Pinus tabulaeformis*. *Sci. Rep.* **2021**, *11*, 7637. [CrossRef] [PubMed]
41. Andleeb, A.; Andleeb, A.; Asghar, S.; Zaman, G.; Tariq, M.; Mehmood, A.; Nadeem, M.; Hano, C.; Lorenzo, J.M.; Abbasi, B.H. A systematic review of biosynthesized metallic nanoparticles as a promising anti-cancer-strategy. *Cancers* **2021**, *13*, 2818. [CrossRef]
42. Patra, J.K.; Baek, K.-H. Green nanobiotechnology: Factors affecting synthesis and characterization techniques. *J. Nanomater.* **2014**, *2014*, 219. [CrossRef]
43. Assis, M.; Groppo Filho, F.C.; Pimentel, D.S.; Robeldo, T.; Gouveia, A.F.; Castro, T.F.; Fukushima, H.C.; de Foggi, C.C.; da Costa, J.P.; Borra, R.C. Ag nanoparticles/AgX (X = Cl, Br and I) composites with enhanced photocatalytic activity and low toxicological effects. *ChemistrySelect* **2020**, *5*, 4655–4673. [CrossRef]
44. Salesa, B.; Assis, M.; Andrés, J.; Serrano-Aroca, Á. Carbon nanofibers versus silver nanoparticles: Time-dependent cytotoxicity, proliferation, and gene expression. *Biomedicines* **2021**, *9*, 1155. [CrossRef]
45. Dong, Z.-Y.; Narsing Rao, M.P.; Xiao, M.; Wang, H.-F.; Hozzein, W.N.; Chen, W.; Li, W.-J. Antibacterial activity of silver nanoparticles against Staphylococcus warneri synthesized using endophytic bacteria by photo-irradiation. *Front. Microbiol.* **2017**, *8*, 1090. [CrossRef]
46. Balakumaran, M.; Ramachandran, R.; Kalaichelvan, P. Exploitation of endophytic fungus, *Guignardia mangiferae* for extracellular synthesis of silver nanoparticles and their in vitro biological activities. *Microbiol. Res.* **2015**, *178*, 9–17. [CrossRef]
47. Singh, T.; Jyoti, K.; Patnaik, A.; Singh, A.; Chauhan, R.; Chandel, S. Biosynthesis, characterization and antibacterial activity of silver nanoparticles using an endophytic fungal supernatant of *Raphanus sativus*. *J. Genet. Eng. Biotechnol.* **2017**, *15*, 31–39. [CrossRef]
48. Mohamed, N.H.; Ismail, M.A.; Abdel-Mageed, W.M.; Shoreit, A.A.M. Antimicrobial activity of green silver nanoparticles from endophytic fungi isolated from *Calotropis procera* (Ait) latex. *Microbiology* **2019**, *165*, 967–975. [CrossRef] [PubMed]
49. Bagur, H.; Poojari, C.C.; Melappa, G.; Rangappa, R.; Chandrasekhar, N.; Somu, P. Biogenically synthesized silver nanoparticles using endophyte fungal extract of *Ocimum tenuiflorum* and evaluation of biomedical properties. *J. Clust. Sci.* **2020**, *31*, 1241–1255. [CrossRef]
50. Bagur, H.; Medidi, R.S.; Somu, P.; Choudhury, P.J.; Karua, C.S.; Guttula, P.K.; Melappa, G.; Poojari, C.C. Endophyte fungal isolate mediated biogenic synthesis and evaluation of biomedical applications of silver nanoparticles. *Mater. Technol.* **2022**, *37*, 167–178. [CrossRef]
51. Chandankere, R.; Chelliah, J.; Subban, K.; Shanadrahalli, V.C.; Parvez, A.; Zabed, H.M.; Sharma, Y.C.; Qi, X. Pleiotropic functions and biological potentials of silver nanoparticles synthesized by an endophytic fungus. *Front. Bioeng. Biotechnol.* **2020**, *8*, 95. [CrossRef] [PubMed]
52. Ramos, M.M.; dos Morais, E.S.; da Sena, I.S.; Lima, A.L.; de Oliveira, F.R.; de Freitas, C.M.; Fernandes, C.P.; de Carvalho, J.C.T.; Ferreira, I.M. Silver nanoparticle from whole cells of the fungi *Trichoderma* spp. isolated from Brazilian Amazon. *Biotechnol. Lett.* **2020**, *42*, 833–843. [CrossRef]
53. Hulikere, M.M.; Joshi, C.G. Characterization, antioxidant and antimicrobial activity of silver nanoparticles synthesized using marine endophytic fungus-*Cladosporium cladosporioides*. *Process Biochem.* **2019**, *82*, 199–204. [CrossRef]
54. Neethu, S.; Midhun, S.J.; Radhakrishnan, E.; Jyothis, M. Green synthesized silver nanoparticles by marine endophytic fungus *Penicillium polonicum* and its antibacterial efficacy against biofilm forming, multidrug-resistant *Acinetobacter baumanii*. *Microb. Pathog.* **2018**, *116*, 263–272. [CrossRef]
55. Kavitha, K.; Baker, S.; Rakshith, D.; Kavitha, H.; Yashwantha Rao, H.; Harini, B.; Satish, S. Plants as green source towards synthesis of nanoparticles. *Res. J. Biol. Sci.* **2013**, *2*, 66–76.
56. Joshi, C.G.; Danagoudar, A.; Poyya, J.; Kudva, A.K.; Dhananjaya, B. Biogenic synthesis of gold nanoparticles by marine endophytic fungus-*Cladosporium cladosporioides* isolated from seaweed and evaluation of their antioxidant and antimicrobial properties. *Process Biochem.* **2017**, *63*, 137–144.
57. Munawer, U.; Raghavendra, V.B.; Ningaraju, S.; Krishna, K.L.; Ghosh, A.R.; Melappa, G.; Pugazhendhi, A. Biofabrication of gold nanoparticles mediated by the endophytic Cladosporium species: Photodegradation, in vitro anticancer activity and in vivo antitumor studies. *Int. J. Pharm.* **2020**, *588*, 119729. [CrossRef]
58. Hemashekhar, B.; Chandrappa, C.; Govindappa, M.; Chandrashekar, N. Endophytic fungus Alternaria spp isolated from *Rauvolfia tetraphylla* root arbitrate synthesis of gold nanoparticles and evaluation of their antibacterial, antioxidant and antimitotic activities. *Adv. Nat. Sci. Nanosci. Nanotechnol.* **2019**, *10*, 035010. [CrossRef]

59. Clarance, P.; Luvankar, B.; Sales, J.; Khusro, A.; Agastian, P.; Tack, J.-C.; Al Khulaifi, M.M.; Al-Shwaiman, H.A.; Elgorban, A.M.; Syed, A. Green synthesis and characterization of gold nanoparticles using endophytic fungi Fusarium solani and its in-vitro anticancer and biomedical applications. *Saudi J. Biol. Sci.* **2020**, *27*, 706–712. [CrossRef] [PubMed]
60. Ratti, R.; Serrano, N.; Hokka, C.; Sousa, C. Antagonistic properties of some microorganisms isolated from Brazilian tropical savannah plants against Staphylococcus coagulase-positive strain. *J. Venom. Anim. Toxins Incl. Trop. Dis.* **2008**, *14*, 294–302. [CrossRef]
61. Romano, L.H. Bioprospecção de Microrganismos Endofíticos Isolados de *Tabebuia* spp. e Hymenaea Courbaril e Identificação da Produção de Metabólitos de Interesse Biotecnológico. Ph.D. Thesis, Federal University of São Carlos, São Carlos, Brazil, 2015; pp. 1–136.
62. Mousa, S.A.; El-Sayed, E.-S.R.; Mohamed, S.S.; Abo El-Seoud, M.A.; Elmehlawy, A.A.; Abdou, D.A. Novel mycosynthesis of $Co_3O_4$, CuO, $Fe_3O_4$, NiO, and ZnO nanoparticles by the endophytic *Aspergillus terreus* and evaluation of their antioxidant and antimicrobial activities. *Appl. Microbiol. Biotechnol.* **2021**, *105*, 741–753. [CrossRef] [PubMed]
63. Rasool, U.; Hemalatha, S. Marine endophytic actinomycetes assisted synthesis of copper nanoparticles (CuNPs): Characterization and antibacterial efficacy against human pathogens. *Mater. Lett.* **2017**, *194*, 176–180. [CrossRef]
64. Hassan, S.E.-D.; Salem, S.S.; Fouda, A.; Awad, M.A.; El-Gamal, M.S.; Abdo, A.M. New approach for antimicrobial activity and bio-control of various pathogens by biosynthesized copper nanoparticles using endophytic actinomycetes. *J. Radiat. Res. Appl. Sci.* **2018**, *11*, 262–270. [CrossRef]
65. Uddandarao, P. ZnS semiconductor quantum dots production by an endophytic fungus *Aspergillus flavus*. *Mater. Sci. Eng. B* **2016**, *207*, 26–32. [CrossRef]
66. Uddandarao, P.; Balakrishnan, R.M.; Ashok, A.; Swarup, S.; Sinha, P. Bioinspired ZnS: Gd nanoparticles synthesized from an endophytic fungi *Aspergillus flavus* for fluorescence-based metal detection. *Biomimetics* **2019**, *4*, 11. [CrossRef]
67. Arya, S.; Sonawane, H.; Math, S.; Tambade, P.; Chaskar, M.; Shinde, D. Biogenic titanium nanoparticles ($TiO_2$NPs) from *Tricoderma citrinoviride* extract: Synthesis, characterization and antibacterial activity against extremely drug-resistant Pseudomonas aeruginosa. *Int. Nano Lett.* **2021**, *11*, 35–42. [CrossRef]
68. Savary, S.; Willocquet, L.; Pethybridge, S.J.; Esker, P.; McRoberts, N.; Nelson, A. The global burden of pathogens and pests on major food crops. *Nat. Ecol. Evol.* **2019**, *3*, 430–439. [CrossRef]
69. Kim, T.; Feng, Q.L.; Kim, J.; Wu, J.; Wang, H.; Chen, G.; Cui, F. Antimicrobial effects of metal ions ($Ag^+$, $Cu^{2+}$, $Zn^{2+)}$ in hydroxyapatite. *J. Mater. Sci. Mater. Med.* **1998**, *9*, 129–134. [CrossRef] [PubMed]
70. Raheman, F.; Deshmukh, S.; Ingle, A.; Gade, A.; Rai, M. Silver nanoparticles: Novel antimicrobial agent synthesized from an endophytic fungus *Pestalotia* sp. isolated from leaves of *Syzygium cumini* (L.). *Nano Med. Eng.* **2011**, *3*, 174–178. [CrossRef]
71. Devi, L.S.; Joshi, S. Ultrastructures of silver nanoparticles biosynthesized using endophytic fungi. *J. Microsc. Ultrastruct.* **2015**, *3*, 29–37. [PubMed]
72. Verma, V.C.; Kharwar, R.N.; Gange, A.C. Biosynthesis of antimicrobial silver nanoparticles by the endophytic fungus *Aspergillus clavatus*. *Nanomedicine* **2010**, *5*, 33–40. [CrossRef]
73. Qian, Y.; Yu, H.; He, D.; Yang, H.; Wang, W.; Wan, X.; Wang, L. Biosynthesis of silver nanoparticles by the endophytic fungus *Epicoccum nigrum* and their activity against pathogenic fungi. *Bioprocess Biosyst. Eng.* **2013**, *36*, 1613–1619. [CrossRef]
74. Netala, V.R.; Bethu, M.S.; Pushpalatha, B.; Baki, V.B.; Aishwarya, S.; Rao, J.V.; Tartte, V. Biogenesis of silver nanoparticles using endophytic fungus *Pestalotiopsis microspora* and evaluation of their antioxidant and anticancer activities. *Int. J. Nanomed.* **2016**, *11*, 5683. [CrossRef]
75. Hossain, A.; Hong, X.; Ibrahim, E.; Li, B.; Sun, G.; Meng, Y.; Wang, Y.; An, Q. Green synthesis of silver nanoparticles with culture supernatant of a bacterium *Pseudomonas rhodesiae* and their antibacterial activity against soft rot pathogen *Dickeya dadantii*. *Molecules* **2019**, *24*, 2303. [CrossRef]
76. Ibrahim, E.; Zhang, M.; Zhang, Y.; Hossain, A.; Qiu, W.; Chen, Y.; Wang, Y.; Wu, W.; Sun, G.; Li, B. Green-synthesization of silver nanoparticles using endophytic bacteria isolated from garlic and its antifungal activity against wheat fusarium head blight pathogen *Fusarium graminearum*. *Nanomaterials* **2020**, *10*, 219. [CrossRef]
77. Hemashekhar, B.; Chandrappa, C.; Govindappa, M.; Chandrasekhar, N.; Ganganagappa, N.; Ramachandra, Y. Green synthesis of silver nanoparticles from Endophytic fungus *Aspergillus niger* isolated from *Simarouba glauca* leaf and its Antibacterial and Antioxidant activity. *Int. J. Eng. Res. Appl.* **2017**, *7*, 17–24.
78. Singh, D.; Rathod, V.; Ninganagouda, S.; Herimath, J.; Kulkarni, P. Biosynthesis of silver nanoparticle by endophytic fungi *Pencillium* sp. isolated from *Curcuma longa* (turmeric) and its antibacterial activity against pathogenic gram negative bacteria. *J. Pharm. Res.* **2013**, *7*, 448–453. [CrossRef]
79. Farsi, M.; Farokhi, S. Biosynthesis of antibacterial silver nanoparticles by endophytic fungus *Nemania* sp. Isolated From *Taxus baccata* L.(Iranian Yew). *Zahedan J. Res. Med. Sci.* **2018**, *20*, e57916. [CrossRef]
80. Ranjani, S.; Ahmed, S.M.; Adnan, M.; Kumar, S.N.; Ruckmani, K.; Hemalatha, S. Synthesis, characterization and applications of endophytic fungal nanoparticles. *Norganic Nano-Met. Chem.* **2020**, *51*, 380–387. [CrossRef]
81. Vijayan, S.; Koilaparambil, D.; George, T.K.; Manakulam Shaikmoideen, J. Antibacterial and cytotoxicity studies of silver nanoparticles synthesized by endophytic *Fusarium solani* isolated from *Withania somnifera* (L.). *J. Water Environ. Nanotechnol.* **2016**, *1*, 91–103.

82. Muhsin, T.; Hachim, A. Antitumor and antibacterial efficacy of mycofabricated silver nanoparticles by the endophytic fungus *Papulaspora pallidula*. *Am. J. Biosci. Bioeng.* **2016**, *2*, 24–38. [CrossRef]
83. Gogos, A.; Knauer, K.; Bucheli, T.D. Nanomaterials in plant protection and fertilization: Current state, foreseen applications, and research priorities. *J. Agric. Food Chem.* **2012**, *60*, 9781–9792. [CrossRef]
84. Kah, M.; Hofmann, T. Nanopesticide research: Current trends and future priorities. *Environ. Int.* **2014**, *63*, 224–235. [CrossRef]
85. Park, H.-J.; Kim, S.-H.; Kim, H.-J.; Choi, S.-H. A new composition of nanosized silica-silver for control of various plant diseases. *Plant Pathol. J.* **2006**, *22*, 295–302. [CrossRef]
86. Rahman, S.; Rahman, L.; Khalil, A.T.; Ali, N.; Zia, D.; Ali, M.; Shinwari, Z.K. Endophyte-mediated synthesis of silver nanoparticles and their biological applications. *Appl. Microbiol. Biotechnol.* **2019**, *103*, 2551–2569. [CrossRef]
87. Nirmala, C.; Sridevi, M. Characterization, antimicrobial and antioxidant evaluation of biofabricated silver nanoparticles from Endophytic Pantoea anthophila. *J. Inorg. Organomet. Polym. Mater.* **2021**, *31*, 3711–3725. [CrossRef]
88. Huang, Y.-W.; Cambre, M.; Lee, H.-J. The toxicity of nanoparticles depends on multiple molecular and physicochemical mechanisms. *Int. J. Mol. Sci.* **2017**, *18*, 2702. [CrossRef]
89. Kai, W.; Xiaojun, X.; Ximing, P.; Zhenqing, H.; Qiqing, Z. Cytotoxic effects and the mechanism of three types of magnetic nanoparticles on human hepatoma BEL-7402 cells. *Nanoscale Res. Lett.* **2011**, *6*, 480. [CrossRef] [PubMed]
90. Baek, M.; Kim, M.; Cho, H.; Lee, J.; Yu, J.; Chung, H.; Choi, S. Factors influencing the cytotoxicity of zinc oxide nanoparticles: Particle size and surface charge. *J. Phys. Conf. Ser.* **2011**, *304*, v012044. [CrossRef]
91. Huang, Y.-W.; Lee, H.-J.; Tolliver, L.M.; Aronstam, R.S. Delivery of nucleic acids and nanomaterials by cell-penetrating peptides: Opportunities and challenges. *BioMed Res. Int.* **2015**, *2015*, 834079. [CrossRef] [PubMed]
92. Chusuei, C.C.; Wu, C.-H.; Mallavarapu, S.; Hou, F.Y.S.; Hsu, C.-M.; Winiarz, J.G.; Aronstam, R.S.; Huang, Y.-W. Cytotoxicity in the age of nano: The role of fourth period transition metal oxide nanoparticle physicochemical properties. *Chem.-Biol. Interact.* **2013**, *206*, 319–326. [CrossRef]
93. Ranjani, S.; Matheen, A.; Jenish, A.A.; Hemalatha, S. Nanotechnology derived natural poly bio-silver nanoparticles as a potential alternate biomaterial to protect against human pathogens. *Mater. Lett.* **2021**, *304*, 130555. [CrossRef]
94. Antisari, L.V.; Carbone, S.; Fabrizi, A.; Gatti, A.; Vianello, G. Response of soil microbial biomass to $CeO_2$ nanoparticles. *EQA-Int. J. Environ. Qual.* **2011**, *7*, 1–16.
95. Lee, S.; Kim, S.; Kim, S.; Lee, I. Effects of soil-plant interactive system on response to exposure to ZnO nanoparticles. *Microbiol. Biotechnol.* **2012**, *22*, 1264–1270. [CrossRef]
96. Lin, D.; Xing, B. Root uptake and phytotoxicity of ZnO nanoparticles. *Environ. Sci. Technol.* **2008**, *42*, 5580–5585. [CrossRef]
97. Hong, F.; Zhou, J.; Liu, C.; Yang, F.; Wu, C.; Zheng, L.; Yang, P. Effect of nano-$TiO_2$ on photochemical reaction of chloroplasts of spinach. *Biol. Trace Elem. Res.* **2005**, *105*, 269–279. [CrossRef]
98. Lee, W.-M.; Kwak, J.I.; An, Y.-J. Effect of silver nanoparticles in crop plants *Phaseolus radiatus* and *Sorghum bicolor*: Media effect on phytotoxicity. *Chemosphere* **2012**, *86*, 491–499. [CrossRef]
99. Nafeh, A.; Mazhar, S. Endophytic nanoparticles: Towards a new therapeutic future. *J. Microbiol. Mol. Genet.* **2021**, *2*, 19–30. [CrossRef]