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Endophytic Microorganisms From the Tropics as Biofactories for the Synthesis of Metal-Based Nanoparticles: Healthcare Applications

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Nanoparticles (NPs) have gained great attention in recent years due to their extensive and innovative applications in the field of medicine. However, conventional physicochemical approaches for the synthesis of NPs may be limited and costly, and the reaction by-products are potentially toxic for human health and the environment. Bio-mediated synthesis of NPs exploiting microorganisms as nanofactories has emerged as an alternative to traditional methods, as it provides economic and environmental benefits. Tropical ecosystems harbor a high diversity of endophytes, which have a diverse array of metabolic pathways that confer habitat adaptation and survival and that can be used to produce novel bioactive compounds with a variety of biological properties. Endophytic bacteria and fungi cultivated under optimum conditions have potential for use in biogenic synthesis of NPs with different characteristics and desired activities for medical applications, such as antimicrobial, antitumoral, antioxidant and anti-inflammatory properties. The bio-mediated synthesis of metal-based NPs can be favored because endophytic microorganisms may tolerate and/or adsorb metals and produce enzymes used as reducing agents. To our knowledge, this is the first review that brings together exclusively current research highlighting on the potential of endophytic bacteria and fungi isolated from native plants or adapted to tropical ecosystems and tropical macroalgae as nanofactories for the synthesis of NPs of silver, gold, copper, iron, zinc and other most studied metals, in addition to showing their potential use in human health.

Keywords: endophyte, tropics, bioactive compounds, green synthesis, nanoparticles, medicine

INTRODUCTION

Nanotechnology is an interdisciplinary field of science related to the manipulation and rearrangement of individual atoms and molecules to create materials at the nanometer scale (1 to 100 nm) (Katranidis and Choli-Papadopoulou, 2012). In recent years, the incorporation of nanostructured materials in human, animal and environmental health and biotechnological sectors has been contributing to the improvement of diagnosis and treatment of diseases (Raffa et al., 2010; Patel and Nanda, 2015; Panda et al., 2021).

Metal-based NPs synthetized by chemical and physical methods have a positive impact on human health care (Alaqad and Saleh, 2016; Xu et al., 2020), including the targeted delivery of anticancer agents (Desai et al., 2021), action against antibiotic-resistant Gram-negative and Gram-positive bacteria (Bankier et al., 2019), pathogenic fungi (Abdelnaby et al., 2021) and viruses (Tortella et al., 2021), and anti-inflammatory activity (Wong et al., 2009). Particular traits such as shape, composition, small size, high surface area and charge give NPs their multi-biomedical properties and applications (Navya and Daima, 2016). Nevertheless, the NPs can have cytotoxicity and genotoxicity effects at some concentrations and time of exposition, which cause concern about their clinical use (Jamuna and Ravishankar, 2014; Rezvani et al., 2019). In addition, studies have shown the potential risks of NPs for both aquatic and terrestrial environments (Bundschuh et al., 2018).

The green synthesis of metal-based NPs using microorganisms has emerged as an attractive and alternative method to provide a more clean and sustainable production, and consequently minimize toxic effects to health and the environment (Pal et al., 2019). Microorganisms can be easily cultivated on a large scale in tiny time, and the culture conditions (e.g. biomass quantity, culture time, temperature and pH) can be optimized to synthetize NPs with stability, size and desired shape (Barabadi et al., 2014; Taran et al., 2017).

The synthesis of metal-based NPs using microorganisms occurs by both intra- and extracellular mechanisms (Ovais et al., 2018). In general, in the intracellular synthesis there is an electrostatic interaction between positive charges of the metallic ions and negative charges of the microbial cell wall, followed by a reduction of the metal ion (M^+) to its metallic form (M^o). This process is catalyzed by microbial reductases and reductases dependent on the cofactors nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) that act as electron carriers in the oxidation-reduction reactions. As a result, the NPs are stabilized by capping proteins in the cytoplasm or periplasmic space. However, a disruption of cells is required to obtain purified NPs (Hulkoti and Taranath, 2014; Busi and Rajkumari, 2019). In contrast, in the extracellular synthesis the culture supernatant, biomass or cell-free extract is mixed with the metal solution, and the NPs are produced outside the microbial cell. This process is carried out by reductases produced and secreted to the culture medium by microbial cells and cofactors. After bio-reduction and nucleation, the synthetized NPs are also stabilized by capping agents (Hulkoti and Taranath, 2014). The NPs synthesized intra- or extracellularly can have different shapes, such as spherical, triangular, oval, cubic and square (Busi and Rajkumari, 2019).

Endophytic bacteria and fungi have been considered as potent biofactories for the synthesis of metal-based NPs with medicinal properties (Rahman et al., 2019; Eid et al., 2020; Rana et al., 2020). These microorganisms colonize inter- and/or intracellular tissues of plants and stablish with them a symbiotic relationship without causing any apparent harm (Petrini, 1991; Hallmann et al., 1997). They may improve plant health and development by several mechanisms, including the production of antimicrobial compounds (Fadiji and Babalola, 2020).

Endophytes can tolerate and/or accumulate metals present in the environmental to alleviate host plant stress and toxicity, and favor its own adaptation and competitive edge over other microorganisms in this niche (Xu et al., 2015; Franco-Franklin et al., 2021). This metal detoxification ability of the endophytes can be explored to synthetize metal-based NPs via intra- and extracellular mechanisms. The supernatant of silver (Ag)-resistant *Bacillus safensis* TEN12 was used for the intracellular synthesis of silver (Ag) NPs with an average size from 22 to 45 nm and spherical shape (Ahmed et al., 2020). Stable and quasi-spherical zinc oxide (ZnO) NPs sized 2–9 nm were synthesized by the zinc-tolerant endophytic *Cochliobolus geniculatus* through the extracellular mechanism (Vijayanandan and Balakrishnan, 2018). Similarly, spherical cobalt oxide (CoO) NPs sized 20 nm were synthesized by the CoO-tolerant endophytic *Aspergillus nidulans* also via the extracellular mechanism (Vijayanandan and Balakrishnan, 2018).

Endophytic microorganisms can produce bioactive secondary metabolites with a high degree of biological activities and structural diversity to be explored in human health (Gupta and Shukla, 2020; Adeleke and Babalola, 2021). Thus, bacteria and fungi isolated from different parts of plants can be easily culturable in laboratory under optimum culture conditions to manufacture NPs with desired characteristics and activities (Zielonka and Klimek-Ochab, 2017; Messaoudi and Bendahou, 2020).

Tropical ecosystems are considered a hotspot of diversity of endophytic microorganisms that contains species not recovered from other areas (Arnold and Lutzoni, 2007; Roy and Banerjee, 2018). The great competition, limited resources and selection pressure in tropical environments favor not only the high diversity of endophytes, but also the production of novel biomolecules with medical properties (Rosa, 2011; Pereira et al., 2017; Sebastianes et al., 2017), opening up perspectives for the synthesis of new NPs for healthcare applications. In this way, several studies have demonstrated the potential of endophytes isolated from native plants or adapted to tropical ecosystems for the green synthesis of silver (Ag) (Balakumaran et al., 2015), gold (Au) (Munawer et al., 2020), copper (Cu) (Hassan et al., 2018), zinc (Zn) (Uddandarao and B, 2016) and other metal-based NPs. Marine macroalgae widespread across the tropics are also a promising source of endophytes for the biosynthesis of NPs with medicinal properties (Manjunath et al., 2017).

An overview of metal-based NPs synthesis from endophytes is shown in **Figure 1**. Our manuscript brings as novelty a literature review focused exclusively on the potential of endophytic bacteria and fungi of a range of host plants and macroalgae from tropical ecosystems for the green synthesis of metal-based NPs with different characteristics and their potential applications in the health sector.

BIOSYNTHESIS OF NANOSTRUCTURAL MATERIALS

Nanoparticulate materials can have overwhelming advantages over micro structured materials. For these materials to be applied

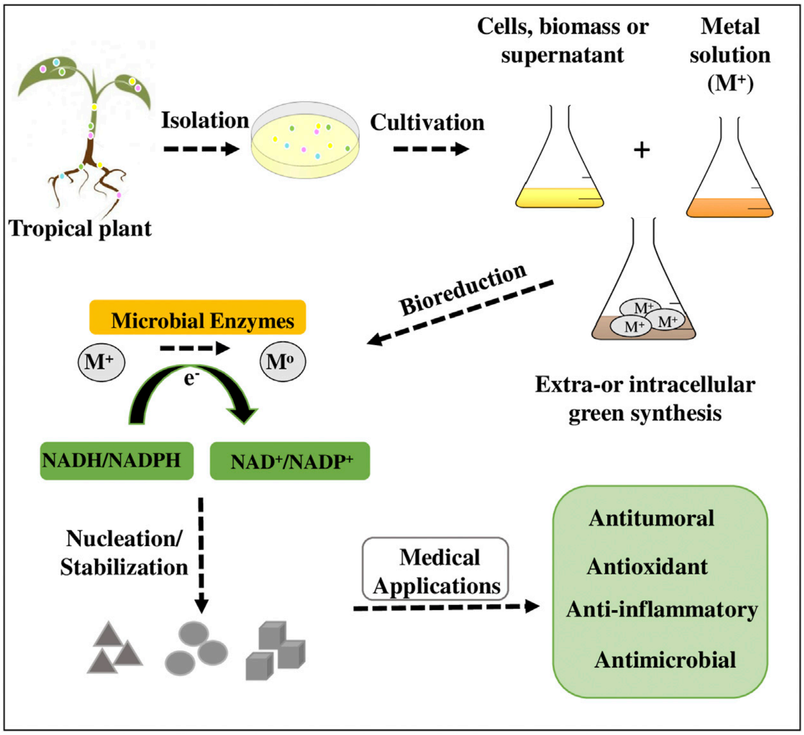

FIGURE 1 | Schematic representation of the general steps for green synthesis of metal-based NPs using endophytic microorganisms isolated from tropical plant.

in the health and wellness sectors, several factors must be considered to define their efficiency, such as chemical composition, size and morphology. When using the green biosynthesis from endophytic microorganisms, the determining variables for the synthetic process include the microorganisms that will be used, how these microorganisms will be used in the biosynthesis and the normal synthesis conditions. These metal reduction processes normally occur through NADH and NADPH-dependent reductases present in different endophytic fungi and bacteria (Durán et al., 2005).

The first point to be considered for the synthesis of nanomaterials from endophytic microorganisms is the isolation of the target fungus/bacteria. Various parts of the target plants/algae such as seeds, roots, leaves and stems are cleaned. Pieces of these plant parts are placed under specific conditions for optimal growth of microorganisms (culture medium, supplements, temperature, time, CO_2 rate, agitation, etc.) (Adeleke and Babalola, 2021). After growth, isolation of a target microorganism can occur, or use all microorganisms present. Once the strategy is defined, the total biomass of the microorganisms can be used, the cell extract (obtained through the filtration of the initial biomass), or the cell-free extract (which contains metabolites produced by the microorganisms) to produce NPs (Andleeb et al., 2021). It is particularly important to define which of the types of interaction mentioned above will be used, as these living systems have intrinsic factors (such as metabolites and enzymes) that will define the sort of nanoparticle obtained. Furthermore, it is worth remembering that each microorganism will produce different types of metabolites and enzymes in different proportions. These factors can act during the biosynthesis process as surfactants, stabilizers or even reducing agents (Patra and Baek, 2014).

As a general procedure for the synthesis of nanoparticulate materials, biomass/cell extract/cell-free extract is added to a solution of the NPs metal precursor salt. Usually, transition metal nitrates, chlorides, sulfates and acetates are used. Reactional conditions of time, pH, temperature, time, pressure and starting reactants are key elements to maximize the interactions necessary for the formation of the NPs. In this way it is possible to control the size, shape and even the composition of the formed NP. After defining all these parameters, a colloid can be obtained from the NPs, or they can be filtered and washed, obtaining a powder as the final product. **Supplementary Table 1** show an overview of metals and metal oxides NPs, respectively, synthesized from endophytic microorganisms from tropical plants.

Silver Nanoparticles (Ag NPs)

Silver as a metal has been used since ancient times due to its microbicidal and/or anti-inflammatory properties (Assis et al., 2020; Alavi and Varma, 2021; Salesa et al., 2021). As a result, it has become a key NP of easy obtention through green biosynthesis by endophytic microorganisms. It is interesting to note that all Ag NPs biosynthesized by endophytic microorganisms derived from tropical plants have spheroidal morphology, using silver nitrate as a source of Ag^+ ions.

The use of endophytic microorganisms located in the roots of tropical plants can be an important pathway for the biosynthesis of Ag NPs. Some works using cell-free extracts (metabolites and proteins generated in culture) of endophytic bacteria SYSU 333150 *Isoptericola* sp. (Dong et al., 2017) and *Streptomyces laurentii* (Eid et al., 2020) reported the obtention of spheroidal Ag NPs with diameter smaller than 40 nm. Other studies investigated cell-free extracts of fungi *Alternaria* sp., *Aspergillus* sp., *Chaetomium* sp., *Cladosporium* sp., *Colletotrichum* sp., *Curvularia* sp., *Guignardia* sp., *Penicillium* sp., *Pestalotia* sp., *Pestalotiopsis* sp., and *Phomopsis* sp. obtained from leaves of *Raphanus sativus* (Singh et al., 2017) and *Azadirachta indica* (Balakumaran et al., 2015), which gave rise to Ag NPs sized 30 nm.

The cell extract of these endophytic microorganisms also becomes a differentiated platform for synthesis, as it allows their interaction specifically with Ag^+ ions and the possibility of bio-reduction to metallic Ag NPs. Some studies demonstrated that cell extracts of *Penicillium* sp., *Alternaria* sp., *Aspergillus* sp. and *Cladosporium* sp. isolated from leaves extract of *Calotropis procera* (Chowdhury et al., 2016; Mohamed et al., 2019), *Aspergillus tubingensis* and *Bionectria ochroleuca* from *Rhizophora magle* and *Laguncularia racemose* (Rodrigues et al., 2013) and *Aspergillus niger* from *Stypandra glauca* (Hemashekhar et al., 2017) can form Ag NPs sized up to 45 nm. Ag NPs smaller than 15 nm can be synthesized in the same way using fungi cell extracts of *Exserohilum rostrata* from *Ocimum tenuiflorum* (Bagur et al., 2020b) and *Penicillium* sp. from *Tinospora cordifolia* (Bagur et al., 2020a).

The total biomass of these microorganisms can also be used to obtain these Ag NPs. The fungi biomass of *Colletotrichum incarnatum*, *Alternaria solani* and *Penicillium funiculosum* (from leaves of *Datura metel* and *Gloriosa superba*) (Devi et al., 2014; Chandankere et al., 2020) and *Trichoderma* spp. (from seeds of *B. excelsa*) (Ramos et al., 2020) was used, resulting in particles smaller than 40 nm. Biomass of endophytic fungi from tropical seaweeds can also be used for the biosynthesis of Ag NPs. Hulikere et al. removed this biomass of *Cladosporium cladosporioides* from the seaweed *Sargassum wightii*, yielding Ag NPs with size of 60 nm (Manjunath and Joshi, 2019). In another work, Neethu et al. obtained Ag NPs with size of 15 nm using cell extract of *Penicillium polonicum* from the seaweed *Chaetomorpha antennina* (Neethu et al., 2018).

Gold Nanoparticles (Au NPs)

Like Ag NPs, the antimicrobial and anti-inflammatory properties of Au NPs are already extensively known. However, since gold is a noble metal with high added value, its use may be compromised. Regarding the synthesis of such metal, the most used Au-based starting reagent is $HAuCl_4$. Endophytic fungi from tropical marine environments are widely used for the biosynthesis of Au NPs. It was found that the biomass of the fungus *Cladosporium cladosporioides* extracted from the seaweed *Sargassum wightii* has the ability to synthesize Au NPs spheres with diameter of up to 60 nm (Manjunath et al., 2017). Au NPs spheres sized approximately 10 nm were obtained from the cell extract of the fungus *Cladosporium sp.* located in the leaves of *Commiphora wightii* (Munawer et al., 2020). Regarding Au NPs with triangular morphology, they were formed by cell extracts of fungi of the genera *Aspergillus* sp. and *Alternaria* sp. found in the stem of *Azadirachta indica* and in the roots of *Rauvolfia tetraphylla*, respectively (Verma et al., 2010; Hemashekhar et al., 2019). Au NPs with needle-like morphology and size of 45 nm were also synthesized, but using the biomass of the fungus *Fusarium solani* present in the roots of *Cleistes fragrans* (Clarance et al., 2020).

In our group research, recent work (Sousa et al., 2021) was conducted highlighting the green synthesis. Through the nanoparticles biosynthesis using *Paenibacillus polymyxa* and *P. terrae* isolated from Brazilian tropical savannah plants *Prunus* spp. (Ratti et al., 2008) and *Tabebuia* spp. (Romano, 2014) respectively, the process was optimized considering the synthesis time, the extract concentration, the wavelength and the particle size. The experiment was divided into phases where the best focus (1, 1:2, 1:4, 1:8 and 1:16) was analyzed, observing through UV-Vis spectroscopy at 540 nm the best absorption of light in relation to time and over 72 h in a 12-h interval. As the best indicators were 1:2 and 1:4, for both bacterial extracts and 12–24 h as the best periods. The next phase was analyzed hourly for 24 h, with the values 1:2 and 1:4, for light absorption at 540 nm and in the spectral range of 300 to 800 nm, demonstrating a statistic of gold nanoparticle for 1:2 dilutions, whose peak at around 540 nm, and as of 7 a.m. are already described. Based on the results of the characterization by DLS and absorbance, such as Au NPs synthesized through crude extractions *P. polymyxa* 1:2 and *P. terrae* 1:2 was as obtaining better results, obtaining the average level of 262 and 372 nm, respectively, in monodispersed systems, with the following occurrences after 7 h of biosynthesis reaction, obtaining greater results between 12 and 24 h. The main absorption was detected at the red spectral range.

Copper-Based Nanoparticles (Cu NPs)

A cheaper alternative to both Ag NPs and Au NPs are Cu NPs. It was found that the fungus *Aspergillus terreus* isolated from the plants *Aegle marmelosa* and *Origanum majorana* is capable of producing spheroidal CuO NPs from $CuSO_4$ (Mani et al., 2021; Mousa et al., 2021). In this case, the use of biomass and cell extract of the fungus led to the formation of CuO NPs with different sizes. It was reported that Cu NPs sized less than 100 nm can also be obtained from marine actinomycetes taken from tropical seaweeds (Rasool and Hemalatha, 2017), and from *Streptomyces capillispiralis* extracted from leaves of *Calendula arvensis* (Hassan et al., 2018). According to the literature, by changing the source of Cu^{2+} ions to $Cu(NO_3)_2$ and using the fungus *Phaeoacremonium* sp. it is possible to modulate the morphology of Cu NPs, obtaining nanorods with size of approximately 97 nm (Morais et al., 2021).

Zinc-Based Nanoparticles (Zn NPs)

Zn-based nanoparticles have attracted great commercial interest, as they are an alternative for the design of new antimicrobial materials with low cellular toxicity. From the biomass of the fungus *Aspergillus flavus* it was possible to obtain ZnS NPs using $ZnSO_4$ as a starting reagent (Uddandarao, 2016). This fungus was isolated from Nothapodytes *foetida* leaves, generating ZnS spheres with diameter of 18 nm. In another study, Uddandarao et al. (2019) were able to perform Gd doping of ZnS NPs by adding $Gd(NO_3)_3$ to the biomass. Furthermore, it was demonstrated that ZnO NPs can also obtained from the cell extract of *Periconium* sp. (Ganesan et al., 2020). ZnO spheres (15 nm) and rods (50 nm), for instance, can be formed using $ZnSO_4$ and $Zn(NO_3)_2$ as starting reagents, respectively (Ganesan et al., 2020; Mousa et al., 2021).

Cobalt-, Titanium-, Iron- and Nickel-Based Nanoparticles (Co, Ti, Fe and Ni NPs)

The fungus *Aspergillus terreus* can be used to perform the reduction of Co, Fe and Ni salts, giving rise to spherical Co_3O_4, Fe_3O_4 and NiO NPs sized 15, 40 and 60 nm, respectively (Mousa et al., 2021). It was reported that spheroidal CoO NPs can also be obtained from the fungus *Aspergillus nidulans* isolated from *N. foetida* leaves (Vijayanandan and Balakrishnan, 2018). Micro- and nanostructured TiO_2 particles of different shapes, such as rod-like, triangular, pentagonal and spherical, can be formed using the biomass of the fungus *Trichoderma citrinoviride* isolated from the roots of *Sorghum bicolor* (Arya et al., 2021).

POTENTIAL APPLICATIONS OF METAL-BASED NPS IN MEDICINE

Metal-based NPs have been successfully synthesized using a diversity of endophytic bacteria and fungi associated with plants and macroalgae found in both tropical terrestrial and marine ecosystems. Some studies related to their characteristics and medical applications are summarized in **Supplementary Table 1** and will be further discussed in detail below.

Antimicrobial and Biofilm Activities

The use of NPs in the clinical area is very important in public health, especially when considering the increasingly worrying resistance of human pathogens to available drugs. Differently from conventional antimicrobials, nanoparticles do not necessarily need to enter microbial cells to start acting, as their action is normally related to the cell wall (Knetsch and Koole, 2011; Wang et al., 2017). In this way, a microorganism could hardly become resistant to them since successive mutations in the same cell would have to occur for it to develop resistance (Pandey et al., 2021). Thus, NPs have the potential to overcome the problems of resistance and multi-resistance to antimicrobials.

The antimicrobial mechanisms of different metal based-NPs synthetized intra or extracellularly by microorganisms are not yet well understood. However, many studies have been demonstrated that these NPs are able to physically interact with the cell wall and membrane causing disintegration and change in its permeability. The penetration of NPs into the microbial cell can lead to production of reactive oxygen species (ROS) and free radicals, besides alterations in mitochondrial respiratory chain proteins, inhibition of DNA replication and its denaturation, ribosomal subunits destabilization and inhibition of translation and protein synthesis, denaturation of proteins and enzymes, and subsequent general metabolic dysfunction and cell death (Wang et al., 2017; Busi and Rajkumari, 2019; Shaikh et al., 2019) (**Figure 2**).

According to Shariq Ahmed et al. (2019), Ag NPs synthesized by an endophytic bacterium isolated from the tropical plant *Pennisetum setaceum* inhibited the growth of *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 35657), *Acinetobacter baumannii* (ATCC 19606), *Pseudomonas aeruginosa* (ATCC 27853), *Salmonella typhimurium* (ATCC 14028) and *Staphylococcus aureus* (MTCC 1430). Furthermore, these nanoparticles were also able to reduce biofilm formation, being the inhibition of pathogens attributed to the action of NPs on the cell walls of the indicators. It is noteworthy that studies on the antimicrobial activity against microorganisms of the "ESKAPE" group, which include the bacteria *Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacteriaceae*, are very relevant since these bacterial pathogens are known to evade conventionally used antibiotics in their treatments through drug resistance (Xie et al., 2018). Among them there is the opportunistic bacterium *A. baumannii*, a human pathogen that has been considered to cause serious medical condition, as it easily develops antimicrobial resistance (Lee et al., 2017) and is increasingly present in cases of hospital infections and intensive care (Anitha et al., 2016).

Bagur et al. (2020b) synthesized Ag NPs from extracts of the tropical endophytic fungus *Exserohilum rostrata* and reported the inhibition of the pathogens *S. aureus*, *E. coli*, *K. pneumoniae* and *P. aeruginosa*, in addition to antibiofilm activity. In their work, the authors compared endophytic extracts with and without the nanoparticles and observed that those with Ag NPs had a greater antimicrobial activity. According to them, this combination possibly intensified the natural potential inhibition of the extracts. Additionally, other works also reached similar results. Bagur et al. (2020a), for instance, showed a possible synergism between bioactive compounds of the extract of the endophytic fungus *Penicillium* sp. and Ag NPs, evidenced by the greater antimicrobial activity of the extracts with Ag NPs against *S. aureus*, *E. coli*, *P. aeruginosa*, and *K. pneumoniae*. Hemashekhar et al. (2017) also observed that extracts of the endophytic fungus *A. niger* with silver nanoparticles were able to inhibit *E. coli*, *P. aeruginosa*, *S. aureus* and *K. pneumoniae*, while the pure extract were not. It is important to mention that both studies used endophytes isolated from tropical plants as well.

CuO NPs synthesized by the endophytic fungus *Aspergillus terreus* FCBY1 isolated from a tropical plant *Aegle marmelos* were tested by Mani et al. (2021) against *Staphylococcus epidermidis*, *Candida albicans*, *Proteus mirabilis*, *Vibrio cholerae*, *Salmonella typhi*, *S. aureus*, *P. aeruginosa*, *K. pnuemoniae*, *E. coli* and *A. niger*. It was shown that all microorganisms had their growth inhibited by CuO NPs – although the inhibition of fungi was lower than that of bacteria. Moreover, no variation was observed in the inhibition of Gram-positive and Gram-negative bacteria. Naturally, the authors pay more attention to bacteria, as the cell walls of both types are morphologically different, which normally contributes to the activity against them. Gram-positive bacteria have a thick layer of peptidoglycan and

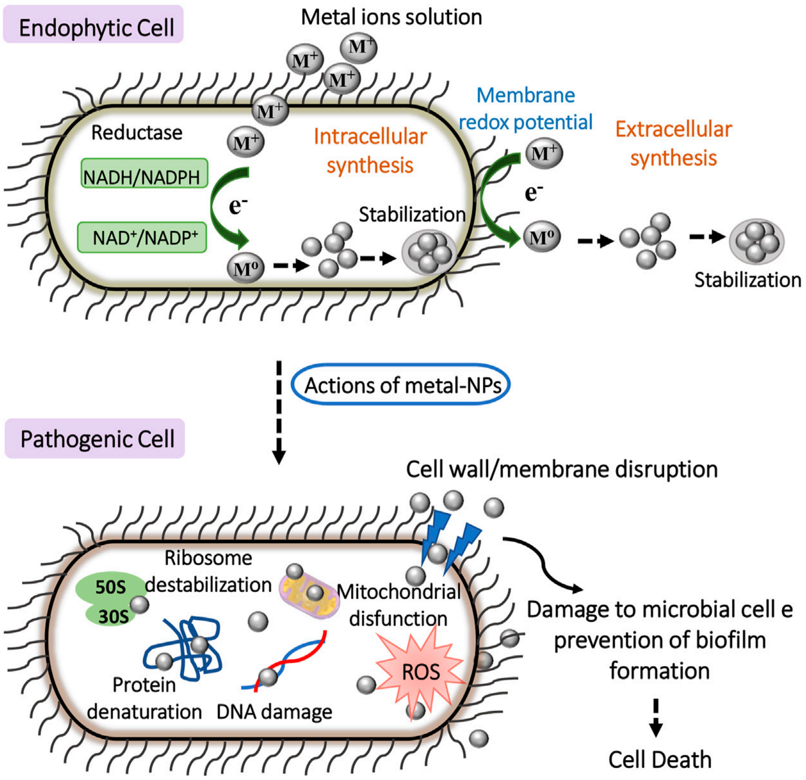

FIGURE 2 | Schematic representation of general antimicrobial mechanisms of metal-based NPs synthetized by intra-or extracellular mechanisms using endophytic cells. The adherence of NPs to pathogen surface cause multiple damage to cellular machinery, inhibit bacterial growth and biofilm formation, and promote cell death.

teichoic acids on their cell wall, while Gram-negative bacteria have a thin layer of peptidoglycan and an outer membrane composed of lipopolysaccharides (LPS), lipoproteins and phospholipids (Tortora et al., 2016). Additionally, Gram-negatives have intracellular efflux pumps in their cytoplasmic membrane that limit the permeability of drugs in their bacterial cell and reduce the action of antibiotics, making the search for new agents against these pathogens more difficult (Page and Heim, 2009; Dorotkiewicz-Jach et al., 2015; Haynes et al., 2017).

Hemashekhar et al. (2019) evaluated the production of Au NPs from the endophytic fungus *Alternaria* spp. isolated from *Rauvolfia tetraphylla* in Tumakuru, India. The synthesized NPs were tested against *E. coli*, *P. aeruginosa*, *K. pneumoniae* and *S. aureus* and were able to inhibit the growth of all strains. Furthermore, the antibiofilm potential of Au NPs, which decreased biofilm formation between *E. coli* and *P. aeruginosa*, was also reported. Biofilms can be defined as a community of microorganisms connected through extracellular products that can be found in different types of environments, including human infections (Reid, 1999). It is estimated that approximately 80% of human infections are linked to the formation of biofilms (Hemmati et al., 2021), which contribute to more complicated disease treatments. Antibiofilm assays are usually performed using biosynthesized Ag NPs against *A. baumannii* (Neethu et al., 2018, 2020), however, they can also be effective against *Enterococcus faecalis* (Halkai et al., 2018), *P. aeruginosa* (Ranjani et al., 2021), *Bacillus cereus* and *V. cholerae* (Chandankere et al., 2020). In this case, bacterial death is caused by the disruption of bacteria integrity. The same effect is observed in biofilms, showing that it does not constitute a barrier to the bactericidal effect of Ag NPs (Neethu et al., 2020).

The production of Cu NPs by a marine endophytic actinomycete isolated from tropical algae was evaluated by Rasool and Hemalatha (2017), who tested these nanoparticles against some clinical pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) *K. pneumoniae*, *P. mirabilis*, *E. coli* and *S. typhimurium*. In this work, two volumes were used to analyze the antimicrobial activity of NPs (50 and 100 μl). Even though both of them were able to inhibit all tested pathogens, including MRSA, greater bioactivity was achieved at the highest volume. Ganesan et al. (2020) used extracts of the endophytic *Periconium* sp. to synthesize ZnO NPs and tested them against *E. coli*, *S. aureus* and *C. albicans*. It was observed that all microorganisms had their growth inhibited by the NPs.

Chowdhury et al. (2016) used Ag NPs synthesized by tropical endophytic *Penicillum* sp. and *Alternaria* sp. and obtained increased antibiotic activity against *E. coli* when compared to *Bacillus subtilis*. In this case, it was suggested that *E. coli* was more susceptible to silver nanoparticles than *B. subtilis*. It is worth mentioning that microorganisms are sources of several secondary metabolites whose production may vary and that synthesized nanoparticles can have different sizes and morphologies, which may interfere with their action (Buzea et al., 2007).

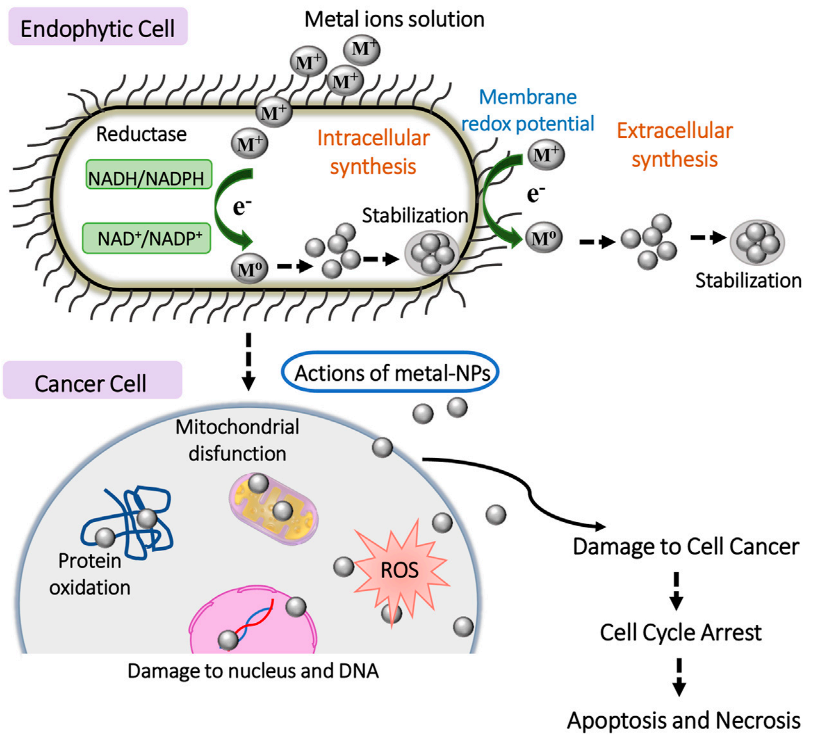

FIGURE 3 | Schematic representation of general anticancer mechanisms of metal-based NPs synthetized by intra-or extracellular mechanisms using endophytic cells. The interaction between the cancer cell surface and NPs and subsequent damage of organelles and biomolecules induces apoptosis and necrosis.

Manjunath et al. (2017) isolated the endophytic fungus *Cladosporium cladosporioides* from the seaweed *Sargassum wightii* found in the tropical ocean and evaluated the production and antimicrobial activity of Au NPs by the endophyte. The human pathogens used were *Bacillus subtilis* (MTCC 441), *Aspergillus niger* (MTCC 281), *E. coli* (MTCC 118), *S. aureus* (MTCC 7443) and *P. aeruginosa* (MTCC 424), all of which had their growth inhibited by the Ag NPs. Electron microscopy tests showed that the NPs acted on the cell walls of the microorganisms, breaking them down. Ranjani et al. (2021) synthesized Ag NPs using extracts of the tropical endophytic fungus *Lasiodiplodia theobromae* and tested them against *P. aeruginosa* ATCC (27853) and *P. aeruginosa,* which were clinically isolated from a patient. Both strains had their growth inhibited by the NPs and with significant activity when compared to positive controls, in addition to reducing the antibiofilm formed by the pathogens. Another important point in this study was the evaluation of the effects of endophytic nanoparticles on the production of pyocyanin, one of the toxins synthesized by *P. aeruginosa*. It was observed that Au NPs reduced by 69% the toxin produced by clinically isolated *P. aeruginosa*, indicating that silver ions possibly crossed the membrane and interfered with the pathogen metabolism.

Antioxidant Activity

The antioxidant activity of NPs has already been explored in several studies (Yang et al., 2019; Bedlovičová et al., 2020), as they protect cells from the damage of ROS. The most common assay used to evaluate the antioxidant activity of biogenic nanoparticles is the DPPH free radical scavenging. This method consists of the reduction of 2,2-diphenyl-1-picrylhydrazyl (DPPH) to methanol in the presence of antioxidants, leading to a color change from violet to yellow. Additionally, the values are calculated through control and sample absorbances (Garcia et al., 2012; Rahman et al., 2015). Another typical technique is the ferric reducing antioxidant power assay (FRAP), which also involves a reduction-dependent color change. The principle of this technique is the reduction caused by antioxidants of ferric 2,4,6-tripyridyl-s-triazine complex $[Fe^{3+}\text{-}(TPTZ)_2]^{3+}$ to ferrous complex $[Fe^{2+}\text{-}(TPTZ)_2]^{2+}$, which present an intense blue color that can be measured by an spectrophotometer at 593 nm (Gulcin, 2020). The DPPH method is frequently used in studies on the biosynthesis of Ag NPs obtained from *Cladosporium cladosporioides* extracted from *Sargassum wightii* (Manjunath and Joshi, 2019) and *Aspergillus niger* from *Simarouba glauca* (Hemashekhar et al., 2017); Au NPs obtained from *Alternaria* spp. isolated from *Rauvolfia tetraphylla* (Hemashekhar et al., 2019); and CuO, Fe_3O_4, NiO and ZnO NPs obtained from different endophytes from tropical environments (Ganesan et al., 2020; Mani et al., 2021; Mousa et al., 2021). Nirmala and Sridevi (Nirmala and Sridevi, 2021) isolated the endophytic bacterium *Pantoea anthophila* from *Waltheria indica* in order to synthesize Ag NPs and evaluate its antioxidant and antimicrobial ability. To determine the antioxidant potential, the authors used the DPPH, ABTS, H_2O_2 and superoxide (O_2^-) radical scavenging assay and

FRAP assay. The NPs showed an excellent antioxidant activity that can be applied in various oxidative stress-related degenerative diseases (Nirmala and Sridevi, 2021).

Antineoplastic Activity

NPs have been increasingly used in therapeutical applications due to their small size and consequent high capacity to interact with cells, proteins and genetic material. Studies have been suggested the electrostatic interaction between the cell surface and NPs and subsequent damage to membrane, ROS generation, protein oxidation, damage to electron transport chain in mitochondria, DNA and cell cycle, and finally induction of apoptosis and necrosis in different cancer cell lines by regulation of essential signaling pathways (El-Sonbaty, 2013; Munawer et al., 2020; Andleeb et al., 2021) (**Figure 3**).

Netala et al. (2016) determined the cytotoxicity effect of biosynthesized Ag NPs against B16F10, SKOV3, A549, PC3 and CHO cell lines. They also analyzed their apoptotic potential against human ovarian carcinoma cells and morphological modifications through microscopic analysis and staining assays. The endophytic fungus *Penicillium* sp. was isolated to produce biogenic Ag NPs, which were submitted to antiproliferative analysis against two types of carcinomas using MTT assay (HepG-2 and MCF-7) (Bagur et al., 2020a). Clarance et al. (2020) used MCF-7 and HeLa cell lines to analyze the anticancer activity of Au NPs synthesized from *Fusarium solani* isolated from *Chonemorpha fragrans*. These biosynthesized Au NPs presented effective cytotoxicity activity as well as apoptosis-inducing activity and cell cycle arrestment. Akther et al. (2019) synthesized biogenic Ag NPs from the endophytic fungus *Botryosphaeria rhodina* isolated from a tropical medicinal plant (*Catharanthus roseus*), which were found to present high anticancer potential determined through MTT assay, DNA fragmentation assay and evaluation of DNA damage by staining assays. The tests were carried out against human lung carcinoma cells (A549). Similarly, Munawer et al. (2020) produced a biosynthesized Au NPs and demonstrated their anticancer ability against MCF-7. The *in vitro* studies included MTT assay, staining assays, evaluation of DNA fragmentation and further comet assay, whereas the *in vivo* studies consisted of acute oral toxicity analysis, treatment exposure after tumor induction, histopathology study and level of apoptosis induction and DNA fragmentation. The authors observed that the *in vitro* anticancer activity was more relevant in Au NPs synthesized from *Cladosporium* sp. isolated from *Commiphora wightii* leaves. The authors concluded that the potential therapeutical application of NPs is, in fact, due to the facilitated interaction between the NPs and a range of molecules within the tumoral milieu.

CHALLENGES ASSOCIATED WITH METAL-BASED NPS SYNTHESIZED BY ENDOPHYTES

Non-toxic, biocompatible, cost-effective and eco-friendly NPs would be ideal for the safe use in medicine. The potential benefits of metal-based NPs synthesized using endophytes for healthcare applications have been well documented (Rahman et al., 2019; Eid et al., 2020; Rana et al., 2020). However, the knowledge about their precise action mechanisms, specificity and toxicity for humans, as well as non-target organisms/cells and the environment represents a great challenge for healthcare applications.

In general, metal-based NPs for usage in medicine can enter the body applying alternate routes, such as digestive, inhalation and skin penetration (De Matteis, 2017). Their physicochemical properties (e.g., surface-to-volume ratio, shape, charge, composition, concentration, solubilization) are important to mediate the interaction with the surface of the cells and penetration, biocompatibility, accumulation and toxicity (Ajdary et al., 2018). Optimization of the NPs synthesis parameters (e.g., yield, time, temperature, pH, metal ion solution and biomass concentration) also should be considered to obtain different NPs with features, stability and desired activities (Singh et al., 2014). Achieve ideal physicochemical properties and synthesis parameters of metallic NPs is still very challenging for development in large-scale of green nano-formulations, once it includes the integration of methods and process that should be reproducible and viable to reach the pharmaceutical market for a security and efficient administration in humans (Dikshit et al., 2021).

The selective cytotoxicity of metal-based NPs is other essential parameter to be evaluated for healthcare applications, because once into the cell these nanomaterials produce damage (e.g., ROS generation, damage to organelles, DNA and other biomolecules) that can lead to activation of cell death pathways (Ajdary et al., 2018; Attarilar et al., 2020). Thus, caution must be taken in NPs use involving living organisms, and both *in vitro* and *in vivo* assays are required.

Although studies using model organisms to assess the cytotoxicity and other effects of NPs are unarguably important and have been carried out (Sayadi et al., 2020; Tortella et al., 2020), to our knowledge the literature available so far to evaluate the NPs synthesized by endophytes from the tropics only addresses *in vitro* studies. Thus, it is other important challenge to be overcome for future safe and effective use of these green NPs in medicine.

There is a huge expectative surrounding the clinic applications of NPs. However, its regulation still involves gaps and is a worldwide challenge. This scenario reflects the lack of full knowledge of precise interaction of many nanomaterials with biological systems and its potential of accumulation and toxic effects that could be applied to organisms and environment (Foulkes et al., 2020). In addition, the differences in responses in *in vitro* assays and even between model animals and humans to nano drugs, the variations in their physicochemical properties which can lead to the alteration of the pharmacokinetics and pharmacodynamics assessment, the diverse administration routes, control of the manufacturing process, scale-up and reproducibility, among other factors, can contribute to difficult the development of a nano drug and its regulatory process (Barata-Silva et al., 2021).

The regulation of nanomaterials is necessary to provide security to pharmaceutical industry and patients. In general, the main international regulatory agencies, among them the European Medicines Agency (EMA) and Food and Drug Administration (FDA), making use of scientific and clinical knowledge in regulatory decisions. However, as there is not standardized regulatory guidance for nano drugs development and evaluation, these agencies seek provide guides and technical standards to pharmaceutical industry (Soares et al., 2018; Đorđević et al., 2021).

Despite the promising advances, the regulatory guidance remains unconsolidated among different regulatory agencies. Therefore, a strategy to evaluate the safety, efficacy, toxicity, compatibility, bioavailability and other parameters of nano drugs for its administration in humans is consider the previous studies and regulation used for the development of traditional medicines by pharmaceutical industry (Barata-Silva et al., 2021). These factors combined with an expensive, complex and time-consuming process of production constitute some of main obstacles for nano drugs clinical translation and their potential entry on the market (Choi and Frangioni, 2010; Hua et al., 2018). However, still there is a great perspective for green synthesis of NPs using endophytes and other microorganisms for future development of new therapeutic agents (Nafeh and Mazhar, 2021; Rehman et al., 2021).

CONCLUSION

In a scenario in which there is an increasing search for new drugs with greater efficiency, less toxicity and rare adverse effects, the green synthesis of NPs has become of great relevance for the health area. The synthesis of NPs using the biogenic approach is also cost-effective, eco-friendly, and easy to scale-up, overcoming the disadvantages of conventional chemical and physical methods. Considering that most studies on endophytic bacteria and fungi have been carried out using host plants from temperate environments, studies on endophytes from tropical environments offer a great opportunity to explore their potential as nano factories for the synthesis of NPs for application in medicine. In fact, metal-tolerant endophytic are effective tools for the synthesis of metal-based NPs. If appropriately exploited, the green synthesis of NPs using endophytes from the tropics can become a promise way for the numerous therapeutic applications of these materials in the imminent future. Despite it, there are still challenges to be addressed by the researchers to develop green metallic NPs for safe and effective biomedical applications for human and the environment.

AUTHOR CONTRIBUTIONS

AB conceived the idea of the manuscript. CS supervised the project. AB, SR, MG, MA, EL and CS wrote, revised and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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