NANOMICROBIOLOGY: EMERGING TRENDS IN MICROBIAL SYNTHESIS OF NANOMATERIALS AND THEIR APPLICATIONS

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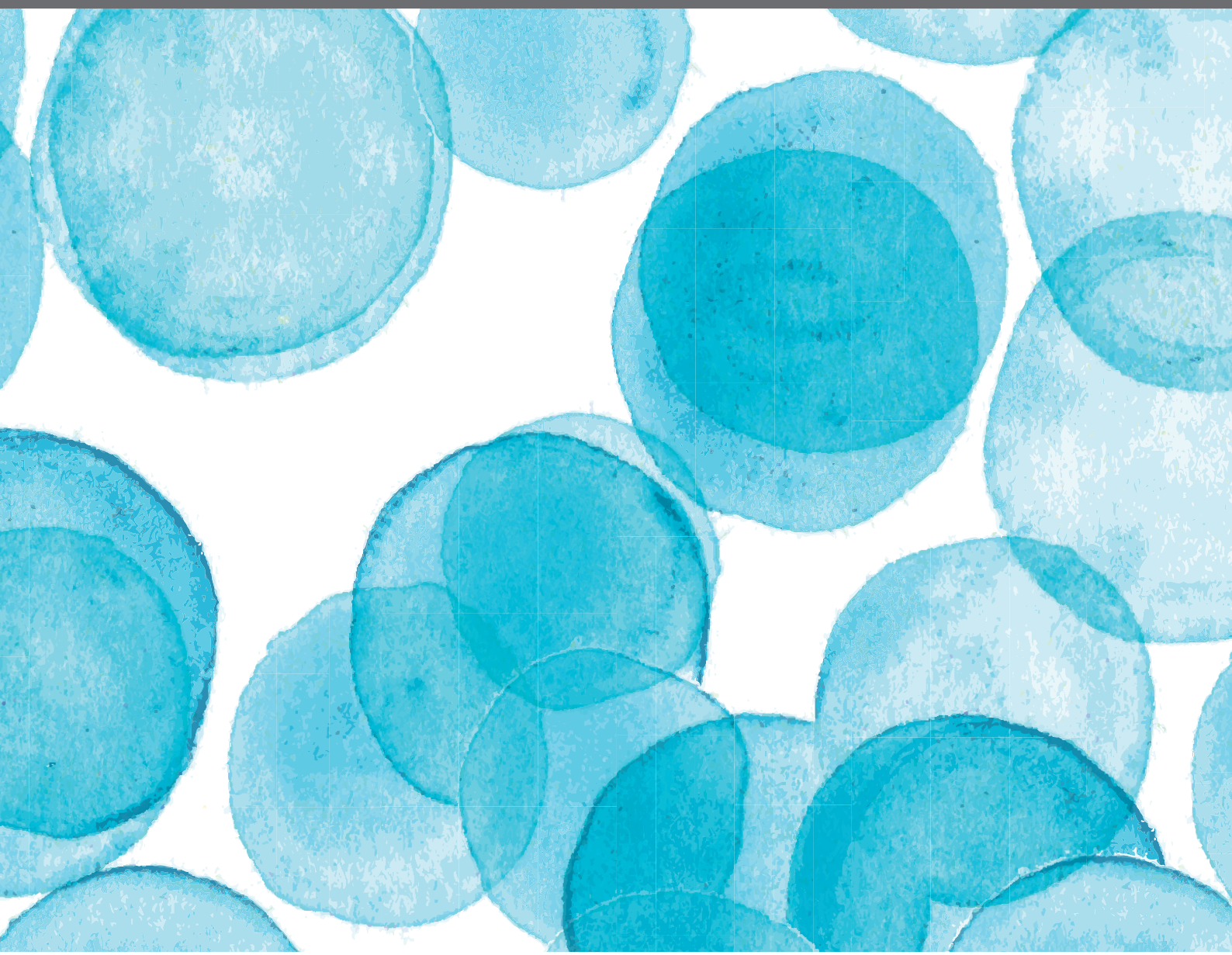

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NANOMICROBIOLOGY: EMERGING TRENDS IN MICROBIAL SYNTHESIS OF NANOMATERIALS AND THEIR APPLICATIONS

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Editorial: Nanomicrobiology: Emerging Trends in Microbial Synthesis of Nanomaterials and Their Applications

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Editorial on the Research Topic

Nanomicrobiology: Emerging Trends in Microbial Synthesis of Nanomaterials and Their Applications

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The Research Topic entitled "*Nanomicrobiology: Emerging Trends in Microbial Synthesis of Nanomaterials and their Applications*" was dedicated to reviews and original research articles toward innovative environmentally benign routes for synthesis of nanoparticles using microbial metabolites as catalysts and stabilizing agents. Microbial nanofactories involve the several microbial metabolites that play a key role in the reduction of metal ions to form nanoparticles with exotic shape, size, physicochemical, and optoelectronic properties. Microbial polysaccharides, peptides, and secondary metabolites help in stabilization of the biogenic nanoparticles. Metal ions can interact with the carboxylic, amino, and sulfhydryl functional groups which further help in their reduction to metal nanoparticles (Rana et al., 2020). Microbial nanofactory derived cationic polysaccharides such as chitosan and anionic polymer like alginate can adhere to the surface of the nanoparticles. Similarly, dextran and pullulan are neutral polymer that can also help in capping or stabilization of the biogenic nanoparticles. Further, chitosan can form complex with DNA/RNA and hence can be used in drug/gene delivery systems (Mizrahy and Peer, 2012). Among several amino acids are responsible for the shape evolution of the AuNPs (Doyen et al., 2016).

Enzyme catalyzed metabolic routes play a significant role in synthesis of nanoparticles in microbes. Several low molecular weight peptide, glutathione (GSH), and proteins such as metallothioneins and phytochelatins are responsible for synthesis of nanoparticles. Similarly, enzymes such as oxidoreductases, NADH-dependent nitrate reductases (NRs), and cysteine desulfhydrases facilitate the biosynthesis of metallic nanostructures within the microbial cells (Rana et al., 2020).

Binding of secondary structures of proteins with the microbially synthesized nanoparticle can enhance biodegradability, impart high stability, significantly reduce toxicity and antigenicity (Bunschoten et al., 2012; Elzoghby et al., 2012).

Chemical and physical routes of nanoparticle synthesis often use toxic chemicals and hazardous reaction conditions. Thus, the articles published under this Research Topic cover microbes as preferred resources for synthesizing nanoparticles with attractive features and diverse applications. Chemolithotrophy mediated generation of energy, cellular integration, and detoxification are considered as key mechanisms for microbial synthesis of nanoparticles.

The review of Mandeep and Shukla highlighted the promising role of nanobiotechnological

potential of microbes for bioremediation of industrial effluents. The ability of nanostructures associated with microbes such as *Pseudomonas aeruginosa*, *Lysinibacillus* sp., Actinomycetes are shown to remove toxic metals (chromium, copper, cobalt, nickel, zinc) along with hazardous dyes and antibiotics. This showcases the promising role of biogenic nanoparticles for ensuring clean water and safe environment toward the UN sustainability goals. Enzymes like reductases, metabolites such as peptides, aliphatic, and aromatic compounds help in metal ion reduction due to electron shuttle or capping of charge.

Biologically generated nanoparticles have immense applications which are highlighted in this special issue. Microbially synthesized silver, platinum, zinc oxide, copper oxide nanoparticles can have promising antibacterial, antifungal, and antiviral activity. Similarly, microbe assisted fabrication of gold nanoparticles may help to inhibit the cancer and reactive oxygen species mediated oxidative stress. Magnetic nanoparticles synthesized by bacteria can be used for targeting specific tissue for drug delivery using external magnetic field. Further, biogenic nanoparticles can be exploited for their uses in food packaging, agriculture, water treatment, and medicine.

Another significant application of the nanoparticles is detection, toxicity, and management of different types of mycotoxins. Nanotechnology driven solution to address the perils of mycotoxicology are not only rapid but also efficient, economical, and specific. This can help in disease management, disease forecasting, controlling disease resistance, detection of mycotoxin, and diagnosis of the toxicity (Rai and Abd-Elsalam, 2019).

Ranpariya et al. demonstrated the role the phytogenic bimetallic nanoparticles comprised of silver and platinum as novel antimicrobial agents. The nanohybrids with size ranging from 20 to 80 nm exhibited high antimicrobial activity against *P. aeruginosa* and *Staphylococcus aureus*. Interestingly, the biogenic nanoparticles showed promising antimicrobial synergy when used in combination with wide range of antibiotics. This can be a powerful strategy to control indiscriminate use of high dosage of antibiotics, which is one of the reasons for emerging multidrug resistance among bacterial pathogens.

In another review, Rattan et al. emphasized the role of lichens, such as *Parmotrema praesorediosum*, *Parmotrema clavuliferum*, *Parmelia perlata*, *Ramalina dumeticola* for producing nanoparticles with broad spectrum antimicrobial activity against both Gram-positive and Gram-negative bacterial pathogens. Further, they presented a comprehensive overview of potential mechanisms in understanding the mode of action of the biogenic nanoparticles against bacteria. Such mechanisms include damage to the cell wall and membranes for efficient penetration within the bacterial cell finally disintegrating the cellular components leading to impairment of the cellular metabolism leading to cell death. Another interesting article by Lahiri et al. elaborated on the biofilm inhibitory potential of the microbially synthesized nanoparticles. They explained that effective penetration of the nanoparticles through the biofilm matrix composed of exopolysaccharides is critical for affecting the quorum-sensing gene cascades that eventually hinders cell-to-cell communication resulting in inhibition of biofilm structure.

Dhanker et al. in their most elaborate and informative review have correlated the expression of metal resistance genes (MRG) in microbes with their ability to synthesize nanoparticles. An interdisciplinary approach using biotechnology, molecular biology, metabolic engineering, synthetic biology, and genetic engineering has led to the development of environmentally benign routes for synthesis of nanoparticles using diverse microbial communities that include bacteria (*Lactobacillus, Rhodopseudomonas capsulate, Rhodococcus* spp., *Shewanella algae*), fungi and yeasts (*Cryptococcus laurentii, Pichia pastoris, Rhodotorula glutinis*) protozoa (*Leishmania* sp., *Tetrahymena thermophila SB210, Tetrahymena pyriformis*), and archae (*Halobiforma* sp. N1, *Sulfolobus acidocaldarius, Sulfolobus tokadaii*). Similarly, Ghosh et al. presented a mechanistic approach for microbial synthesis of nanoparticles where nanotization was considered as a way to ameliorate stress in microbe. Moreover, they established the fact that biogenesis of nanoparticles is a biodefense mechanism in microbes that involves metal excretion/accumulation across membranes, enzymatic action, efflux pump systems, binding at peptides, and precipitation. Hence, exploration of the interaction between metal ions with proteins, DNA, organelles, membranes, and their subsequent cellular uptake would help in the deciphering the cellular, biochemical, and molecular mechanisms of nanotization of metals. *Delftia acidovorans* was reported to secrete a secondary metabolite and a non-ribosomal peptide "delftibactin" which reduced Au^{3+} into Au^{0} and adhered to them, thus reducing its toxicity.

Kapoor et al. indicated the advantages of microbial route for fabrication of nanoparticles. This easy, rapid, low cost, clean, non-toxic, environmentally benign, and sustainable approach for reducing metal into their corresponding nanoparticles followed by stabilization can serve as a pollution abatement tool. Hence, micro-organisms such as, bacteria, actinomycetes, filamentous fungi, yeast, algae, and viruses can led to bioremediation by eliminating toxic metals and promote environmental cleanup. On a similar note, Mukherjee et al. presented the promises of algae and blue green algae for synthesis of nanoparticles. They explored the possibilities of various applications of the phycogenic nanoparticles such as antioxidant, antibacterial, and antifungal activities. In another interesting study exploring the fungus *Beauveria bassiana* encapsulated in nanoparticles of biopolymers such as, soy oil, corn starch, cellulose, lignin, alginate, and humic acid showed better biocontrol properties against *Spodoptera cosmioides* with a mortality rate of up to 90% (Felizatti et al.). Hence such formulations can have promising applications for pest control that strongly rationalize the application of nanotechnology for agriculture.

Also, the enzyme hydrogenase was principally believed to be involved in reduction of U^{6+} and Se^{6+} by *Micrococcus lactyliticus* and *Clostridium pasteurianum*, respectively. Likewise, hydrogenases from sulfate reducing bacteria (SRB) is capable of reducing metals such as Tc^{7+} and Cr^{6+}. Riddin et al. (2006) proposed the mechanism of reduction of Pt(IV)

to Pt(0) in SRB (Sulfate Reducing Bacteria) in a two-step enzymatic process wherein Pt(IV) was first reduced to Pt(II), an intermediate ion by oxygen-sensitive cytoplasmic hydrogenase/reductant, which then diffused to periplasmic space where it gets reduced to Pt(0) by an oxygen-tolerant periplasmic hydrogenase enzyme.

The content of this Special Issue can be summarized as use of microbially synthesized diverse nanomaterials with attractive physicochemical properties for applications in medicine, food, agriculture, and environment. The mechanisms presented here help to understand the cellular and molecular events in microbes toward metal adsorption, intake, accumulation, nanoparticle synthesis and stabilization. In view of the background, this Special Issue will enable researchers and bioengineers to optimize the nanoscale processes of the microscale organisms for developing tailor made nanostructures with desired morphological features and applications.

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MINI REVIEW
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Microbial Nanotechnology for Bioremediation of Industrial Wastewater

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Pollutant removal from industrial effluents is a big challenge for industries. These pollutants pose a great risk to the environment. Nanotechnology can reduce the expenditure made by industries to mitigate these pollutants through the production of eco-friendly nanomaterials. Nanomaterials are gaining attention due to their enhanced physical, chemical, and mechanical properties. Using microorganisms in the production of nanoparticles provides an even greater boost to green biotechnology as an emerging field of nanotechnology for sustainable production and cost reduction. In this mini review, efforts are made to discuss the various aspects of industrial effluent bioremediation through microbial nanotechnology integration. The use of enzymes with nanotechnology has produced higher activity and reusability of enzymes. This mini review also provides an insight into the advantages of the use of nanotechnology as compared to conventional practices in these areas.

Keywords: microbial nanotechnology, nanoparticles, bioremediation, carbon nanotubes, industrial effluents, green technology

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INTRODUCTION

Water is essential for the continuation of life on earth, so the removal of pollution from water is just as crucial. Industrialization has put immense pressure on water use due to its use in production. Increased production leads to the generation of a huge amount of industrial effluents. The treatment of these industrial effluents is required in a strict and cost-effective way for the sustainable development of industries and the environment. Various electrochemical, advanced oxidation processes, and valorization techniques have been applied to reduce the toxicity of effluents from wastewater and for making its use sustainable (Gupta and Shukla, 2020). But these techniques are not cost effective for all industries. The development of nanotechnology and nanoscience has opened new avenues for the remediation of water pollutants. The nanotechnological pathways are more efficient than their conventional counterparts due to their smaller size, high surface area to volume ratio, and superior chemical properties (Baruah et al., 2019). Synthesis of green nanomaterials from microorganisms and extracts of other organisms have paved a path toward the eco-friendly remediation of pollutants. Iron nanoparticles are green nanoparticles which are used in remediation due to their redox potential while reacting with water, magnetic susceptibility, and non-toxic nature (Bolade et al., 2020).

Membrane-associated nanomaterials are also an effective method for effluent removal. Nanomaterials improve membrane permeability, stinking resistance, mechanical and

temperature strength, and present innovative functions for pollutant degradation. Nano-catalysts also play a major role in the enhancement of degradation reactions (Corsi et al., 2018). Apart from membranes and nano-catalysts, metal-organic frameworks (MOFs) are employed for the removal of heavy metals from wastewater. These MOFs are synthesized by the coordination of organic ligands with metal ion precursors. MOFs can be made more effective by the coordination of functional groups with metal as opposed to the organic ligand. This is because of the less steric hindrance of metals (Deshpande et al., 2020).

In this mini review, we will discuss the use of such nanoparticles for the removal of pollutants in industries. Also, the use of microorganisms and enzyme-assisted green nanotechnology to remove and valorize waste materials is discussed.

NANOTECHNOLOGY IN WASTEWATER TREATMENT

The smaller size of nanomaterials makes them suitable for use in the treatment of wastewater. They have specific chemical, physical, and biological properties that enhance their use in various applications. Different nanomaterials, such as carbon-based (Nanocomposites or Nanotubes), metals and their oxides-based nanomaterials, have been used for effluent removal from wastewater. Wastewater management practices consist of photocatalytic degradation, adsorption, filtration through nanoparticles, and observation of different contaminants and pollutants (Palit and Hussain, 2020). **Figure 1** shows the use of various nano-techniques applied for bioremediation of industrial effluents.

Nano-Adsorbents and Nanofiltration Membranes

Nanoparticles have been widely used as adsorbents to remove harmful contaminants from industrial wastewater. Nano-adsorbents can remove organic and inorganic pollutants (Kumari et al., 2019). They are categorized mainly as carbon-based, metal, and metal oxide-based nanoparticles. Carbon-based nanoparticles mainly include carbon nanotubes (CNTs), activated carbon, graphene, and, to some extent, fullerene (Kumari et al., 2019). Carbon nanotubes act as adsorbents for toxic chemicals from manufacturing industries or pharmaceutical wastewater. Kariim et al. (2020) prepared multi-walled carbon nanotubes (MWCNTs) from Fe-Ni supported on activated carbon using the chemical vapor deposition (CVD) technique. Adsorption characteristics of 2.5961 and 2.1363 were found for metronidazole and levofloxacin, respectively, which come in a range of good adsorption of 2–10. The enthalpy change showed that metronidazole was chemisorbed and levofloxacin was physisorbed. Similarly, MWCNTs are also able to adsorb metals from wastewater. The carboxylated MWCNTs were able to achieve increased adsorption of As(V) and Mn(VII) at 250 and 298 mg/g, respectively. The thermodynamic results showed metal removal takes place through chemisorptions (Egbosiuba et al., 2020).

Activated carbon modified nano-magnets have also been used for the removal of fluoride ions from wastewater. The nanocomposite was able to remove 97.4% fluoride ion from synthetic wastewater by sorption with an uptake of 454.54 mg/g (Takmil et al., 2020). Recently, microbial fuel cells and nanocatalysts are also used for the generation of bioelectricity. Electrodes coated with Iron(II)molybdate nanocomposites were able to enhance the efficiency of microbial fuel cells. Using this method, the maximum columbic efficiency of 21.3 $\pm$ 0.5%, the power density of 106 $\pm$ 3 $mW/m^{2,}$ and COD removal competence of 79.8 $\pm$ 1.5% was achieved (Mohamed et al., 2020). Superparamagnetic composite of iron oxide nanoparticles with activated carbon was found to be suitable to remove Cr(VI) from wastewater. The treated wastewater was suitable for discharge according to the environmental protection agency (EPA)'s recommendations. Magnetic separation and sorption were utilized for the removal of heavy metal (Nogueira et al., 2019). A graphene-based nanocollector was prepared by Hoseinian et al. (2020). They prepared an amino-functionalized graphene oxide nanocollector to remove nickel ions by using an ion floatation process. They were able to achieve around 100% removal of nickel ions from the wastewater using this economical, efficient, and stable nanocollector (Hoseinian et al., 2020).

Metal and metal oxide-based nano-adsorbents also play a vital role in the removal of pollutants from wastewater. Studies have revealed that coating magnetic nanoparticles with other supports led to an increase in their adsorption efficiency. Magnetic nanoparticles coated with silver showed 36.56% chemical oxygen demand (COD) removal from wastewater, which was 6.16% higher than the uncoated magnetic nanoparticles (Najafpoor et al., 2020). Similarly, a magnetic polymer of Co_3O_4@SiO_2 magnetic nanoparticles coated with nylon 6 was able to adsorb 666.67 mg/g Pb (II) from wastewater at 298K. The polymer was reusable up to six cycles with a little loss in its adsorption capacity of $<$ 30% (Mohammadi et al., 2020). Thus, these nanoparticles, alone as well as in conjugation with other favorable supports, can remove pollutants from industrial effluents. Their reusability and stability make them cost effective and environmentally friendly. Similarly, metal oxide-based nanomaterials work efficiently in effluent treatment. Nano-porous magnesium oxide obtained from the solid waste from the ductile iron industry was able to adsorb 1,000 $mg.g^{-1}$ of toxic dye from the wastewater. The adsorbent properties were enhanced by using a 1:1 mixture of sodium dodecyl sulfate (SDS) and polyoxyethyleneoctyl phenyl ether (TX100). This helped to achieve a suitable pore size of 16 nm (Pourrahim et al., 2020). Almomani et al. (2020) used magnetic nanoparticles, made from iron oxide, to remove heavy metals from wastewater. The iron oxide nanoparticles grafted on hyperbranched polyglycerol were able to remove nickel, copper, and aluminum from wastewater in 35 s. Moreover, the organic content and phosphorous do not affect the adsorption efficiency of nanoparticles, while nitrogen reduced the removal of heavy metals.

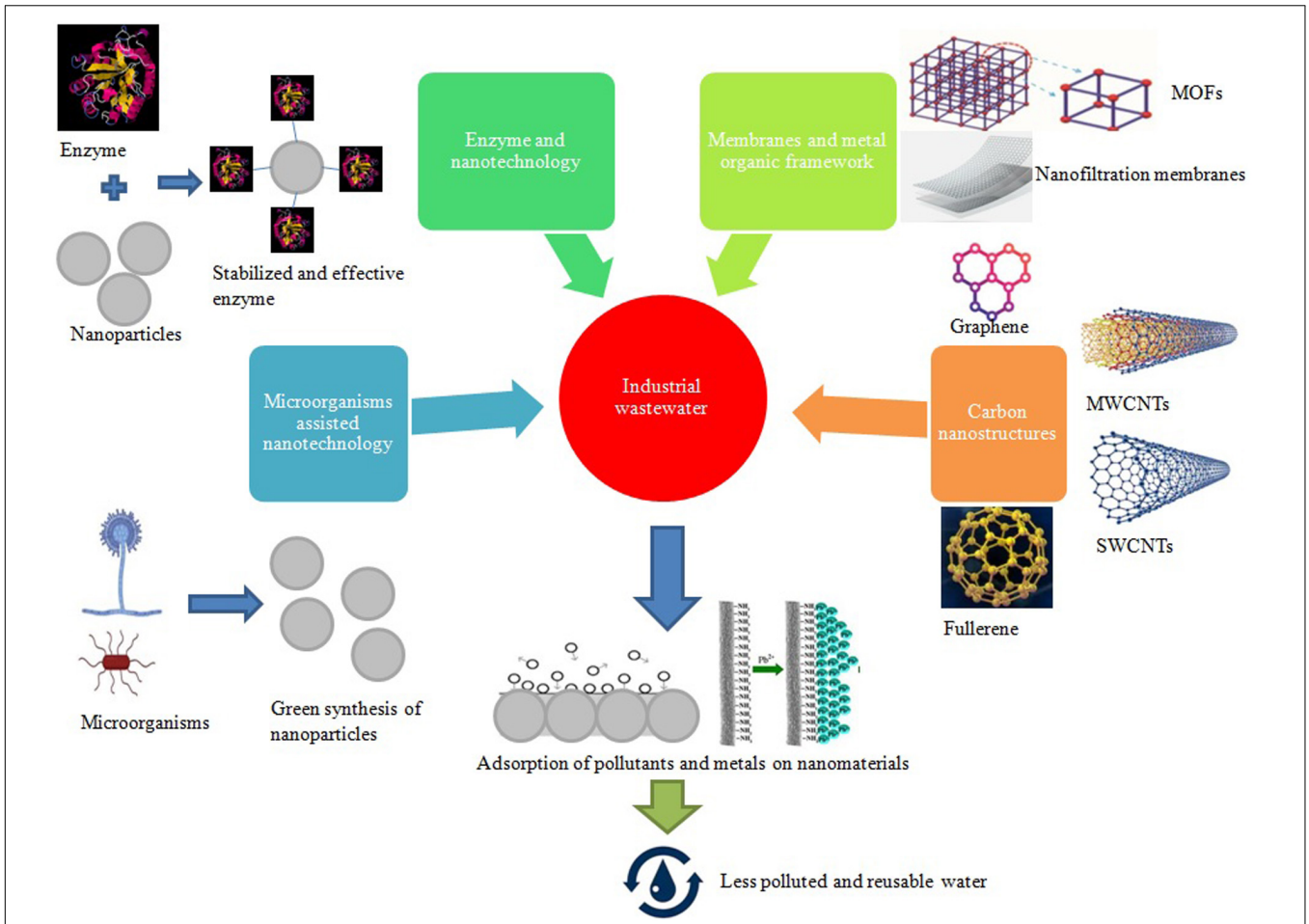

FIGURE 1 | Utilization of various nanotechnology approaches in combination with microbial assistance for wastewater bioremediation. MOFs: Metal organic frameworks; MWCNTs: multi-walled carbon nanotubes; SWCNTs: Single-walled carbon nanotubes.

Nanofiltration (NF) membranes also play a vital role in the recovery of nutrients from industrial effluents. NF90 gives the highest rejection (70%) of phosphorous from pulp and paper industry effluent. But the problem in the fouling of membrane arises due to the high phosphorous content (Leo et al., 2011). Shalaby et al. (2020) used gold nanoparticles woven with a polymer blend of the NF membrane to achieve a higher recovery of phosphorous from wastewater. They were able to achieve 96.1% rejection of trivalent phosphate with increased fouling resistance and hydrophobicity of the membrane (Shalaby et al., 2020). In another study, Ceramic supported graphene oxide (GO)/Attapulgite (ATP) composite membrane was prepared for the removal of heavy metals. The membrane was able to reject nearly 100% of metal ions of copper, nickel, lead, and cadmium. It is valuable to prepare such a membrane due to its increased flux speed, immense water stability, and outstanding rejection ability (Liu et al., 2019). There are some concerns related to the chemical nature of nanomaterials with commercialization. So, researchers have now utilized microorganisms for the generation of green nanostructures. These microorganisms-supported nanotechnological applications have led to a revolution in the field of green nanotechnology.

MICROORGANISMS ASSISTED NANOTECHNOLOGY

Biofabrication of nanomaterials and the simultaneous use of microbes makes the use of nanotechnology more sustainable and eco-friendly. The chemically produced nanoparticles may have some disadvantages in relation to the use of chemicals and self-agglomeration in aqueous solution. So, the green synthesis of nanoparticles from plant extract, fungal, and bacterial enzymes can be a potential solution. They act as reductive agents for the metal complex salt and generate metallic nanoparticles. These nanoparticles attain superior solidity in an aqueous environment because of co-precipitation or by adding proteinaceous and bioactive elements onto the outer face of the nanoparticles. Mahanty et al. (2020) biofabricated iron oxide nanoparticles from *Aspergillus tubingensis* (STSP 25) obtained from the rhizosphere of *Avicennia officinalis* in Sundarbans, India. The

synthesized nanoparticles were able to remove more than 90% of heavy metals [Pb (II), Ni (II), Cu (II), and Zn (II)] from wastewater with a regeneration capability of up to five cycles. The metal ions were chemically adsorbed on the surface of the nanoparticles in endothermic reactions (Mahanty et al., 2020). In another study, exopolysaccharides (EPS) obtained from *Chlorella vulgaris* were used to co-precipitate with iron oxide nanoparticles. The Fourier-transform infrared spectroscopy (FT-IR) analysis revealed the successful modification of nanoparticles by functional groups of EPS. Further, it was observed that the nanocomposite was able to remove 91% of PO_4^{3-} and 85% of NH_4^+ (Govarthanan et al., 2020).

The synthesis of nanoparticles with the help of microorganisms has provided a cost-effective and eco-friendly strategy. Copper nanoparticles were synthesized from *Escherichia* sp. SINT7, which is copper resistant. The biogenic nanoparticles were shown to degrade azo dye and textile effluent. At a lower concentration of 25 mg/L, the reduction of reactive black-5, congo red, direct blue-1, and malachite green was 83.61, 97.07, 88.42, and 90.55%, respectively, while this was reduced at 100 mg/L concentration to 76.84, 83.90, 62.32, and 31.08%, respectively. The industrial effluent was also treated and there was a reduction in the suspended solids and chloride and phosphate ions in treated samples. The performance of such biogenic nanoparticles gives a boost to cost-effective and sustainable production from industries (Noman et al., 2020). Cheng et al. (2019) prepared iron-sulfur nanoparticles without using extra sulfur. These nanoparticles were able to degrade Napthol Green B dye through the extracellular transfer of electrons. The use of *Pseudoalteromonas* sp. CF10-13 in the preparation of nanoparticles provides an eco-friendly method for biodegradation. The endogenous production of nanoparticles inhibited the production of harmful gases and metal complexes. The use of biogenic particles is a superior technology to apply in the remediation of industrial effluents. But besides the production of nanoparticles directly from the microorganisms, there are several other ways in which microorganisms can help in boosting nanotechnology. For instance, the microorganisms could provide catalytic enzymes which, along with nanoparticles, help in remediation of effluents. **Table 1** provides brief information about the use of nanotechnology in the bioremediation of wastewater. Microorganisms also help in the production of useful products from industrial waste, which will be discussed further.

NANOTECHNOLOGY AND ENZYME TECHNOLOGY

The combination of enzymes with nanotechnology is of the utmost importance to make nanomaterials less harmful to the environment. When enzyme molecules are present with nanomaterials, they minimize their cell interaction through steric hindrances and decrease in the surface energy (Dwevedi, 2019). Since enzymes are eco-friendly and provide a supplementary distinctiveness of catalysis, this makes nanomaterials more adaptable and efficient in bioremediation and green energy production. Conversely, immobilized enzymes on nanomaterials are highly stable due to resistance in unfolding, being less vulnerable to diffusional constraints, being able to be used in multiple cycles, and having enhanced kinetic characteristics (Ding et al., 2015). The large surface area of nanomaterials improves immobilization efficiency through elevated enzyme loading. Immobilized enzymes can be easily separated from the reaction blend, predominantly when the immobilizing matrix of magnetic nanomaterials is used. Multimeric enzymes such as oxidoreductases can also be stabilized by immobilizing them on nanomaterials. Enzyme immobilization on solid substrates leads to changes in structures, mainly increasing β-sheet structure and decreasing the α-helical structure; such modifications are not observed when nanomaterials are used for enzymes' immobilization (Secundo, 2013).

Studies have revealed the superiority of the combination of these two technologies. Darwesh et al. (2019) showed the effect of immobilized peroxidase enzyme on wastewater bioremediation. They found that glutaraldehyde-modified iron oxide magnetic nanoparticles provided pH and temperature stable immobilized enzymes. The immobilized peroxidase enzyme was able to remove green and red azo dyes individually in 4 h. It took 6 h to completely remove the dyes when a combination of both the dyes was used at the same time at lab-scale experiments (Darwesh et al., 2019). Laccase is widely used for the treatment of industrial effluents. Various composites of magnetic nanoparticles have been utilized to immobilize laccase for biodegradation. In a study, an Fe_3O_4 and chitosan composite was used as a magnetic carrier for laccase immobilization. The covalently bound laccase was stable and able to remove 2, 4-Dichloro-Phenol (2, 4-DCP) and 4-Choloro-Phenol (4-CP) effectively even up to 10 cycles. The breakdown of 4-CP and 2,4-DCP reached 75.5% and 91.4% after 12 h (Zhang et al., 2020). In another experiment, Li et al. (2020) used Fe_3O_4 core and chelated Cu^{2+} of carbon shell to immobilize laccase. These Fe_3O_4@C-Cu^{2+} nanoparticles possessed a simple immobilization method, high enzyme activities, and high loading capacity, reusability, and stabilities of the immobilized laccase. The immobilized laccase was able to degrade synthetic dyes, reactive blue 19, crystal violet, Procion red MX-5B, azophloxine, brilliant green, and malachite green to approximately 81, 79, 75, 88, 93, and 99 (%) respectively in the first cycle. After 10 continuous reuses, the degradation rates were 65, 71, 60, 78, 80, and 94 (%), respectively (Li et al., 2020). Similarly, immobilized lignin peroxidase on Fe_3O_4@SiO_2@polydopamine nanoparticles was able to reduce organic pollutants to a higher extent than the free enzyme. Immobilized lignin peroxidase dissipated 100% of dibutyl phthalate, phenol, tetracycline, and 5-chlorophenol. The removal of benzo(a)pyrene, phenanthrene, and fluoranthene was observed at 65, 79, and 73%, respectively (Guo et al., 2019). In another study, the recombinant cyanate hydratase was immobilized on iron-oxide-filled magnetic MWCNTs. The action of the immobilized enzyme on synthetic wastewater sample was able to remove Cu, Fe, Cr, and Pb by 29.63, 35.53, 39.31, and 34.48%, respectively. Also, the amount of cyanate was reduced by $\geq$ 84% (Ranjan et al., 2018, 2019). Thus, it is evident from such studies that enzyme technology, along with nanotechnology, provides a stable and efficient environment for the degradation of industrial effluents.

TABLE 1 | Bioremediation of different industrial effluents using advanced nanotechnology processes.

Sr. no.	Nanotechnology applied	Modification	Associated microorganisms	Removal or adsorption capacity	Advantage/Mechanism	Specific feature	References
1.	NiO and MgO nanoparticles	Silica-embedded	–	Maximum uptake of 41.36, 13.76, 7.23 (ions per nm^2) for Cr^{3+}, Cu^{2+}, and Zn^{2+}	Spontaneous, endothermic, and physical adsorption of Cu^{2+} and Cr^{3+} and exothermic and chemical of Zn^{2+}	Regeneration and reusability proved sustainability	Abuhatab et al., 2020
2.	Electrospunnanofibrous webs	Bacterial encapsulation	*Pseudomonas aeruginosa*	55–70% removal of methylene blueat different concentrations	Biological removal of dye	Genetic engineering or more potent bacterial cell could prove more promising	Sarioglu et al., 2017
3.	Mesoporous organosilica nanoparticles (MONs)	Incorporation of ferrocene	–	High removal rate of dyes by MONs-50% and metals by MONs-25%	More surface area and πnjugation derived from non-covalent interaction facilitated by ferrocene	Novel organic-inorganic hybrid nanomaterial	Yang et al., 2019
4.	Cobalt and cobalt oxide nanoparticles	Microwave and reductive chemical heating	–	43.6 and 39.4% degradation of murexide dye by Cobalt and cobalt oxide nanoparticles, respectively	Irradiation and large surface area	Greener, easy, and faster to make, cost-effective and photocatalytic degradation efficiency	Adekunle et al., 2020
5.	Electrospuncyclodextrinfibers	Bacterial encapsulation	*Lysinibacillus* sp. NOSK	Removal efficiency of Ni(II) = 70 ± 0.2%, Cr(VI) = 58 ± 1.4% and Reactive black 5 = 82 ± 0.8	Bacterial bioremediation	Cyclodextrin provides extra carbon source for growth of bacteria	San Keskin et al., 2018
6.	Zirconia nanoparticles	Synthesis from microbial cell free culture supernatant	*Pseudomonas aeruginosa*	Tetracycline adsorption of 526.32 mg/g	Chemisorptions and strong electrostatic interaction among zwitter ions	Green synthesis of nanoparticles and sustainable bioremediation	Debnath et al., 2020
7.	Enzyme immobilized nanoparticles	Laccase immobilization	*P. ostreatus*	Degradation of bisphenol-A = 90% and carbamazepine = 10%	Oxidation by immobilized laccase	Reusable enzyme and cost-effective	Ji et al., 2017
8.	Graphene oxide and carbon nanotubes	Nano-sized nickel metal organic framework	–	Methylene blue adsorption of 222 mg/g	Hydrophobic and/or π-π interactions, high surface area, occurrence of the pores among the MOFs and the platforms and diverse morphological features of mixed nanocomposites	Superior interaction of nanocomposite	Ahsan et al., 2020
9.	Silica nanoparticles	Synthesized from actinomycetes	Actinomycetes	80% decolorization of industrial effluent	Photocatalytic degradation	Cost-effective and sustainable	Mohanraj et al., 2020

VALORIZATION OF WASTE USING MICROORGANISMS AND NANOTECHNOLOGY

Conversion of waste materials to useful products using technology is attracting the attention of researchers around the world. Using this approach, we can reduce waste and generate useful products simultaneously. This practice is widely used in industries for the production of adsorbents, clinker, biogas, biohydrogen, biomolecules, and many more products (Gupta and Shukla, 2020). Nanotechnology has helped in the enhancement of the production rate for efficient conversion of waste into resources. Kumar and colleagues in 2019 described the use of nanoparticles to enhance dark fermentation reactions for increased biohydrogen production (Kumar et al., 2019). Supplementation of fermentative bacteria with nanoparticles has opened new avenues for biohydrogen generation from wastewater. Elreedy et al. (2019) utilized mixed culture bacteria along with single, dual, and multiple nanoparticles to generate biohydrogen. They found that biohydrogen production was the maximum (14% more than the single nanoparticles use) when multiple nanoparticles were used. The different nanoparticles increased hydrogenase and dehydrogenase activity, leading to increased biohydrogen production (Elreedy et al., 2019). Similarly, the addition of both nickel oxide and hematite nanoparticles gave 1.2–4.5-fold increased biohydrogen production than the sole nanoparticles. The highest hydrogen yield of 8.83 mmol/g COD was obtained in the combination of nanoparticles. This increase is owed to the increased activity of hydrogenase and ferredoxin oxidoreductase enzymes (Gadhe et al., 2015). Thus, nanotechnology can also be used to generate green energy for sustainable industrial growth and eco-friendly production.

FUTURE PERSPECTIVE AND CHALLENGES

Nanotechnology has generated interest among researchers due to its beneficial effects, such as its large provided surface area, the capability of multiple uses, its stability at harsh conditions, easy and efficient manipulations in materials, increased interaction, and many more. The integration of microorganisms and enzymes with nanotechnology has provided a greener approach toward the management of industrial effluents (Dixit et al., 2020; Zhang et al., 2020). The risk associated with chemically synthesized nanoparticles can be minimized through the use of microorganisms. The residues left are either biocompatible or can be easily separated using simple filtration/precipitation techniques. The bigger challenge lies in the commercialization of these nanotechnological aspects. Only 1% of these nanotechnological aspects are commercialized so far (Dwevedi, 2019). So, the application of these easy and efficient microorganisms-assisted nanotechnology techniques on a large scale will be a stepping stone for industries. This requires continuous support and confirmation from researchers and government funding to nurture the power of nanotechnology for sustainable and cost-effective production in industries.

CONCLUSION

Nanotechnology integrated with microorganisms has provided a green approach toward the bioremediation of industrial effluents. The discussed generation of nanomaterials with the help of microorganisms provides superior avenues for cost-effective and sustainable effluent remediation. Enzyme nanotechnology has provided stable, highly active, and long-lasting enzymes that offer multiple uses. This technique should be pursued further at a commercial scale to exploit its full potential. Further work can be accelerated toward the generation of biohydrogen and bioelectricity from industrial waste, as discussed in waste valorization. This will boost the industrial economy through green energy generation.

AUTHOR CONTRIBUTIONS

Mandeep wrote the first draft of the manuscript. The final draft was read and edited by PS. Both authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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frontiers in Microbiology

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Antimicrobial Synergy of Silver-Platinum Nanohybrids With Antibiotics

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Various bacterial pathogens are responsible for nosocomial infections resulting in critical pathophysiological conditions, mortality, and morbidity. Most of the bacterial infections are associated with biofilm formation, which is resistant to the available antimicrobial drugs. As a result, novel bactericidal agents need to be fabricated, which can effectively combat the biofilm-associated bacterial infections. Herein, for the first time we report the antimicrobial and antibiofilm properties of silver-platinum nanohybrids (AgPtNHs), silver nanoparticles (AgNPs), and platinum nanoparticles (PtNPs) against *Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus*. The AgPtNHs were synthesized by a green route using *Dioscorea bulbifera* tuber extract at 100°C for 5 h. The AgPtNHs ranged in size from 20 to 80 nm, with an average of ∼59 nm. AgNPs, PtNPs, and AgPtNHs showed a zeta potential of −14.46, −1.09, and −11.39 mV, respectively. High antimicrobial activity was observed against *P. aeruginosa* and *S. aureus* and AgPtNHs exhibited potent antimicrobial synergy in combination with antibiotics such as streptomycin, rifampicin, chloramphenicol, novobiocin, and ampicillin up to variable degrees. Interestingly, AgPtNHs could inhibit bacterial biofilm formation significantly. Hence, co-administration of AgPtNHs and antibiotics may serve as a powerful strategy to treat bacterial infections.

Keywords: biogenic synthesis, silver-platinum nanohybrids, characterization, antimicrobial synergy, antibiofilm

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INTRODUCTION

Recently, nanobiotechnology has got wide attention due to multiple applications in electronics, catalysis, textiles, food industries, and therapeutics. Among various nanoparticles, silver nanoparticles (AgNPs) are used in biosensing, biomedical imaging, and drug delivery (Tarannum et al., 2019). Further, AgNPs are also used for designing antimicrobial surfaces, cosmetics, paints, and plastics. Because of their bactericidal and fungicidal properties, AgNPs are also used for the fabrication of wound dressings (Wilkinson et al., 2011; Robkhob et al., 2020). Similarly, platinum nanoparticles (PtNPs) are also known for their excellent antimicrobial activity and ability to inhibit the growth of unwanted and harmful bacteria (Tahir et al., 2017).

Bacterial biofilms are complex communities where the bacterial cells adhere to the surface and each other being embedded in a protective exopolymeric substance. Induction of multidrug resistance in the biofilm associated cells is attributed to the enhanced cell-to-cell communication (quorum sensing), and notable exchange of genetic material by horizontal gene transfer. It is speculated that the bacteria growing in biofilms are often thousands of times more tolerant to antimicrobial treatment than their planktonic counterparts (Verderosa et al., 2019). Thus, it is very difficult to treat nosocomial infections associated with pathogenic biofilm on implants, catheters, stents, heart valves, and pacemakers that pose a potential health risk (Francolini and Donelli, 2010). Clinically significant pathogens like *Pseudomonas aeruginosa* (Gellatly and Hancock, 2013), *Escherichia coli* (Beloin et al., 2008), and *Staphylococcus aureus* (Gordon and Lowy, 2008) have exhibited biofilm formation as predominant virulence mechanism. Biofilm associated diseases like vaginitis (Machado et al., 2016), otitis (Post, 2001), gingivitis (Vieira Colombo et al., 2016), conjunctivitis (Behlau and Gilmore, 2008), urethritis (Delcaru et al., 2016), and colitis (von Rosenvinge et al., 2013) are challenging to treat. *P. aeruginosa* biofilms in the lungs of cystic fibrosis patients is a serious medical concern which is known to cause acute and chronic lung infections resulting in significant morbidity and mortality (Wagner and Iglewski, 2008). Chronic wound infections caused by *P. aeruginosa* and *S. aureus* (Omar et al., 2017), are reported to be responsible for over 80% of the 100,000 limb amputations carried out every year in diabetic patients (James et al., 2008). Similarly, Moazzezy et al. (2020) reported *E. coli* to be highly heterogeneous group of biofilm forming uropathogens causing urinary tract infection. The bacterial biofilms is challenging to treat with available antibiotics because the drug cannot penetrate in the deeper parts of the biofilm. Moreover, several other mechanisms existing in the biofilm forming bacteria like enzymatic degradation of the antibiotics, efflux pumps and alteration of the target site by mutations render the drug ineffective. Hence, there is a need to develop novel antimicrobial agents that can significantly inhibit biofilm formation. Nanoparticles with efficient bactericidal effects and antibiofilm effects have come up as potential alternative and complementary agents against biofilm associated microbial infections.

Various physical and chemical methods for synthesizing nanoparticles, have been reported, which include chemical reduction, template method, electrochemical, or ultrasonic-assisted reduction, photoinduced or photocatalytic reduction, microwave-assisted synthesis, irradiation reduction, microemulsion, and biochemical reduction. These methods involve toxic chemicals and hazardous conditions and significantly compromise the biocompatibility of the resulting nanoparticles for the biomedical applications (Jamkhande et al., 2019). Hence, there is an urgent need to develop green and environmentally benign route which will help to synthesize nanoparticles with broad-spectrum therapeutic potential.

Several bacteria, fungi, algae, and medicinal plants have been employed to synthesize nanoparticles of gold, silver, copper, platinum, and palladium, etc. (Iravani, 2011). Synthesis of nanoparticles using microbes requires a tedious culturing process, optimization, aseptic condition, and downstream processing. Whereas, medicinal plants with numerous phytochemical diversities such as terpenes, polyphenols, flavonoids, alkaloids, coumarin, and saponins have served as attractive materials for both reduction of metal ions to their corresponding nanoparticles and their stabilization (Singh et al., 2016). Several plants such as *Ocimum tenuiflorum, Solanum trilobatum, Syzygium cumini, Centella asiatica*, *Citrus sinensis, Carica papaya, Citrus limon, Desmodium triflorum, and Euphorbia hirta,* etc. have been reported to synthesize metal nanoparticles with exotic shapes and sizes with significant biomedical applications (Iravani, 2011; Logeswari et al., 2015). Microbial interaction with the biogenic nanoscale metals is noteworthy as significant bactericidal efficacy is exhibited by metal nanoparticles in compared to their bulk counterparts. Further, synergistic antimicrobial action with multimetal complexes can be of utmost significance as they might induce higher oxidative stress thereby efficiently killing the microbes.

Herein, we report the enhanced bactericidal activity of the biogenic silver-platinum bimetallic nanohybrids (AgPtNHs) which was synthesized using *Dioscorea bulbifera* tuber extract. Further, the antimicrobial synergy with various antibiotics was also evaluated. The effect of the AgPtNHs on the biofilm-forming activity of the microbes was also examined and the morphological alterations of the bacterial biofilms on treatment with the AgPtNHs have been studied by using scanning electron microscopic and atomic force microscopic analyses.

MATERIALS AND METHODS

Synthesis of AgPtNHs

Dioscorea bulbifera tuber extract (DBTE) was prepared as per our earlier protocol (Ghosh et al., 2012). The synthesis of AgPtNHs was achieved by the addition of 5 mL of DBTE in 95 mL of an aqueous solution containing 10^{-3} M of both $H_2PtCl_6.6H_2O$ and $AgNO_3$ followed by incubation at 100°C for 5 h. Synthesis of only AgNPs was achieved by reacting 5 mL of freshly prepared DBTE with 95 mL of 10^{-3} M aqueous $AgNO_3$ solution at 40°C for 5 h. PtNPs were synthesized due to the reduction of $PtCl_6^{2-}$ ions on the addition of 5 mL of DBTE to 95 mL of 10^{-3} M aqueous solution of $H_2PtCl_6.6H_2O$ which was incubated at 100°C for 5 h. The synthesis of the material was confirmed by recording the UV-visible spectrum of the solution after 5 h on a spectrophotometer (SpectraMax M5, Molecular Devices Corporation, Sunnyvale, CA, United States) operating at a resolution of 1 nm.

Characterization

After completing the synthesis, preliminary confirmations of biosynthesized AgNPs, PtNPs, and AgPtNHs were carried out through visual observation of color change. The bioreduced nanoparticles were further characterized by using several standard techniques, such as UV-vis spectroscopy, transmission electron microscopy (TEM), energy dispersive spectra (EDS), and dynamic light scattering (DLS).

Fourier-Transform Infrared Spectrophotometry

Fourier-Transform Infrared Spectrophotometry (FTIR) was employed to understand the underlying mechanism of the synthesis of the nanoparticles using DBTE. In this method, DBTE after and before synthesis of AgPtNHs was subjected to Fourier-transform infrared (FTIR, IRAffinity-1, Shimadzu Corporation, Tokyo, Japan) spectroscopy measurement using the potassium bromide (KBr) pellet technique in diffuse reflection mode at a resolution of 4 cm^{-1}. An infrared source of wavelength lying within 500–4,000 cm^{-1} was used.

Antimicrobial Activity

The effects of AgNPs, PtNPs, and AgPtNHs were evaluated against *E. coli*, *P. aeruginosa,* and *S. aureus,* on Mueller Hinton Agar (MHA) plates using well diffusion assay. Overnight grown cultures of the test organisms (OD_{600} = 0.05) were spread plated on MHA plates and wells were made on the surface with the help of a sterile cork borer of diameter 5 mm. 30 μL of nanoparticles suspension (100 μg/mL) was added in the wells, followed by incubation at 37°C for 18 h, the zone of inhibition was measured (Karmakar et al., 2020).

Antimicrobial Synergy

Agar well diffusion technique was used for evaluating the antimicrobial synergy of the nanoparticles in the presence of antibiotics. The antibiotics used were streptomycin, rifampicin, chloramphenicol, novobiocin, and ampicillin. The test pathogens were inoculated in sterile Mueller Hinton Broth (MHB) and incubated in a shaker for overnight at 37°C. 100 μL of the overnight grown culture was spread uniformly on MHA plates. Wells were made on the agar surface with the help of a sterile cork borer with 6 mm diameter and 30 μL of the nanoparticles, a mixture of nanoparticles and antibiotics, and only antibiotics (100 μg/mL) were added. The plates were then incubated at 37°C for 18 h and observed for a zone of inhibition around the well. The diameters of the zone of inhibition were measured and the degree of antimicrobial synergy was evaluated. All experiments were performed in triplicates.

Antibiofilm Activity

The biofilm inhibitory potential of the nanoparticles was evaluated by using the gentian violet staining method (Ghosh et al., 2015a). In brief, 5 μL of overnight grown bacterial cultures (OD adjusted to 0.05 at 600 nm) of *E. coli*, *P. aeruginosa*, and *S. aureus* were incubated in the absence and in the presence of nanoparticles (at a final concentration of 10 μg/well) supplemented in MHB in 96 well microtitre plates. The microtitre plates were then incubated for 48 h at 37°C under static conditions. Thereafter, nonadherent cells were removed by aspiration and the wells with biofilm were washed thrice with sterile phosphate-buffered saline (PBS). Then 0.1% gentian violet was added in each well and incubated for 10 min at room temperature, and the excess stain was removed by repeated washing with water. The wells were then dried in a laminar air flow and 200 μL of absolute ethanol was added to each well and further shaken at 1,020 rpm for 10 s. The value of absorbance at 570 nm was recorded in a multiplate reader. Biofilm indices were calculated after normalizing with appropriate controls. All biofilm assays were repeated thrice.

Biofilm Visualization by Atomic Force Microscopy

The biofilm inhibition was carried out on sterile grease-free glass coverslips as per the procedure mentioned above with a final volume of 2 mL in six well plates. The biofilms of *E. coli, P. aeruginosa*, and *S. aureus* were allowed to form on glass slides incubated for 48 h in the presence of nanoparticles (at a final concentration of 10 μg/mL). The glass coverslips were washed with sterile PBS followed by fixation with glutaraldehyde and sequential dehydration with ethyl alcohol and then dried in a vacuum. Morphological features of the untreated and treated biofilms on the glass surfaces were analyzed by using atomic force microscopic (AFM) imaging. Atomic force measurements were carried out using a multimode scanning probe microscope (Model number MMAFMLN, VeecoMetrology, Santa Barbara, CA, United States) equipped with a Nanoscope VI controller. AFM micrographs were generated in tapping mode with the probe, tap190 (Budget SensorsAFM tips, Bulgaria).

Statistical Analysis

All values were expressed as mean ± standard error of mean (S.E.M.), n = 3, and statistical significance was determined by analysis of variance (ANOVA two factor) with $^{*}P < 0.05$.

RESULTS

Synthesis and Characterization of AgPtNHs

The syntheses of AgNPs, PtNPs, and AgPtNHs were completed in 5 h. The digital images of the samples taken after the synthesis is presented in the inset of **Figure 1** and the appearance of brown color confirmed the formation of the nanoparticles. AgNPs with light brown color were well dispersed in the colloidal solution while PtNPs settled down like a loose mass with blackish-brown color. On the other hand, AgPtNHs formed relatively well dispersed dark colloidal suspension. The UV-Vis. absorption spectra of the samples were measured, as shown in **Figure 1**. The AgNPs exhibited a prominent peak at 420 nm in the UV-visible spectra while PtNPs and AgPtNHs showed a formless peak.

Further, the morphologies of the synthesized AgPtNHs, were studied using TEM. As evident from the TEM micrographs in **Figure 2**, very small independent nanoparticles of AgPtNHs with a size of ∼2 nm assembled to form nanoclusters with the overall size distribution from 20 to 80 nm with the average being 59 nm. The AgPtNHs were stable and discrete and formed spherical shaped nanoclusters. Also, the nanoparticles were seen to be stabilized by the biological components of the plant extract.

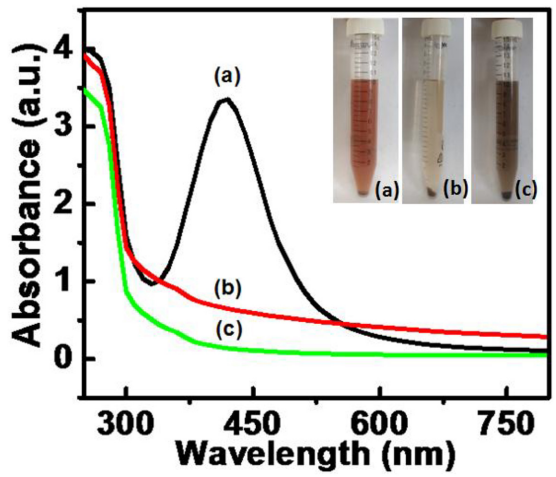

FIGURE 1 | UV-visible spectra for nanoparticles synthesized by DBTE with insets representing the visible color change on complete synthesis after 5 h. **(a)** AgNPs; **(b)** AgPtNHs; and **(c)** PtNPs.

The inset of **Figure 2d** shows that the granular AgPtNHs are assembling to form larger nanoclusters.

The EDS measurement was done to find out the existence of Ag and Pt in the AgPtNHs, as shown in **Figure 3**. The spectra confirmed the presence of both elemental Ag and Pt in the AgPtNHs. Further, zeta potential measurements were carried out to evaluate the stability of the nanoparticles because the antimicrobial activity is a function of stability of nanoparticle. Zeta values, as shown in the inset of **Figure 3**, further rationalize the observation where AgNPs showed more negative value (−14.46 mV) followed by AgPtNHs (−11.39 mV) and PtNPs (−1.09 mV).

FTIR Analysis

Fourier-transform infrared (FTIR) spectra of DBTE before and after synthesis of AgNPs, PtNPs, and AgPtNHs is presented in **Figure 4**. Some typical peaks observed at 3,400, 2,100, 1,636, and 1,215 cm^{-1} were present in all the spectra. Those peaks might have originated from the different vibration bands (i.e., flavonoids, terpenoids, phenanthrenes, amino acids, proteins, and glycosides) present within the DBTE. The strong peak at ∼3,400 cm^{-1} is a characteristic of the hydroxyl group in polyphenolic compounds present in the plant extract. The other bands at 2,100, 1,636, and 1,212 cm^{-1} are assigned to C≡C stretching of the alkyne, C=C groups, or conjugated C–C with a benzene ring phenolic groups (Ghosh et al., 2011, 2012). There were some additional peaks which appeared after synthesis that included 1,738 and 1,368 cm^{-1}, which might have originated from C=O carbonyl stretch from carboxylic acid and C–N stretching vibration of aromatic ring, respectively (Song et al., 2010; Ghosh et al., 2012). The sharpness of the peak representing the O–H bond was reduced in the FTIR spectrum of DBTE after synthesis of the nanoparticles, which confirmed the bioreduction efficiency of DBTE. Therefore, the FTIR results demonstrated that the DBTE could perform dual functions of reduction and stabilization of AgNPs, PtNPs, and AgPtNHs. The overall observation confirmed that the presence of complex compounds in DBTE could bind to nanoparticles either through free amine groups via electrostatic attraction of

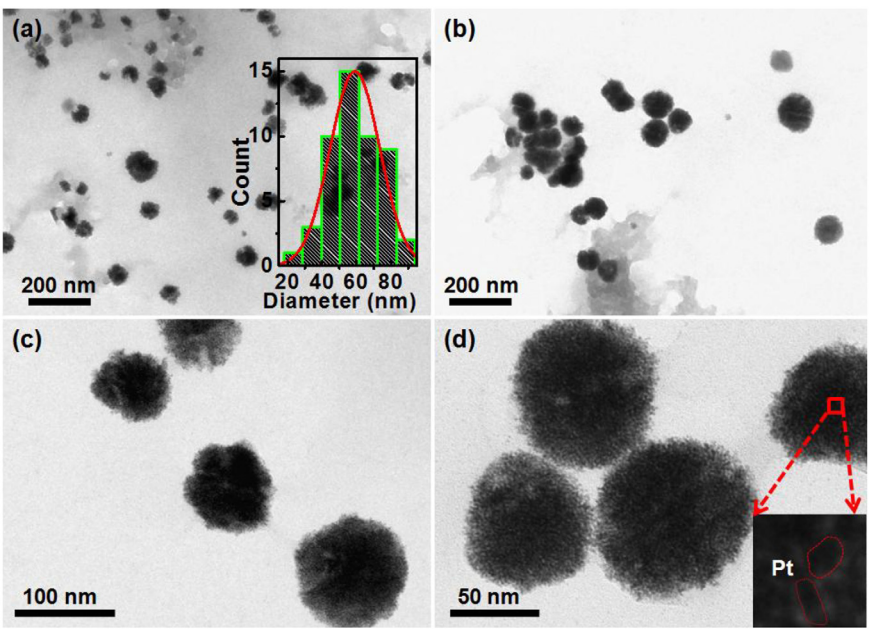

FIGURE 2 | TEM image of AgPtNHs synthesized by DBTE. **(a)** Images showing nanoclusters and inset showing histogram of particle size distribution; **(b)** Discrete AgPtNHs; **(c)** Magnified images of AgPtNHs; and **(d)** Granular nanoparticles assembling to form larger nanoclusters.

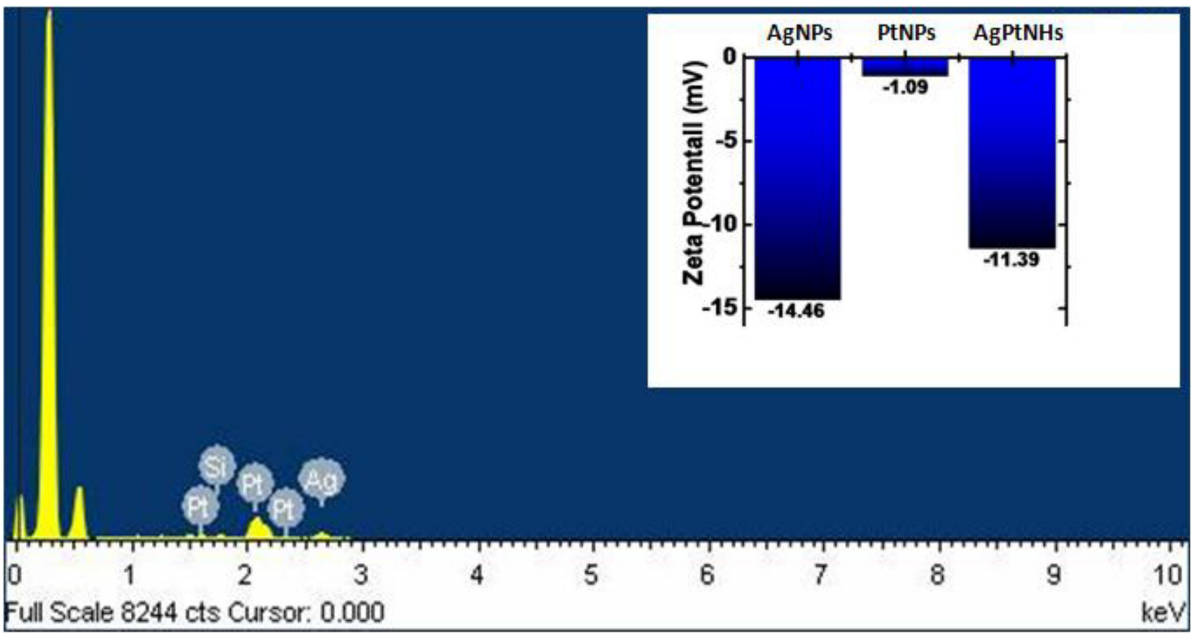

FIGURE 3 | Representative spot EDS profile confirming the presence of Ag and Pt in the AgPtNHs synthesized by DBTE. Inset represents zeta potential values of the biogenic nanoparticles.

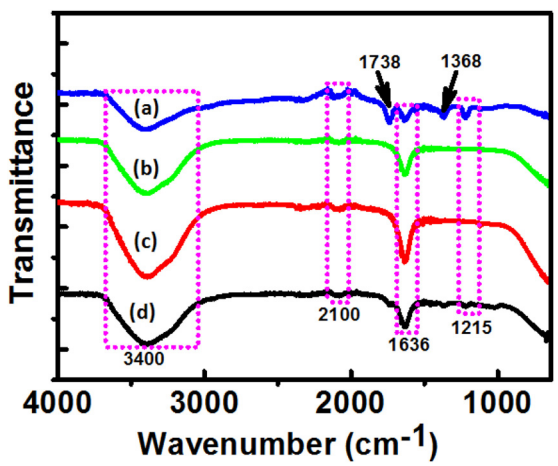

FIGURE 4 | Fourier transform infrared absorption spectra of dried *Dioscorea bulbifera* tuber extract (DBTE) after complete bioreduction of **(a)** AgNPs; **(b)** PtNPs; **(c)** AgPtNHs; and **(d)** before bioreduction.

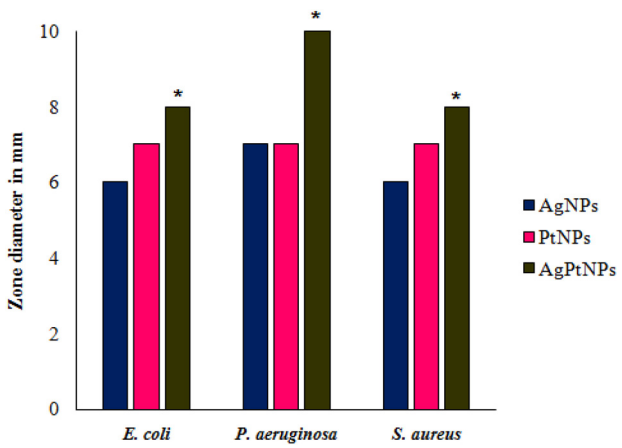

FIGURE 5 | Antimicrobial activity of biogenic nanoparticles synthesized by DBTE. *$P < 0.05$; the mean difference in the antimicrobial activity is significant in AgPtNHs at the 0.05 level by two factor ANOVA.

negatively charged carboxylate groups and therefore stabilized the phytogenic nanoparticles (Vigneshwaran et al., 2007).

Antimicrobial Activity

The biogenic nanoparticles showed variable degrees of antimicrobial activity against the three test pathogens as represented in **Figure 5** in terms of zone of inhibition. AgNPs showed the highest activity against *P. aeruginosa* while identical inhibition was observed against *E. coli,* and *S. aureus*. PtNPs also showed a similar level of inhibition against all bacteria. Interestingly, the inhibitory activity of AgPtNHs was more against all test pathogens in compared to individual AgNPs or PtNPs. AgPtNHs showed the highest inhibitory zone of 10 mm against *P. aeruginosa* followed by *E. coli* (8 mm), and *S. aureus* (8 mm).

Antimicrobial Synergy

To study the antimicrobial synergy, the activities of the individual antibiotics and in combination with the nanoparticles were

evaluated and the fold increase in terms of the zone of inhibition was determined. **Table 1** shows the synergistic antimicrobial activity of various antibiotics in combination with AgNPs. The activity of streptomycin was found to get enhanced 8 folds against *E. coli* when supplemented with AgNPs. Rifampicin exhibited the highest antimicrobial synergy in combination with AgNPs against *S. aureus* (15 folds) followed by intermediate activity against *E. coli* (4.64 folds). Chloramphenicol showed intermediate synergy in presence of AgNPs against both *E. coli* and *S. aureus*. Novobiocin exhibited high synergistic inhibition of *S. aureus* (15 folds) followed by *E. coli*. Interestingly, ampicillin exhibited selectivity toward Gram-positive bacteria during synergistic activity in combination with AgNPs. *S. aureus* was inhibited up to 12.14 folds by the combination of ampicillin and AgNPs.

The antimicrobial synergy of antibiotics in combination with PtNPs showed the selectivity and variability as observed in **Table 2**. Supplementation with PtNPs significantly enhanced the inhibitory activity of streptomycin selectively against Gram-negative bacteria *E. coli* (10.76 folds) and *P. aeruginosa* (8 folds). In the presence of PtNPs antimicrobial activity of rifampicin was increased notably against Gram-positive bacteria, *S. aureus* (16.02 folds). Likewise, increment in the activity of chloramphenicol in the presence of PtNPs was notable against Gram-positive pathogen *S. aureus* (8 folds). The highest antimicrobial synergy of novobiocin with PtNPs was seen against *S. aureus* (16.36 folds), followed by *E. coli* (10.76 folds) while intermediate and low synergy was evident against *P. aeruginosa*. As observed in **Table 3**, antimicrobial activity of rifampicin and novobiocin increased significantly up to 15 and 13.69 folds, respectively, in combination with AgPtNHs against *S. aureus*.

Antibiofilm Activity

The effect of phytogenic nanoparticles on the biofilm-forming ability of the bacterial pathogens was checked which revealed variability in the degree of inhibition as represented in **Figure 6**. A high degree of biofilm inhibition was observed on treatment with AgPtNHs while treatment with PtNPs showed a comparatively lower biofilm inhibition. *E. coli* and *P. aeruginosa* showed almost identical levels of biofilm inhibition up to 75.16 ± 1.02% and 76.18 ± 1.42% in the presence of AgPtNHs. Pure AgNPs, on the other hand showed 39.11 ± 0.52% and 40.49 ± 2.47% biofilm inhibition against *E. coli* and *P. aeruginosa*, respectively, while inhibition by PtNPs was lower. Inhibition of *S. aureus* biofilm with AgPtNHs (56.7 ± 1.81%) was more as compared to both AgNPs (52.72 ± 0.84%) and PtNPs (49.98 ± 1.23%).

Atomic Force Microscopy

The effect of biogenic nanoparticles on bacterial biofilms was confirmed by using AFM image analysis. **Figure 7** depicts the prominent differences between the architecture of untreated and treated bacterial biofilms on the glass surface. Untreated biofilms showed a packed lawn of bacteria without exposing the glass surface underneath. Treatment with AgNPs compromised the cell adhering capability in *E. coli* resulting in the interrupted biofilm while AgPtNHs showed high biofilm elimination. Untreated *P. aeruginosa* biofilms showed uniformly embedded bacterial cells in the polymeric matrix that was significantly reduced on treatment with AgNPs, PtNPs, and AgPtNHs.

Atomic force microscopy observations could be strongly correlated with the antibiofilm activity where overall biofilm inhibition against *S. aureus* was lower in compared to other bacteria. In spite of treatment with AgNPs and PtNPs, the glass surfaces were covered with *S. aureus* biofilms which reduced substantially on treatment with AgPtNHs.

DISCUSSION

Biological synthesis of nanoparticles is widely preferred due to non-involvement of harmful toxic chemicals which otherwise make the resulting nanoparticles non-biocompatible and hazardous during therapeutic application. Biogenic routes of synthesis are rapid, efficient and economical as the metabolites in the extracts generally act as potential reducing as well as stabilizing agents (Garg et al., 2020).

Dioscorea bulbifera, commonly known as air potato, has numerous medical applications owing to its inherent antibacterial, antifungal, plasmid curing, antidiabetic, antioxidant, and anticancer properties. Traditionally it has been used as a purgative, aphrodisiac, anthelmintic, rejuvenating tonic, diuretic, deflatulent and has been widely used for ameliorating scrofula, hemorrhoids, hematological disorders, diabetic disorders, polyurea, worm infestations, and skin diseases (Ghosh et al., 2015b; Kundu et al., 2020).

The therapeutic activity of the medicinal plants is attributed to the rich phytochemistry. Several medicinal plants such as *Callicarpa maingayi, Cissus quadrangularis, Tribulus terrestris, Centella asiatica, Murraya koenigii, Alternanthera sessilis, Artemisia nilagirica,* and many more are thus explored for the synthesis of various metal nanoparticles (Kuppusamy et al., 2016). Notably, the earlier reports are mostly on AgNPs, AuNPs, CuNPs, and other individual nanoparticles. A very few reports exist on bi-metallic nanoparticles synthesized by using medicinal plants. Zhan et al. (2011) reported Au–Pd bimetallic nanoparticles with approximately 7 nm size and well defined spherical shape using *Cacumen platycladi* leaf extract in an aqueous environment. The synthesis was complete after incubation for 2 h under vigorous stirring. Likewise, Salunke et al. (2014) showed that aqueous root extract of *P. zeylanica* (PZRE) rendered hexagonal blunt-ended AgAuNPs with a size of 90 nm apart from spherical AgNPs (60 nm), and triangular AuNPs (20–30). The resulting nanoparticles showed efficient antimicrobial and antibiofilm activities. In another study, ginger rhizome powder (GP) was used to fabricate three different bimetallic catalysts namely copper-silver (Cu-Ag/GP), copper-nickel (Cu-Ni/GP), and nickel-silver (Ni-Ag/GP) complexes employing a robust adsorption method for applications in catalytic dye degradation (Ismail et al., 2018). However, this is the first report on the synthesis of AgPtNHs using *D. bulbifera* as reducing and stabilizing agent which was completed within 5 h time at 100°C temperature. This can be

TABLE 1 | Zone of inhibition (mm) of different antibiotics against bacteria in the absence and in the presence of AgNPs (30 μ g/well).

Antibiotics	*E. coli**			*P. aeruginosa**			*S. aureus**		
	A	B	C	A	B	C	A	B	C
Streptomycin	7	21	8.00	8	14	2.06	9	15	1.78
Rifampicin	8	19	4.64	8	9	0.27	8	32	15.00
Chloramphenicol	8	22	6.56	7	9	0.65	7	20	7.16
Novobiocin	7	22	8.88	8	10	0.56	6	24	15.00
Ampicillin	8	14	2.06	7	8	0.31	8	29	12.14

All the experiments were performed in triplicate, and standard deviations were negligible. Fold increases (C) for different antibiotics against three bacterial pathogens were calculated as $(B^2 - A^2)/A^2$*, where A, B are the inhibition zones in mm for antibiotic only and antibiotic in combination with AgNPs, respectively. In the absence of bacterial growth inhibition zones, the well diameters (6 mm) were used to calculate the fold increase (C). *P < 0.05; the mean difference in the synergy is significant among the bacteria at the 0.05 level by two factor ANOVA.*

TABLE 2 | Zone of inhibition (mm) of different antibiotics against bacteria in the absence and in the presence of PtNPs (30 μ g/well).

Antibiotics	*E. coli**			*P. aeruginosa**			*S. aureus**		
	A	B	C	A	B	C	A	B	C
Streptomycin	7	24	10.76	8	24	8.00	9	13	1.09
Rifampicin	8	13	1.64	8	12	1.25	8	33	16.02
Chloramphenicol	8	19	4.64	7	11	1.47	7	21	8.00
Novobiocin	7	24	10.76	8	14	2.06	6	25	16.36
Ampicillin	8	18	4.06	7	12	1.94	8	15	2.52

All the experiments were performed in triplicate, and standard deviations were negligible. Fold increases (C) for different antibiotics against three bacterial pathogens were calculated as $(B^2 - A^2)/A^2$*, where A, B are the inhibition zones in mm for antibiotic only and antibiotic in combination with PtNPs, respectively. In the absence of bacterial growth inhibition zones, the well diameters (6 mm) were used to calculate the fold increase (C). *P < 0.05; the mean difference in the synergy is significant among the bacteria at the 0.05 level by two factor ANOVA.*

TABLE 3 | Zone of inhibition (mm) of different antibiotics against bacteria in the absence and in the presence of AgPtNHs (30 μ g/well).

Antibiotics	*E. coli**			*P. aeruginosa**			*S. aureus**		
	A	B	C	A	B	C	A	B	C
Streptomycin	7	20	7.16	8	12	1.25	9	15	1.78
Rifampicin	8	15	2.52	8	11	0.89	8	32	15.00
Chloramphenicol	8	20	5.25	7	10	1.04	7	18	5.61
Novobiocin	7	23	9.80	8	8	0.00	6	23	13.69
Ampicillin	8	13	1.64	7	13	2.45	8	15	2.52

All the experiments were performed in triplicate, and standard deviations were negligible. Fold increases (C) for different antibiotics against three bacterial pathogens were calculated as $(B^2 - A^2)/A^2$*, where A, B are the inhibition zones in mm for antibiotic only and antibiotic in combination with AgPtNHs, respectively. In the absence of bacterial growth inhibition zones, the well diameters (6 mm) were used to calculate the fold increase (C). *P < 0.05; the mean difference in the synergy is significant among the bacteria at the 0.05 level by two factor ANOVA.*

the potential green route for the rational fabrication of various other nanohybrids.

The appearance of blackish brown color at 100°C indicated that the completion of both AgPtNHs and PtNPs syntheses were facilitated at higher temperature. A similar observation was reported during synthesis of PtNPs using *Diopyros kaki* leaf extract where increasing the reaction temperature up to 95°C resulted in almost 100% conversion of platinum ions to PtNPs (Song et al., 2010). Evidences of featureless peak were also found during synthesis of platinum palladium bimetallic nanoparticles (PtPdNPs) in our earlier report (Ghosh et al., 2015c). Unlike core–shell bimetallic nanoparticles, which display two bands in UV-visible absorption spectra, the featureless spectra AgPtNHs indicated the possible formation of a nanoalloy (Elemike et al., 2019; Unuofin et al., 2020).

The exotic shape of the AgPtNHs was found to be very small nanospheres aggregated as spherical nanoclusters with an average size of ∼59 nm. Similarly, nanoassembly was also noticed during nanoparticles synthesis by *P. zeylanica* root extract where very small spherical nanoparticles flocked together to form larger nanostructures (Salunke et al., 2014). The magnitude of zeta potential is the key determinant of potential stability of colloid and the particles with zeta potential values more positive than +30 mV or more negative than −30 mV are considered to be most stable. In contrast, the colloids are least stable at the isoelectric point, where the zeta potential is zero. Herein, the

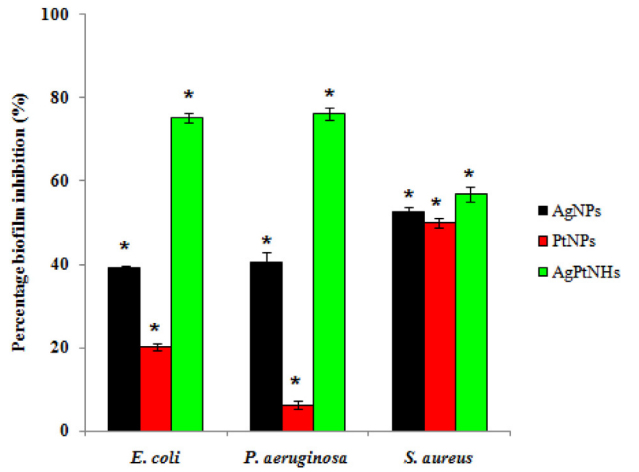

FIGURE 6 | Biofilm inhibition by biogenic nanoparticles synthesized by DBTE. The data is indicated as the mean ± SEM; (n = 3).*P < 0.05; the mean difference in the antibiofilm activity is significant among the nanoparticles at the 0.05 level by two factor ANOVA.

ζ values varied in the range from −1 to −15 mV, depending upon the type of nanoparticles. The AgPtNHs were more stable compared to PtNPs due to more negative zeta potential. Thus they remained more suspended as a stable colloidal solution unlike the PtNPs that settled faster. AgNPs formed uniform homogenous suspension with maximum negative zeta potential. Saeb et al. (2014) reported synthesis AgNPs using *Escherichia hermannii* (SHE), *Citrobacter sedlakii* (S11P), and *Pseudomonas putida* (S5) where the therapeutic potential was found to be a function of particle size and stability as reflected by its zeta potential. AgNPs synthesized using SHE exhibited the best antimicrobial activity due to small size (4–12 nm) and stability (-22 mV).

The phytochemistry of medicinal plants plays a very significant role in reducing the metal ions to the corresponding nanoparticles as well as their stabilization. The FTIR analysis showed that synthesis and capping of AgPtNHs might be brought about by the functional groups specific to flavonoids, terpenoids, phenanthrenes, amino acids, proteins, and glycosides present within the DBTE extract. Carbonyl stretch from carboxylic acid and C–N stretching vibration of aromatic compounds were also observed. These observation can be strongly rationalized due to the compounds such as diosgenin, dioscorin, dioscin, phytosterols, alkaloids, tannin, starch, ascorbic acid, beta-carotene, protein, riboflavin, and many others which are reported in *D. bulbifera* tubers or rhizomes (Ghosh et al., 2015a; Kundu et al., 2020).

Further, the effect of the phytogenic nanoparticles was checked for their antimicrobial properties. Increased cases of multidrug resistance among bacteria have become a global threat. Microbial pathogens generally gain antibiotic resistance by the following mechanisms: (a) alteration of microbial drug target proteins, (b) enzymatic degradation or inactivation of drug, (c) decreased membrane permeability, and (d) increased efflux of the drug (Kumar et al., 2013). Hence, it is very critical to explore the complementary and alternative therapies to treat microbial infections. Metal nanoparticles with the combined effect of two or more metals can be useful in designing new antimicrobial agents. In this study, the bioreduced AgPtNHs exhibited superior antimicrobial activity against the test pathogenic bacteria which was comparatively higher than the AgNPs and PtNPs, individually.

Although there are well established mechanisms on antimicrobial properties of AgNPs, the rationale behind its synergy with the PtNPs are still unknown. AgNPs can depolarize cell membrane in bacteria which alters membrane permeability resulting in leakage of the bacterial metabolites leading to cell death (Vazquez-Muñoz et al., 2019). Likewise incorporation of Pt containing hybrid nanoparticles like Ti-PtNPs resulted in enhanced killing of the bacterial pathogens due to leakage of cytosolic proteins (Selvi et al., 2020). Moreover, combination of Ag and Pt components might have multiple mode of action and cascade of events behind synergistic enhancement of antimicrobial efficiency. The hybrid metal nanoparticles may bind more strongly with the bacterial cell wall and generate oxidative stress due to production of free radical that can include superoxide (O^{2-}) and hydroxide radicals (OH). Additionally, binding of the nanoparticles with the thiol group of essential enzymes can lead to their inactivation through the respiratory burst activity. Furthermore, the AgPtNHs might have interacted with nucleic acid (DNA) and interrupted the cellular transport system. The possible mechanism involved in the antibacterial activity of AgPtNHs is displayed in **Figure 8**. Another reason behind antimicrobial synergy of AgPtNHs in combination with antibiotics might be due to the disruption of the cell wall and membrane, that increase the permeability and facilitates easy entry of antibiotics within the bacterial cells. Hence, the bacteria became more susceptible to the antibiotics in the presence of the AgPtNHs. Also, the simultaneous action of antibiotics and AgPtNHs will make it difficult for pathogenic bacteria to develop resistance. Hence, this combinational therapy can be further developed as novel formulations to treat nosocomial infections.

Raghupathi et al. (2011) reported that antimicrobial activity of the nanoparticles is size dependent. The smaller nanoparticles of size 12 nm showed more potent antimicrobial activity against *S. aureus* compared to the larger particles (100 nm). Hence, the AgPtNHs with the size distribution between 20 and 80 nm probably showed an intermediate activity. However, this hurdle can be overcome by synthesizing similar nanohybrids employing solvothermal synthesis using optimal precursors. Raghupathi et al. (2011) used solvothermal synthesis for fabricating ZnO NPs with size between 2 and 25 nm which were otherwise 100 nm.

In another study, Singh et al. (2018) also reported that small particles interact more easily with the cell surface and are internalized into the cytoplasm due to less spatial hindrance. The greater surface area of smaller nanoparticles can more effectively interact with the cellular components of the bacteria after entry within the cytoplasm. AgNPs can release Ag^{+} ions via oxidation resulting in enhanced generation of reactive oxidative species that damages the cellular components and eventually results in cell death. Hence, fabricating AgPtNHs in future with smaller

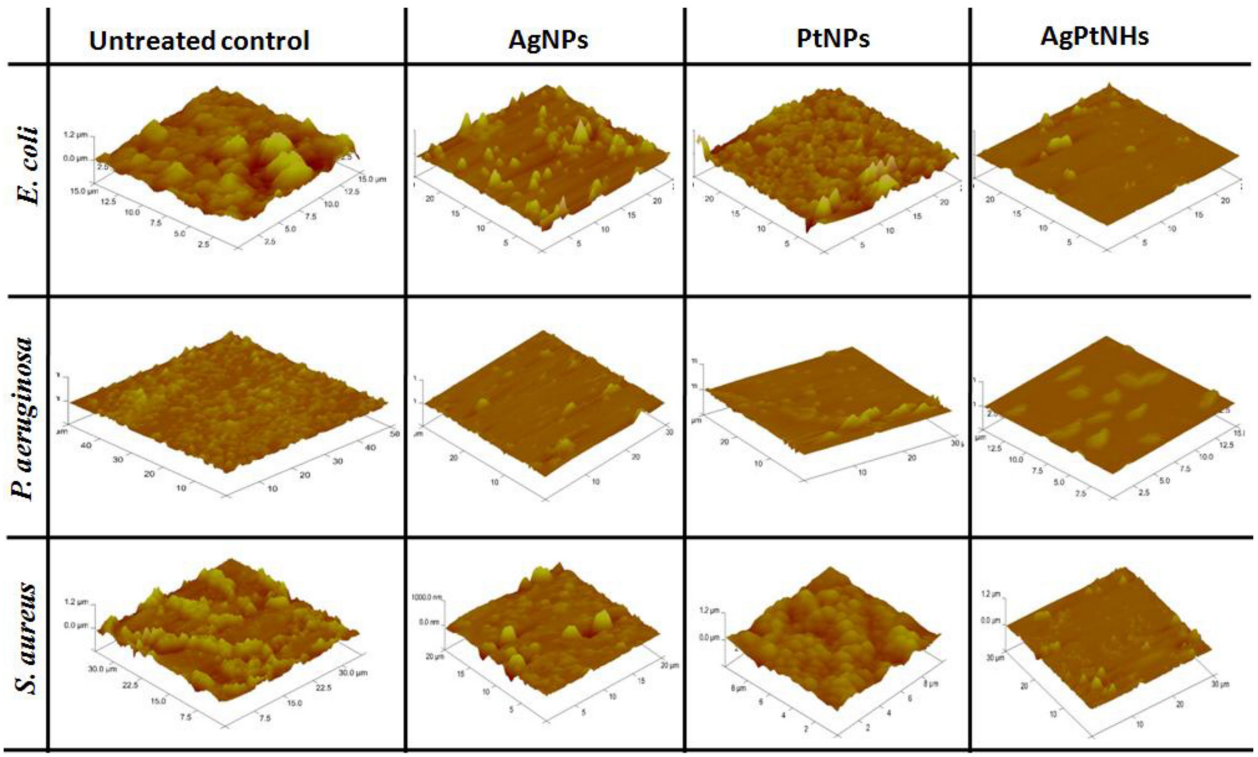

FIGURE 7 | Atomic force microscopic images of untreated and treated biofilms.

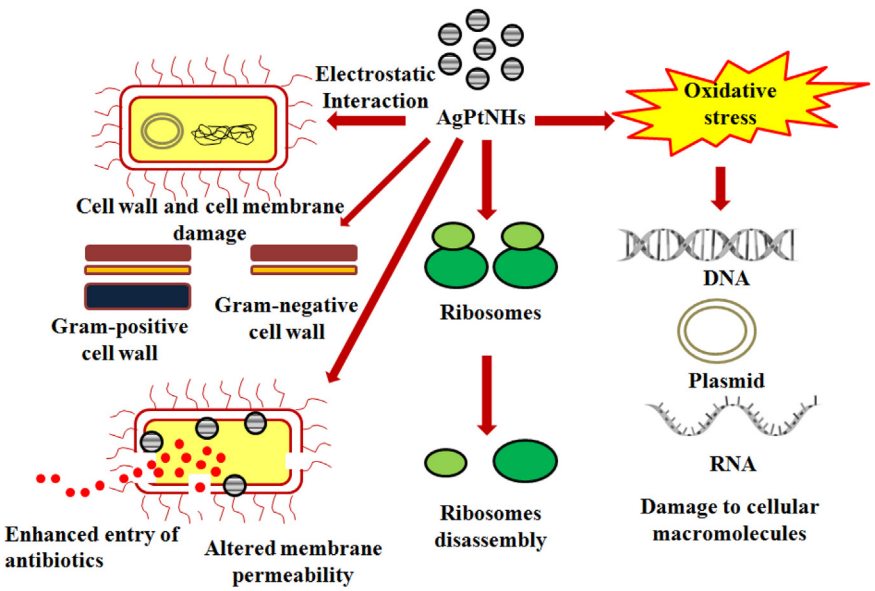

FIGURE 8 | Possible mechanism of antimicrobial synergy of AgPtNHs in combination with antibiotics.

size will be an additional contributing factor to their enhanced antibacterial effect.

Pathogenic bacteria are highly responsible for nosocomial (hospital-borne) infections, which mainly occur due to biofilm formation on indwelling medical devices and implants such as heart valves, pacemakers, vascular grafts, catheters, prosthetic joints, intrauterine devices, sutures, and contact lenses (Ghosh et al., 2020). Several biofilm driven infections include dental caries and root canal infections, bacterial vaginosis, cardiovascular disease, diabetic foot infections, and urinary

tract infections along with prostatitis (Malik et al., 2013; Lanter et al., 2014; Delcaru et al., 2016; Jung et al., 2017; Walsh, 2020). Interestingly, AgPtNHs exhibited higher antibiofilm activity in compared to individual AgNPs or PtNPs. Previous reports showed that Ag nanocomposites (64 μg/mL) and cationic amphiphile could penetrate into the biofilms and eradicated them. Furthermore, AgNPs were reported to penetrate and disperse into biofilm matrixes and then deliver Ag^+ flux to the bacterial wall to eradicate the biofilms (Dai et al., 2017). Our results showed that Gram-positive bacteria were more resistant to AgPtNHs compared to Gram-negative bacteria. This variation in antimicrobial and antibiofilm activity between Gram-positive and Gram-negative microorganisms is often attributed to difference in the cell wall structures (Al-Sharqi et al., 2019). *S. aureus* may have a stronger defense system against AgPtNHs due to the presence of a thicker cell wall that prevents the action of the AgPtNHs, rendering the bacterium comparatively more resistance to the antimicrobial activity of AgPtNHs. Moreover, the cell wall of Gram-negative bacteria possesses a stronger negative charge than Gram-positive bacteria due to the presence of lipopolysaccharides (LPS), which promotes adhesion of AgPtNHs, causing the bacteria to be more susceptible to AgPtNHs antimicrobial action. Hence, electrostatic attraction between negatively charged bacterial cells and positively charged AgPtNHs is crucial for the bactericidal and antibiofilm efficacy.

The strong antimicrobial synergy and antibiofilm activity suggest that phytogenic hybrid nanoparticles composed of elemental silver and platinum could be valuable in discovering new nanomedicine for treating pathogenic bacterial infections.

CONCLUSION

In this work the result showed that the AgPtNHs were synthesized by using aqueous extract of *D. bulbifera* tuber to evaluate their antimicrobial synergy in combination with the antibiotics against both Gram-positive and Gram-negative bacterial pathogens. The nanocluster shaped AgPtNHs were monodispersed with an average diameter of ∼59 nm. Phytochemicals present in DBTE facilitated the synthesis of AgPtNHs by reducing the metal ions and also their stabilization. Three test pathogens, *E. coli*, *P. aeruginosa*, and *S. aureus* were inhibited by AgPtNHs alone while the combination of AgPtNHs with antibiotics such as rifampicin and novobiocin showed high antimicrobial synergy. Biofilm formation was significantly inhibited by the phytogenic AgPtNHs which irreversibly eradicated bacterial biofilms on glass surfaces. The obtained nanocomposites could effectively eradicate bacterial biofilm at a low concentration of 10 μg/well. Combined treatment of AgPtNHs and antibiotics for killing bacteria is advantageous as it would lower the concentration of antibiotics used which otherwise triggers multidrug resistance. Thus, combined antimicrobial therapy is expected to be more efficient for preventing bacterial regrowth than conventional antibacterial agents.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

BR, GS, SK, KB, and SS performed all the experiments, analyzed the data, and interpreted the results and wrote the initial draft of the manuscript. NK supervised and designed the imaging experiments and analyzed the data, and wrote the manuscript. PK supervised the characterization experiments, analyzed the data, and participated in the writing of the manuscript. SG conceived the idea, designed and supervised the study, analyzed the data, and wrote the manuscript. PK, SG, and NK revised and finalized the manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Microbiology

REVIEW
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Microbiologically-Synthesized Nanoparticles and Their Role in Silencing the Biofilm Signaling Cascade

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The emergence of bacterial resistance to antibiotics has led to the search for alternate antimicrobial treatment strategies. Engineered nanoparticles (NPs) for efficient penetration into a living system have become more common in the world of health and hygiene. The use of microbial enzymes/proteins as a potential reducing agent for synthesizing NPs has increased rapidly in comparison to physical and chemical methods. It is a fast, environmentally safe, and cost-effective approach. Among the biogenic sources, fungi and bacteria are preferred not only for their ability to produce a higher titer of reductase enzyme to convert the ionic forms into their nano forms, but also for their convenience in cultivating and regulating the size and morphology of the synthesized NPs, which can effectively reduce the cost for large-scale manufacturing. Effective penetration through exopolysaccharides of a biofilm matrix enables the NPs to inhibit the bacterial growth. Biofilm is the consortia of sessile groups of microbial cells that are able to adhere to biotic and abiotic surfaces with the help extracellular polymeric substances and glycocalyx. These biofilms cause various chronic diseases and lead to biofouling on medical devices and implants. The NPs penetrate the biofilm and affect the quorum-sensing gene cascades and thereby hamper the cell-to-cell communication mechanism, which inhibits biofilm synthesis. This review focuses on the microbial nano-techniques that were used to produce various metallic and non-metallic nanoparticles and their "signal jamming effects" to inhibit biofilm formation. Detailed analysis and discussion is given to their interactions with various types of signal molecules and the genes responsible for the development of biofilm.

Keywords: micronanotechnique, nanoparticles, antibiofilm, quorum-sensing, quorum quencher

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INTRODUCTION

Most chronic infections in humans are found to be caused by biofilm. Biofilm is the syntrophic association of microbial cells that remain adhered to biotic or abiotic surfaces with self-synthesized hydrated polymeric substances (Costerton et al., 1999). The development of biofilm occurs *via* the adherence of planktonic bacterial cells to a surface such as medical devices and prosthetics. It also leads to the development of valve endocarditis, chronic otitis media, cystic fibrosis, and wound-associated infections (Donlan, 2001; Santos et al., 2011; Abidi et al., 2013).

The ability of the bacterial cells to adapt to and monitor various environmental conditions depends on the mechanism of cell-to-cell communication, which is density-dependent and based on contact-associated exchange of chemical substances (Lobedanz and Søgaard-Andersen, 2003; Phelan et al., 2012), chemical signaling (Eberhard et al., 1981), and signaling associated with electrical impulse (Nielsen et al., 2010; Shrestha et al., 2013).

Such a density-dependent communication system in bacteria attributed by small chemical substance (auto inducers) is termed "quorum sensing" (QS). This process was first observed within *Vibrio fischeri* (Nealson et al., 1970) and the term QS was given by Fuqua et al. (1994). The QS machinery comprise of acyl homoserine lactones (AHLs) which are the group of auto inducing peptides that play an important role in causing bacterial pathogenesis. Various virulence factors are produced through QS which include exotoxin A, lection, pyocyanin, and elastase in *Pseudomonas aeruginosa*, whereas protein A, enterotoxin, lipases, hemolysins, and fibronectin were reported in *Staphylococcus aureus* (Yarwood et al., 2004; Carnes et al., 2010). The developed virulence factors help the bacterial cells to evade the host immune system pathogenicity. The formation of biofilm is a multistep process that involves the transcription of various genes with respect to the planktonic form of microbial cells of the same organism (Donlan, 2002). The conversion of the planktonic to its sessile forms results in the enhancement of various chemical substances, resulting in genetic changes within the cells. Thus the sessile micro colonies develop a thick extracellular polymeric substance (EPS) comprising of exopolysaccharides, proteins, extracellular DNA (e DNA), and other polymeric substances that act as a physical barrier around the bacterial cells. This condition results in the maturation of biofilm *via* the process of quorum sensing (QS; Lahiri et al., 2019). The development of biofilm occurs through the mechanism of irreversible attachment of the bacterial cells upon the surface followed by the production of QS molecules, transportation of substances within the biofilm, metabolism of substrate by various sessile micro colonies, development of EPS, and finally the metastasis of the sessile colonies (Lahiri et al., 2019). Although use of antibiotics is the first choice to combat bacterial infection, the rapid increase in antibiotic resistance due to uncontrolled use of antibiotics has become a major health concern (Laxminarayan et al., 2013; Chioro et al., 2015; Zhao et al., 2017; Zhong and Zhao, 2018; Ma et al., 2019; Sarkar et al., 2020). The development of most antibiotics is based on targeting the protein synthesis machinery that in turn results in the destruction of the pathogenic cells (Nikaido, 2009) – precisely the planktonic cells. However, the biofilm-causing sessile cells often remain unaffected and lead to survival of the pathogen.

The traditional approach that was involved in treating biofilm was the combinatorial use of various antibiotics that exhibits various mechanisms of killing. But with the development of antibiotic resistance, conventional drugs are failing to inhibit the formation of biofilm. The development of EPS around the micro colonies prevents the penetration or zero diffusion of antibiotics within the biofilm. The development of EPS around the micro colonies prevents the penetration causing zero or reduced diffusion of antibiotics within the biofilm. Moreover, alterations in the microenvironment within biofilm matrices result in the development of the concentration gradient of metabolites causing reduced or almost no growth of bacteria. It has also been observed that the fluctuation in the microenvironment results in the alteration of nutrient supply, generation of oxidative stress, low availability of water, starvation, and change in temperature which in turn results in the development of adaptive stress responses within the bacterial cells (Singh et al., 2017). It has also been observed that the fluctuation in the microenvironment results in the alteration of nutrient supply, oxidative stress, low availability of water, starvation, and change in temperature which results in the development of adaptive stress responses within the bacterial cells. This is followed by the transformation of the bacterial cells to a highly protected spore-like state, known as persisters, which is also a potent cause of developing resistances towards antibiotics (Stewart, 2002). This issue warrants the exploration of new drugs or drug-like compounds to combat the biofilm.

Recently, the use of various nanoparticles (NPs) has become popular to treat bacterial infections as an alternative to antibiotics. Since NPs follow a totally different mechanism of action to target the bacteria and do not need to penetrate the bacterial cell, new pathways emerged (Wang et al., 2017a).

Microbiologically-synthesized nanoparticles are found to be more advantageous as compared to chemically-synthesized counterparts, as the former does not need very stringent conditions like a pure starting material. The requirement of optimal conditions and clement temperatures (20–30°C) make microbiologically-synthesized NPs more commercially viable (Vaseghi et al., 2018). Moreover, the presence of a biological capping agent on some micro biogenic nanoparticles, as a protective covering against oxidation, agglomeration, and aggregation, offer a higher stability (Durán and Seabra, 2012). Hence, microbiologically-synthesized NPs are often considered to be a better option for antibacterial therapies (Capeness et al., 2019).

Hence, the aim of the present review is to describe the efficiencies of various microbiologically-synthesized nanoparticles as potent antibiofilm agents with special reference to their ability to inhibit quorum sensing through affecting their regulator gene cascade.

SYNTHESIS OF MICROBIAL NANOPARTICLES

Recently, technological advancements in the field of nanoparticles (NPs) have revolutionized their applicability in healthcare sectors

due to the adjustable physico-chemical properties, which include thermal and electrical conductivities, absorption of light, melting point, and enhancement of catalytic activity by altering the surface-to-volume ratio. The field of nanotechnology encompasses the process of synthesizing nano-dimensional particles possessing various shape- and size-dependent properties (Rafique et al., 2017). Various types of NPs, including silver nanoparticles (AgNPs), show wide applications in the healthcare domain that include hyperthermia of tumors (Iravani, 2014), delivery of drugs, medical imagining, chemical sensors, catalysis, wireless electronic logic, computer transistors, memory chips, and its antimicrobial efficacy (Das et al., 2014).

Conventionally, NPs are synthesized *via* various physical, chemical, and mechanical processes such as ultra-sonication, radiolysis, microwave, spray pyrolysis, electro spinning, sol-gel method, chemical reduction, and inert condensation methods. But the urgent need for a less time consuming, low cost, high yield, non-toxic, and environment-friendly process has shifted the focus towards greener approaches (Khandel and Kumar-Shahi, 2016; Fang et al., 2019).

Biogenic sources like bacteria fungi and various parts of plants play an effective role in stabilizing the NPs (Durán et al., 2005). The green synthesis of NPs utilizes microbial cells like fungi, yeast, and bacteria as the process can be controlled by manipulating the culture conditions, like nutrient, pH, pressure, and temperature. The microbial system possesses an intrinsic mechanism of synthesizing NPs from metallic salts (Li et al., 2011).

Studies have shown that bacterial cells play an important role in the conversion of heavy metals to metallic NPs. The existence of various types of interactive pathways present within the bacterial cells is responsible for the synthesis of the metallic NPs. Another advantage of implementing bacterial cells is their ability to produce sustainable nanoparticles at a large scale (Fariq et al., 2017). It has also been observed that fungi play a predominant role in the synthesis of NPs *via* both extracellular and intracellular enzymes that are present within cells (Fariq et al., 2017). Enzymes like nicotinamide adenine dinucleotide (NADH)-dependent reductase was responsible for the synthesis of metallic NPs (Guilger-Casagrande and Lima, 2019). Nitrate reductase enzyme and anthraquinones from *Fusarium oxysporum* was responsible for the reduction of silver ions. Another study revealed that extracellular NADH-dependent nitrate reductase from the same fungi and quinolones were used to synthesize AgNPs (Anil Kumar et al., 2007). NADH-dependent oxidoreductase from fungi is also responsible for the synthesis of AuNPs (Kitching et al., 2015). Studies also showed that α-NADH-dependent reductase and nitrate reductase was used for the synthesis of NPs. Due to the presence of larger amounts of biomass in fungi, the yield of NPs is usually higher compared to bacterial cells. Although bacteria are more commonly used in synthesizing metallic NPs, the fungi could be more advantageous due to the presence of mycelia that provide greater surface area for interactions. The amount of enzyme produced by the fungi is higher compared to that of bacteria; thus the rate of conversion of the metallic salts to metallic NPs is faster. The fungal cell wall also played an important role in the mechanism of absorption and the reduction of metal ions for the formation of NPs (Khandel and Shahi, 2018).

The components of fungal cells, like the cell wall, cell membrane, protein, enzymes, and other intracellular components, play a vital role in the synthesis of the nanoparticle. Various parameters like temperature, pH, biomass, and other physical factors participate in regulating the synthesis of metallic NPs like AgNPs. These nanoparticles have various properties which have proven to be useful for human welfare, largely with antimicrobial (antibacterial, antifungal, and antiviral) activities. In fact, the mechanism of biosynthesis of AgNPs by fungi or fungal-based materials does not require any toxic agents during the NP recovery and purification process (Wei et al., 2009). But, like other nanoparticles, mycogenic AgNPs have some disadvantages. The biosafety of the use of AgNPs and their biocompatibility need to be tested prior to application, especially in the field of healthcare. The main obstacle for industrial production of mycogenic metallic NPs lie in the fact that most of the fungal species known for nanoparticle production have been reported to be pathogenic to human and plant. On the contrary, *Trichoderma reesei*, being a nonpathogenic fungus, is now well accepted as an industrially-adapted strain for the production of AgNPs (Dorcheh and Vahabi, 2016). Some other limitations that are associated the fungi-mediated NPs synthesis are higher cost of production and longer time of biosynthesis (Jeevanandam et al., 2016). The advantage of using bacterial species for the synthesis of NPs is to its fast growth and easier mechanism of manipulating genetic expressions (Lovley and Woodward, 1996). The use of bacterial species for the purpose of synthesizing metallic NPs is due to its ability to survive at higher concentrations of metallic ions (Haefeli et al., 1984).

MECHANISM OF SYNTHESIS OF MICROORGANISM-ASSISTED NANOPARTICLES

Processes of both intracellular and extracellular synthesis of nanoparticles (NP) by microorganisms from metals, metal oxides, or metalloids have been well documented in literature (Patil and Chandrasekaran, 2020). The extracellular process involves reduction of metal ions for NPs synthesis by microbial enzymes and proteins, bacterial or fungal cell wall components, or organic molecules present in the culture medium, whereas the intracellular process involves initial electrostatic attraction of metal ions by carboxyl groups of the microbial cell wall, resulting in passage of metal ions through the cells and reduction by intracellular proteins and cofactors to produce NPs (Siddiqi et al., 2018). Biochemical mechanisms involving microorganism-mediated nanoparticle synthesis can be seen as a part of microbial resistance mechanisms for cellular detoxification. This involves alterations in the solubility of inorganic and toxic ions by enzymatic reduction and/or precipitation in the form of nanostructures. Both extracellular and intracellular bio-catalytic synthesis mechanisms have been proposed, which mainly involves oxidoreductase enzymes (e.g., NADH-dependent nitrate reductase,

NADPH-dependent sulfite reductase flavoprotein subunit α, and cysteine desulfhydrase) and cellular transporters (Grasso et al., 2019). Nano-dimension materials are biosynthesized within the microorganisms by binding target ions from the surroundings and converting these toxic metal ions into the corresponding element metal through cellular enzymes. Based on the location of synthesis of nanoparticles, it can be classified into intracellular or extracellular. The intracellular method involves transporting ions into the microbial cell to form nanoparticles in the presence of enzymes. The extracellular mode involves trapping the metal ions on the cell surface and reducing ions in the presence of enzymes (Li et al., 2011).

MICROBIAL ENZYMES IN BIO REDUCTION OF METAL, METALLOID, AND NON-METAL IONS TO NANOPARTICLES

Microbial conversion of metal and metalloids to respective nanoparticles can be accomplished by the extracellular enzymes produced by different bacteria and fungi. Extracellular enzymes, such as nitrate reductase, can help in electron transfer from certain donors (e.g., hydroxyl groups) to Ag^+ and thus helps in conversion to metallic AgNPs. It has been observed that the functional groups, such as ▬NH_2, ▬OH, ▬SH, or ▬COOH, of microbial proteins help in stabilization of the NPs by providing binding sites to the metal ions followed by its reduction into NPs on the cell wall or in the periplasmic space. In some cases, proteins act as the main reducing or capping agents during the formation and stabilization of NPs. Intracellular enzymes like cytochrome oxidases are also found to help in the reduction of metal ions to NPs *via* electron transfer between cytoplasm components (e.g., NADH/NADPH), vitamins, and organic acids. Intracellular reductase can initiate the biosynthesis and stabilization of NPs in three possible ways: periplasmic reductase can directly reduce M^+ to M, bio reduction at the cytoplasm or periplasm produces M from M^+, or bioconversion of M^{2+} to M^+ in cytoplasm and M formation can occur (Klaus et al., 1999; Mishra et al., 2017; Lv et al., 2018; Siddiqi et al., 2018).

Metalloids such as Te^{2+} and Se^{2+} are harmful to both health and the environment and also involve toxic chemical reductants during their degradation (Presentato et al., 2018). Bio-inspired reductants can be an option for their efficient degradation and decontamination as they produce minimum or no toxic products in the entire degradation process. One such example is the aerobic disintegration of SeO_3^{2-} by *Actinomycete rhodococcus* into Se-NPs. The reduction of SeO_3^{2-} to Se-NPs is based on the LaMer mechanism where Se-nucleation seeds were formed, which assemble to form the nanoparticles that precipitated as nano-crystals from the suspension due to higher free energy and lower stability in solutions (Jana, 2015). In another study, Se-NPs were produced both intra-cellularly and extra-cellularly by *Enterobacter cloacae* Z0206 *via* the enzyme fumarate reductase possessing selenite reducing factor. Se-NPs were also produced by microorganisms such as *Citrobacter freundii Y9* (anaerobic synthesis) and *Pseudomonas putida* (aerobic synthesis). In the latter case, it is found that thiol-containing amino acids (such as cysteine) help in the chelation of SeO_3^{2-} which in turn forms seleno di-glutathione. This again can act as the substrate of glutathione reductase, producing an unstable intermediate Se^0. Spherical nanoparticles of Se and Te are also formed by microbial species such as *Ochrobactrum* sp. MPV1 and *Stenotrophomonas maltophilia* SeITE02. The detoxification of tellurite to black Te-NPs can be achieved with the help of NADH-dependent reductase (Song et al., 2017; Wang et al., 2017b; Xu et al., 2018).

Intracellular magnetosomes in some bacteria like *Magnetospirillum magneticum* help in the encapsulation of Fe_2O_3-NPs in its dissolved form with the help of some multicellular proteins (e.g., ferritin or iron reductase enzymes). Bacterial magnetosomes are organelles of magnetotactic bacteria for geomagnetic navigation and comprises of magnetic nano crystals of magnetic minerals magnetite (Fe_3O_4) or greigite (Fe_3S_4) that remain surrounded by biological membranes made up of proteins, glycolipids, and phospholipids. The synthesis of magnetosomes is dependent on various environmental conditions, cellular stress, and cell proliferation cycles. The development of the magnetosomes involves transportation of iron outside the bacterial cell membranes *via* the vesicles that are formed, alignment of magnetosomes in a chain, development of crystals, and maturation of the crystals that are being formed (Kuzajewska et al., 2020). The membrane of the magnetosome differs from the plasmalemma on the basis of its composition and provides an appropriate environment for the purpose of biomineralization. This development of magnetosome is a highly controlled process that is regulated by unique protein sets encoded by the magnetosome island (Barber-Zucker and Zarivach, 2017). Supersaturating concentrations of iron also caused nucleation of magnetite at the interface of magnetosome membranes. It has been observed that the formation of vesicles occurs prior to the biomineralization event. Thus, pumping of supersaturating amounts of iron into the vesicles could be performed easier *via* the MamB and MamM proteins, such as in the case of *Magnetospirillum magneticum*. Interactions between the ions of the crystal and the surface proteins help in achieving a better nucleation process. It was also observed that the morphology of magnetite nanoparticles is dependent on the solution chemistry and physical conditions such as super saturation state, iron supply direction, concentration of activator and inhibitor ions or molecules, pH, redox potential, and temperature (Faivre and Schüler, 2008).

These metal oxide nanoparticles use $FeCl_3$ as a common precursor. For example, metal oxide nanoparticles of CuO and SnO_2 were previously made using microorganisms *Morganella morganii* and *Erwinia herbicola*, respectively, utilizing enzymes such as NADH involving redox reactions. The metabolites secreted by the bacteria in the culture broth can induce the reduction and stabilize the newly-formed metal NPs (Srivastava and Mukhopadhyay, 2014; Obayemi et al., 2015).

Nanoparticles of transition metal chalgonides have been synthesized by various researchers. For example, CdS-NPs can be formed by *Moorella thermoacetica* extra-cellularly by the addition of $Cd(NO_3)_2$ in bacterial culture media which helps

in the photosynthetic reduction of CO_2 to acetic acid. CdS-NPs can be produced both extra-cellularly and intra-cellularly by *Desulfovibrio caledoniensis*. It is a three-step process that involves ATP sulfurylase-mediated activation of the anaerobic reduction of sulfate being present within bacteria as well as ferredoxin or NADH-mediated reduction of the resultant adenosine-phosphosulfate (APS) complex to sulfite followed by assimilatory or dissimilatory sulfite reductase which reduced sulfite to sulfide. PbS nano crystals can also be biosynthesized by controlling the concentration of poly-etheneglycol in the *Clostridiaceae* sp. where SO_4^{2-} is first reduced to S^{2-} by the sulfate-reducing bacteria, and then S^{2-} gradually combined with Pb^{+2} to precipitate as PbS-NPs (Qi et al., 2016; Yue et al., 2016). Studies have also shown that grapheme-associated highly dispersed Pd-Ag bimetallic NPs can be synthesized using *Shewanella oneidensis* MR-1(Han et al., 2019). The conversion of graphene oxides to grapheme nano sheets can be achieved through the use of crude polysaccharides obtained from *Pleurotus flabellatus* (Dasgupta et al., 2017; **Figure 1**).

MICROBIAL EXOPOLYSACCHARIDES FOR SYNTHESIS OF NANOPARTICLES

Exopolysaccharides (EPSs) from bacterial cells are produced extra-cellularly and play vital roles in surface adherence and cell-cell communication. EPSs possess the ability of reducing metal ions to produce nanoparticles and also help in the stabilization of the NPs by acting as a capping agent. Therefore, the EPSs are used as an alternate choice for microbiological production of numerous metal nanoparticles. Bacterial EPSs mainly comprise of carbohydrates such as D-glucose, L-fucose, D-mannose, D-galactose, N-acetyl-D-glucosamine, N-acetyl D-galactosamine, and non-carbohydrate components which are responsible for the anionic nature to the EPSs. These organic groups tend to increase the lipophilicity of the EPSs and directly influence their interaction with cations such as metal ions. Metal ions in contact with EPS are chelated and then reduced and stabilized by various functional groups *via* electrostatic bonds. For example, oxidation of ▬OH groups to form ▬C═O groups and oxidation of ▬CHO groups to form ▬COOH groups play an important role during metal nanoparticles synthesis. The polymeric structure of EPSs create a network by ▬H bonding in which nanoparticles stabilize with subsequent preventions of their agglomeration and precipitation (Escárcega-González et al., 2018). Various types of functional groups that are associated with EPS of both Gram positive and Gram negative acts as reductive and stabilizing agents for the purpose of synthesizing NPs with the capping and chelating processes (Emam and Ahmed, 2016). This helps in the regulation of size, particle dispersion, and shape of the NPs (Kanmani and Lim, 2013). The ability of the NPs to develop broader applicability is due to the muco-adhesion properties that help in the development of non-specific protein receptor recognition by the NPs (Kanmani and Lim, 2013). In previous research it was revealed that structurally known EPS from succinoglycanbacteria were used for the synthesis of AgNPs. It is a polymeric substance produced by *Sinorhizobium meliloti* that helped in the reduction of the metal by inducing oxidation of the aldehyde group to a carboxyl group with the help of nucleophilic insertion (Kwon et al., 2009). Curdlan is another type of EPS comprising of (1, 3)-β-D-glucan repeated units that are joined by β-(1, 3)-glycosidic bonds and are produced predominantly by *Alcaligenes faecalis*, *Rhizobium* sp., and *Agrobacterium* sp. These are used for the purpose of synthesizing and stabilizing NPs (Zhang and Edgar, 2014). Curdlan, a water insoluble polymeric substance, can be carboxylated or oxidized to curdlan derivatives for the purpose of synthesizing NPs. Leung et al. (2010) synthesized AgNPs with the help of carboxymethylated-curdlan. The persistence of the negatively-charged hydroxyl group and carboxyl groups resulted in better reduction of the silver ions. Dextran is another predominant component of EPS that helps in the synthesis of grapheme NPs (Hu et al., 2016). Chemically, dextran is a multifaceted

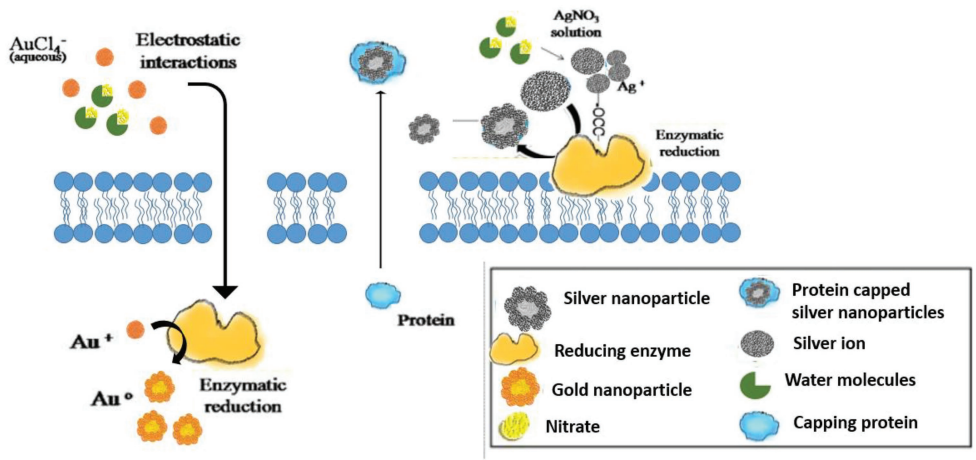

FIGURE 1 | Microbial enzymes in bio reduction of metal, metalloid, and nonmetal ions to nanoparticles.

branched glucan comprising of glucose residues that remain interlinked with α-(1,6) glycosidic linkages and are predominantly produced by certain groups of lactic acid bacteria like *Leuconostoc mesenteroides* and *Streptococcus mutans*. Bankura et al. (2012) synthesized size-controlled AgNPs using the aqueous solution of dextran which acted as both reductant and stabilizer.

Au NPs can also be green synthesized using *Cupriavidus metallidurans* and *Delftia acidovorans* Au nuggets can be obtained from the bacterial biofilms (Johnston et al., 2013). Experimental observations revealed that nano particulate Au can inhibit biofilm formation (Reith et al., 2010). Au NPs bring about inhibition of biofilm by altering the surface chemistry and hydrophobicity as well as interacting with lipids and proteins that are present on the bacterial cell membrane (Ikuma et al., 2015). This alters the penetration of the NPs within the biofilm. The ability of NPs to penetrate the biofilm depend on the charge existing on the surface, size of the NPs, and the chemistry and concentration of NPs (Ikuma et al., 2015). The penetration of the NPs is followed by its interaction with the structural components of the biofilm, causing the disintegration of the biofilm (Qayyum and Khan, 2016; Pinto et al., 2019). It has been further observed that modified groups of the Au NPs can increase its inhibition potential either on single or multiple types of cells present within the biofilm. Various types of forces, like Van der Waals, hydrogen-bonds, electrostatic, and hydrophobic interactions, can effectively inhibit the biofilm (Yu et al., 2018).

MICROBIAL BIO SURFACTANTS FOR SYNTHESIS OF NANOPARTICLES

Bio surfactants are microbial surface-active amphiphilic molecules produced mainly by bacteria, fungi, and yeasts. Their hydrophilic moiety consists of carbohydrates, cyclic peptides, amino acids, carboxylic acids, or phosphates and the hydrophobic moiety comprises mainly of long-chain fatty acid or hydroxyl fatty acid. These are divided to two types *viz*. low-molecular-weight surface active agents (LMW) such as glycolipids, lipopeptides, and phospholipids and high molecular-weight polymers (HMW) mainly referred to as bio emulsifiers such as emulsan (Pati et al., 2020). They can also be classified as: (i) hydroxylated and cross-linked fatty acids (mycolic acids); (ii) glycolipids (rhamnolipids); or (iii) lipopolysaccharides. Bio surfactants can act as excellent capping agents during the synthesis of metallic nanoparticles *via* biogenic processes (Płaza et al., 2014). Their mechanism of action involves adsorption onto metallic nanoparticles, surface-stabilizing the nanoparticles, and preventing subsequent aggregation, thereby helping in stabilization process (Kiran et al., 2011; Gahlawat and Choudhury, 2019). Biosurfactants are the groups of amphipathic molecules possessing both hydrophobic and hydrophilic moieties creating partitions at the interface between fluid phases possessing various degrees of hydrogen bonding and polarity (Rodrigues et al., 2006). The micro emulsions, i.e., the water-soluble droplets that are present within, act as a micro-reactor. The increase in the concentration of the surfactants results in a decrease in the size of droplets, thereby reducing the particle size. The presence of water plays an important role in regulating the size and the morphology of the NPs. The size of the particle and mono dispersity is dependent on the molar ratio (R) of the water (Han et al., 2008).

MICROBIAL SYNTHESIS OF NANOPARTICLES THROUGH BIO MINERALIZATION

Some microorganisms possess the unique property of mobilizing/immobilizing the metal salts by reducing them into metal ions which precipitate within or outside the microbial cells. They, with the help of efflux pumps, accomplish the complexation and inactivation of metals, with their subsequent precipitation by changing the oxidation state of the metals *via* redox reactions.

For example, gold (I)-thiosulfate enters *Acidithiobacillus thiooxidans* cells metabolically and are broken down to Au(I) and thiosulfate ($S_2O_3^{2-}$) ions. Thiosulfate acts as an energy source while Au(I) reduces itself to elemental gold intracellularly. These elemental gold precipitates inside the bacterial cells to form NPs during the late stationary growth phase and are released from the cells later on. Finally, the gold particles in the bulk solution are grown into micrometer-scale wire and octahedral gold (Lengke and Southam, 2005).

In another study, it was proposed that the sulfate-reducing bacteria bring about the reduction of the gold (I)-thiosulfate complex through three possible pathways: iron sulfide formation, localized reducing effects, or a metabolic pathway. The first process involves the adsorption of gold (I)-thiosulfate on the surfaces of iron sulfide freshly formed by sulfate-reducing bacteria producing elemental gold. The second process involves localized reducing conditions causing the gold (I)-thiosulfate complex reduce to hydrogen sulfide (HS^-) by sulfate-reducing bacteria which was released through the outer membrane pores resulting into precipitation of elemental gold. The third process involved decomplexation of gold (I)-thiosulfate complex to Au(I) and thiosulfate ions which are later released from the cells (Lengke and Southam, 2005; Lengke et al., 2006).

MICROBIAL SYNTHESIS OF MAGNETIC NANOPARTICLES

The bacterial magnetic nanoparticle (BMP) formed from magnetotactic bacteria (MTB), known as magnetosomes, which are a type of magnetic nanoparticle, has a lot of possibilities in nano biotechnology (Vargas et al., 2018). These are intracellular magnetic particles comprising of oxides and sulfides of iron within the bacterial cell that act as a bacterial compass needle helping bacterium to migrate along oxygen gradients in aquatic environments, under the influence of the Earth's geomagnetic field. BMPs have the ability to disperse in aquatic medium and are usually carried by phospholipid vesicles.

Bio mineralization of BMPs occurs *via* multiple steps; the first step involves a GTPase-mediated invagination of the

cytoplasmic membrane followed by assembly into a linear chain along the cytoskeletal filaments. The second step involves trans membrane iron-transporter-mediated accumulation of ferrous ions inside the vesicles. The final step involves magnetite crystal nucleation by triggering BMP proteins which includes the accumulation of supersaturating iron concentrations, and partial reduction and dehydration of ferrihydrite to magnetite (Arakaki et al., 2008).

In another study, magnetite was synthesized by *Shewanella oneidensis* involving both passive and active methods. Active utilization of ferrihydrite as a source of electron acceptor to form Fe^{2+}in a high pH environment followed by localized conversion of Fe^{2+} and Fe^{3+} near negatively charged cell walls leads to super saturation, causing magnetite to precipitate (Li et al., 2011). The membrane controls the particle size, crystallization, and particle morphology in the particle size, crystallization, and particle morphology. The phospholipids bilayer can entrap the bacterial nanoparticles and contains about 20–40 species of membrane proteins (Grünberg et al., 2004).

The BMPs used in the nano biotechnology and nano medicine are mainly extracted from species of *Magnetospirillum gryphiswaldense* MSR-1 and *Magnetospirillum magneticum* AMB-1, although there are other species of MTB that can be cultivated (Chen et al., 2016).

MICROBIAL SYNTHESIS OF STABLE QUANTUM DOT NANOPARTICLES

Recently, fluorescent or quantum dots (QDs) nanoparticles have been widely used in several biological, biomedical, optical, and optoelectronic applications such as biosensors, photovoltaics, optoelectronics, transistors, oil exploration, biomedicine, imaging, and solar cells due to its unique size-dependent properties. Their increased utility is due to their biocompatibility and lesser toxic by-product generation during its synthesis, indicating a pathway to greener technology. So far, synthesis of CdS, CdSe, and CdTe QDs involved the use of harmful chemicals such as bidentate thiols [e.g., dithiothreitol (DTT), mercaptosuccinic acid (MSA), mercaptopropionic acid (MPA)], and ligands with different functional groups (amino, hydroxyl, and carboxylic acid, among others). Researchers have isolated bacteria that are cadmium- and tellurite-resistant Antarctic bacteria *Pseudomonas* (eight isolates), *Psychrobacter* (three isolates) and *Shewanella* (one isolate) capable of synthesizing CdS and CdTe QDs when exposed to toxic oxidizing heavy metals like Cd and Te with a time-dependent change in fluorescence emission color (Plaza et al., 2016). The CdSe nanoparticles are one of the examples that exhibit fluorescent tags. Cui et al. (2009) reported intracellular synthesis of CdSe nanoparticles in *S. cerevisiae* using genetic engineering techniques. The genes involved in glutathione biosynthesis, namely *GSH1*, *GSH2*, and *GLR1*, become silent in yeast and after interaction with inorganic ions resulted in a significant reduction in fluorescence, which in turn was proportional to the amount of CdSe nanoparticle synthesis. It was found that Na_2SeO_3 was reduced to selenocysteine $(Cys\text{-}Se)_2$, a complex of selenium-containing cysteine, which after the addition of $CdCl_2$ generated CdSe nanoparticles. In another work by Bruna et al. (2019), CdS QDs by polyextremophile halophilic bacteria *Halobacillus* sp. DS2 were synthesized with increased tolerance to NaCl (Bruna et al., 2019). A tunable ternary CdSAg QD involving cation exchange were synthesized by Órdenes-Aenishanslins et al. (2020). Nanoparticles were also produced within bacterial cells extra-cellularly *via* exposure to cysteine and $CdCl_2$ in a reaction. This reaction was dependent on S^{2-} generation mediated by cysteine desulfhydrase enzymes and utilized cellular biomolecules to stabilize the nanoparticle.

MICROBIAL ORGANIC PARTICLES FOR NANOPARTICLE SYNTHESIS

Bacterial cellulose (BC) are used to form nano fibers and to instill a bactericidal property in the nano fibers. A combination of bactericidal chitin (Ch) with bacterial cellulose (BC) nano fibers was developed to form a nanocomposite of BC-Ch in a process that is considered a green approach. *Acetobacter aceti* was also fed with Ch_{79d} to biosynthesize bio-BC-Ch_{79d} nanocomposites to produce 50–100-nm-wide nanofibrils (Butchosa et al., 2013).

A number of microbial components are found to be involved in the formation of nanoparticles (**Table 1**), which are found to act as potent antibiofilm agents through inhibition of the quorum-sensing process.

MECHANISM OF QUORUM SENSING

The process of QS is the mechanism of interaction between the bacterial cells *via* the production of extracellular chemicals known as Auto inducers (AIs). This mechanism helps in the process of synchronizing the bacterial cells and their various expressions to respond to the changes of the environment. This process is observed in both Gram-positive and Gram-negative bacterial cells. Studies have shown that Gram-negative bacterial cells possess three major groups of Ais, whereas the Gram positive bacterial cells communicate with the help of auto inducing peptides (AIPs; Raffa et al., 2005). The mechanism of QS can be inhibited by the process of quorum quenching (QQ; Dong et al., 2002). Various mechanisms are involved in the process of QQ that comprise of competitive inhibition and cleavage of the QS signals. This predominantly brings about the inhibition of QS. The chemical that inhibits the mechanism is referred to as Quorum sensing inhibitor (QSI), whereas the enzymes involved in such inhibition are QQ enzymes. It has often been noticed that QQ enzymes can inhibit QS by targeting AHLs. Several classes of enzymes are capable of degrading AHL signal, such as acylases and oxido reductases that are predominantly of a bacterial origin. It has been also observed that the half-life of AHL is dependent on pH and temperature (Yates et al., 2002; Delalande et al., 2005). There are two novel AHL enzymes, namely *N*-acyl homoserine lactonase (AiiA) and esterase (Est), that can be isolated from *Altererythrobacter* sp. S1-5 (Wang et al., 2019). The former enzyme can hydrolyze

TABLE 1 | Contribution of microbes in the formation of nanoparticles.

Classification	Microorganism	Microbial component	Raw material	Element used	Nanoparticle size (nm)	Morphology	Synthesis location	References
Bacteria	*Lactobacillus rhamnosus*	EPS		Ag	10	Spherical, triangular, rod, and hexagonal	Extracellular	Kanmani and Lim, 2013
	Bacillus licheniformis Dahb1	EPS		ZnO	100	Hexagonal	Extracellular	Abinaya et al., 2018
	Brevibacterium casei MSA19	Biosurfactant		Ag			Extracellular	Kiran et al., 2010
	Bacillus amyloliquifaciens KSU-109	Biosurfactant	Surfactin	CdS			Extracellular	Singh et al., 2011
	Pseudomonas aeruginosa BS-161R.	Biosurfactant	Rhamnolipid	Ag			Extracellular	Kumar et al., 2010
	Bacillus cereus			Ag	20–40	Spherical	Extracellular	Sunkar and Nachiyar, 2012
	Kocuria flava			Cu	5–30	Spherical	Extracellular	Kaur et al., 2015
	Pseudomonas aeruginosa JP-11			CdS	20–40	Spherical	Extracellular	Raj et al., 2016
	Shewanella loihica PV-4			Pd and Pt	2–7	Spherical	Intracellular	Ahmed et al., 2018
	Ochrobactrum sp. MPV			Te		Spherical, rod	Intracellular	Zonaro et al., 2017
	Bacillus cereus			Ag	20–40	Spherical	Extracellular	Sunkar and Nachiyar, 2012
	Escherichia coli			Ag	8	Spherical	Extracellular	Mahanty et al., 2013
	Geobacillus sp.			Au	5–50	Quasi hexagonal	Extracellular	Correa-Llantén et al., 2013
	Bacillus subtilis			Ag	20–25	Spherical	Extracellular	Srinath et al., 2018
	Nocardiopsis sp. MBRC-1			Ag	45	Spherical	Extracellular	Manivasagan et al., 2013
	Pseudomonas fluorescens			Au	50–70	Spherical	Extracellular	Rajasree and Suman, 2012
	Serratianematodiphila			Ag	10–31	Spherical crystalline	Extracellular	Malarkodi et al., 2013
	Shewanellaoneidensis			U	150		Extracellular	Satyanarayana Reddy et al., 2010
	Magnetospirillummagneticum			Fe_3O_4	10–60	Cuboidal, rectangular and spherical NPs	Intracellular	Obayemi et al., 2015
	Shewanellaoneidensis MR-1			CdSe	3.3		Intracellular	Tian et al., 2017
	Escherichia coli			CdTe	62		Extracellular	Kominkova et al., 2017
	Clostridiaceae sp			PbS	Cubic NPs	50	Extracellular	Yue et al., 2016
	Erwinia herbicola			SnO_2	15–45	Spherical andtetragonal NPs	Extracellular	Srivastava and Mukhopadhyay, 2014
	Serratia marcescens			Bi	<150	Irregular	Intracellular	Nazari et al., 2012

(Continued)

TABLE 1 | Continued

Classification	Microorganism	Microbial component	Raw material	Element used	Nanoparticle size (nm)	Morphology	Synthesis location	References
Actinomycetes	*Streptacidiphilus durhamensis*			Ag	8–48	Spherical		Buszewski et al., 2018
	Streptomyces griseoruber			Au	5–50	Spherical, hexagonaland triangular		Ranjitha and Rai, 2017
	Streptomyces xinghaiensis OF1			Ag	5–20	Spherical		Wypij et al., 2018
	Rhodococcus sp. NCIM2891			Ag	10–15	Spherical		Otari et al., 2014
Fungi	*Penicillium diversum*			Ag	10–15	Spherical		Ganachari et al., 2012
	Fusarium oxysporum JT1			Au	22	-		Thakker et al., 2013
	Trichoderma harzianum			CdS	3–8	Spherical		Bhadwal et al., 2014
	Aspergillus terreus			ZnO	28–63	Spherical		Baskar et al., 2015
	Colletotrichum sp.			Al_2O_3	30–50	Spherical		Suryavanshi et al., 2017
Yeast	*Rhodosporidium diobovatum*			PbS	2–5	Spherical		Seshadri et al., 2011
	Saccharomyces cerevisiae			Ag, Au Nanoplates	2–20	Spherical, hexagonal and triangularnanoplates		Korbekandi et al., 2016; Yang et al., 2017
	Pichia kudriavzevii			ZnO	10–60	Hexagonal wurtzitestructure		Moghaddam et al., 2017
	Rhodotorula glutinis			Ag	15	Spherical		Cunha et al., 2018
Virus	Tobacco mosaic virus (TMV)			Pd, Au	3–4, 5	Carbon nanotubes, spherical		Kobayashi et al., 2012; Fan et al., 2013
	M13 virus			TiO_2	20–40	Mesoporous nanowires		Chen et al., 2013
	Hepatitis E virus			Nanoconjugates	27–34	Icosahedral		Chen et al., 2018
	Potato virus X			Nanocarriers	13	Helical		Le et al., 2017
Algae	*Sargassum muticum*			ZnO	0–57	Hexagonal		Sanaeimehr et al., 2018
	Gelidium amansii			Ag	27–54	Spherical		Pugazhendhi et al., 2018
	Laminaria japonica			Ag	31	Spherical to Oval		Kim et al., 2016
	Cystoseira baccata			Au	8	Spherical		González-Ballesteros et al., 2017
	Chlorella vulgaris			Pd	5–20	Spherical		Garole et al., 2019
	Spirogyra varians			Ag	35	Quasi spherical		Salari et al., 2016
	Chlorella vulgaris			Au	2–10	Spherical		Annamalai and Nallamuthu, 2015

and inactivate a variety of acyl homoserine lactones (AHLs). Quorum sensor molecules involved in bacterial quorum sensing (QS) were extracted and purified from *Bacillus* sp. 240B1. After its covalent immobilization onto magnetic nanoparticles (MNPs), the quorum quenching ability of r-AiiA-MNP nano biocatalyst was evaluated and was found to be effective in inhibiting QS (Beladiya et al., 2015). The las system comprises of the *lasR* regulatory gene that codes for the Las R protein, while lasI synthase is regulated by *lasI* gene which is associated with the synthesis of signaling molecule of the AHL family, i.e., 3-oxo-C12-HSL. The LasR/3-oxo-C12-HSL is responsible for activating the virulence gene. The *rhl* system comprises of *rhlR* and *rhlI* genes. These further results in the activation of the las system that is responsible for the production of pyocyanin, rhamnolipids, and swarming motilities. The rhl system is regulated by the las system. PQS intermediates between the two other systems. The PqsA_E acts as a precursor for 2-heptyl-4-quinolones (HHQ) and regulates the conversion of HHQ to 2-heptyl-3-hydroxy-4-quinolone (PQS; **Figure 2**; Carette et al., 2020).

MECHANISM OF QUORUM SENSING IN GRAM-NEGATIVE BACTERIA

The Gram-negative bacterial cells communicate *via* signaling molecules, termed as auto inducers (AI), such as acetyl homoserine lactone (AHL) and other chemical molecules whose synthesis is dependent on S-adenosylmethionine (SAM; Walker et al., 2011). SAM acts as an amino acid subtract required for the synthesis of acyl homoserine lactones (Whitehead et al., 2001). A study showed that *E. coli* comprising of plasmid associated *lux I* requires the presence of SAM for the synthesis of *N*-(3-oxooctanoyl)-L-homoserine lactone (Hanzelka and Greenberg, 1996).

The AI produced by the bacterial cells can easily diffuse through the outer layer of the cell membrane. Enhancement of AIs is observed during high cell density (HCD) and thus regulates the transcriptional factors for the genes that are associated with the process of QS. Various types of signaling molecules are associated with the Gram-negative bacterial cells like 3-hydroxy-palmitic acid from *Ralstonia solanacearum* and 2-heptyl-3-hydroxy-4-quinolone from *P. aeruginosa* (Flavier et al., 1997). The latter is an opportunistic nosocomial disease-causing organism remaining associated with infections like cystic fibrosis (CF), lung infection, and various types of dermal and burn wound infections (Ammons et al., 2009). These Gram-negative bacteria comprise of three major QS circuits. One such circuit is the *lasI* encoding protein LasI that is associated with the production of auto inducer as well as the gene *LasR* that in turn encodes for the transcriptional activator LasR. Another profound QS circuit comprises of gene *rhlI*, associated with the synthesis of autoinducer-N-(butonyl)-L-Homoserine lactone and rhlR that is responsible for the transcriptional activator RhlR (Pearson et al., 1994, 1995). The third QS circuit which is also observed in *P. aeruginosa* is related to alkyl quinolones, especially 2-heptyl-3-hydroxy-4-quinolones that are predominantly regulated by *pqsABCDEH* and *PqsR* regulator genes (Pesci et al., 1999).

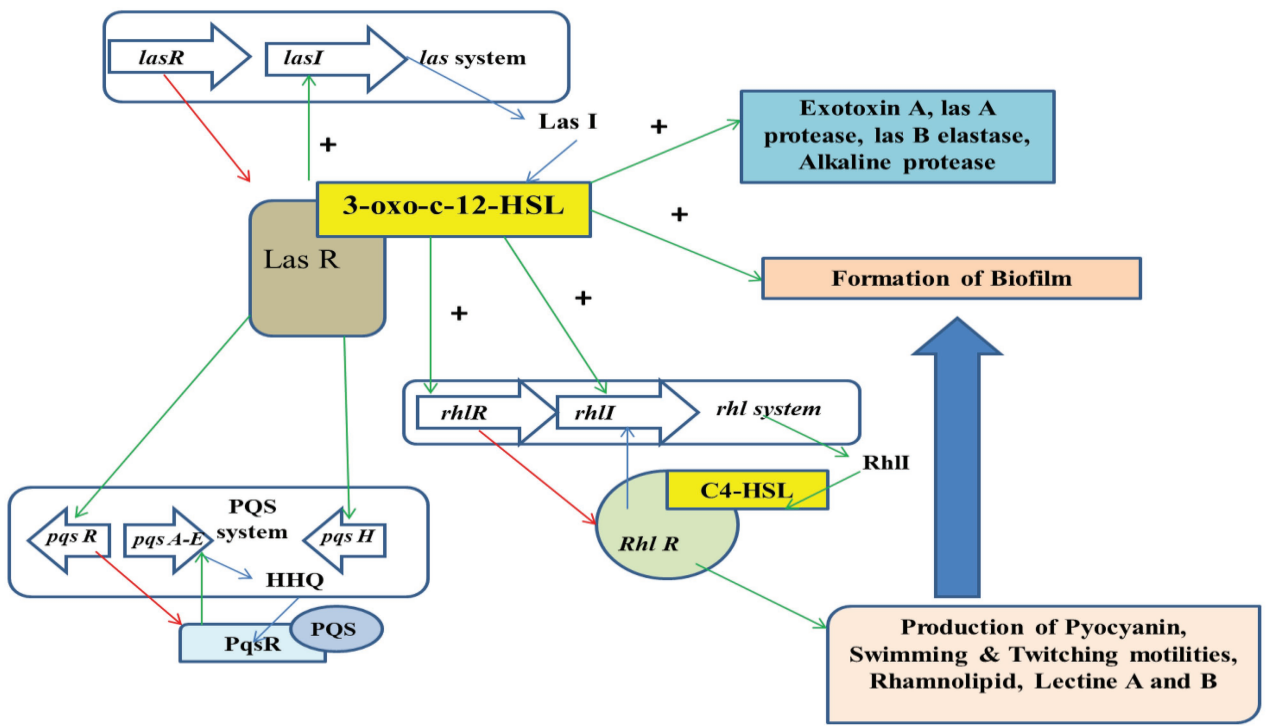

FIGURE 2 | Regulation of the mechanism of QS.

MECHANISM OF INHIBITION OF QUORUM SENSING BY MICRO BIOGENIC NPS

Information pertaining to the inhibition in the mechanism of QS by NPs are very limited as only a few studies have been performed; this therefore remains a somewhat underexplored field despite being interesting. NPs act as potent inhibitors of QS by affecting the mechanism of cell-cell communication or inhibition of the signals associated with the mechanism of QS, thereby hindering the synthesis of various types of the signaling molecules and preventing the formation of molecule-receptor complex. This in turn stops the signal transduction cascade (Sadekuzzaman et al., 2015) Silver nanoparticles (AgNPs) have been used as QQ agents due to their strong antimicrobial activity (Castellano et al., 2007; Chen and Schluesener, 2008).

The scientific communities have shown their interest in the use of AgNPs due to their broad range of antimicrobial activities (Kim et al., 2007; Lara et al., 2011; Brandt et al., 2012) and the convenience during application for their physico-chemical properties and surface area to volume ratio (Kim et al., 2007; **Figure 3**). Various other types of NPs, like AuNPs, TiO_2, SiO_2, and ZnO, from microbial sources possess the efficacy of inhibiting the QS cascade and thus inhibit the formation of the biofilm (Shah et al., 2008; Samanta et al., 2017; Al-Shabib et al., 2018).

NP-ASSOCIATED INHIBITION OF QUORUM SENSING CASCADE

The growth of the sessile communities of bacteria within the biofilm can only be checked by quorum sensing (QS), a bacterial cellular communication system that is a non-cytotoxic process (Høiby et al., 2010). The success in the treatment of any kind of chronic infections is devising an efficient mechanism of delivering the drug molecules up to the target cells. NPs have played a pivotal role in the mechanism of inhibiting the process of QS, and thus could inhibit biofilm formation.

The nano materials possess dimensions at the scale of nanometers possessing chemical and physical properties different from that of the bulk materials (Wang et al., 2017a). NPs are proven to be the most accepted drug delivering vehicle, possessing the ability to inhibit the growth of the microbial cells and thus can fight against pathogenic organisms. NPs show various mechanisms pertaining to the inhibition of biofilm and microbial growth. Various studies were conducted to predict the probable inhibition mechanism of microbial growth by the NPs. It was observed that ZnO NP has the ability of inhibiting the NorA efflux pump present in *S. aureus* (Banoee et al., 2010). It has been further observed ZnO NP, along with the antibiotic ciprofloxacin, could enhance the zone of inhibition by 22–27% of *E. coli* and *S. aureus*, respectively (Banoee et al., 2010). Studies also showed that iron oxide NPs coated with polyacrylic acid help in inhibiting *Mycobacterium smegmatis* by enhancing the efflux inhibition (Padwal et al., 2015).

INHIBITION OF QUORUM SENSING BY MICRO BIOGENIC SILVER NANOPARTICLES

The antimicrobial potential of AgNPs has made it an important therapeutic agent. But advancements in the era of antibiotics has resulted in the minimization of the use of silver (Castellano et al., 2007; Li et al., 2009). The presence of wide spectrum antimicrobial activities by AgNPs due to its high surface area to volume ratio has been a key factor in its success (Kim et al., 2007; Lara et al., 2011; Brandt et al., 2012). Various studies have been conducted that showed that silver composites and silver have significant roles as antimicrobial agents (Panáček

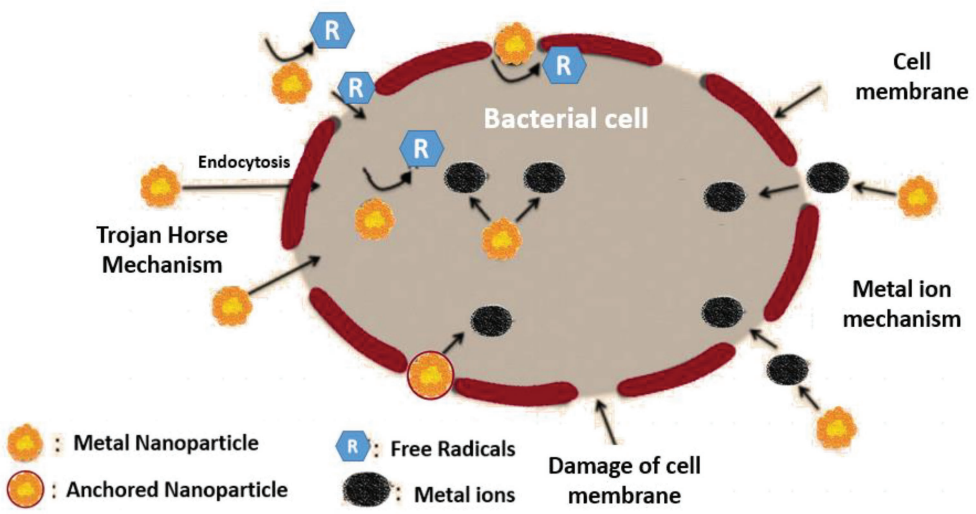

FIGURE 3 | Mechanism of NPs to bring about damage to the bacterial cells.

et al., 2006; Naik et al., 2013). AgNPs also act as potent bactericidal agents against *S. aureus*, *P. aeruginosa*, and *E. coli* (Khurana et al., 2016). Literature has shown that AgNPs can be used as potent anti-QS agents, thus hindering the formation of the biofilm and production of violacein by *C. violaceium* (Jagtap and Priolkar, 2013). It has been further observed that green-synthesized NPs played a key role in controlling infections associated with microbes. Studies have revealed that Ag NPs have the potentiality of blocking the synthesis of signaling molecules by inhibiting LasI/Rhl I synthase. Ag NPs had the potential of inhibiting the QS of *P. aeruginosa* (Ali et al., 2017). In-silico studies comprising of molecular docking revealed that Ag NPs have the potency of locking the active sites of various proteins comprising of LasI or RhlI synthase along with their surrounding residues being present. Ag NPs effectively block the active sites and thus efficiently inhibit the mechanism of QS. Ag NPs possess the ability of inhibiting the QS-genes by blocking the transcriptional regulatory proteins which inactivates the LasR or RhlR system. Ag NPs also possess the ability to act effectively as anti-QS agents by inhibiting signaling molecules like LasI and RhlI. Studies have also shown that micro-fabricated forms of Ag NPs synthesized from *Rhizopus arrhizus* metabolites inhibit the QS mechanism of *P. aeruginosa* (Singh et al., 2015b). It was observed that micro fabricated Ag NPs were able to bring about a marked reduction in the production of signaling molecules at a concentration of 0-25 μg/ml. It was further observed that these micro-fabricated NPs were able to bring about a reduction of 79–84% of *lasA* and *lasB* genes' expression and down regulated these genes. The expression of the targeted QS genes, like *lasA*, *lasB*, *lasI*, *lasR*, *rhlI*, *rhlR*, *rhlA*, *phzA1*, and *fabH2*, is activated by the AHL-LasR complex. The down regulation of the QS genes was achieved by the myco-fabricated Ag NPs. Its mechanism against various virulence factors such as LasB ealastase, LasA protease, rhamnolipid, and pyocyanin occurred *via* phzA1, rhlA, and lasAB operons. The production of AHL is enhanced by *rhlR* via and the signal cell receptor RhlR. Similarly, RhlR is also associated with the activation of fabH2 and rhlAB operons. Thus myco-fabricated Ag NPs help in the down regulation of *rhlR* and thereby decrease the production of RhlR (Singh et al., 2015a; **Figure 4**).

INHIBITION OF QUORUM SENSING USING MICRO BIOGENIC GOLD NANOPARTICLES

In recent times, the use of Au NPs have attracted various researchers due to their catalytic properties that are largely used in the field of diagnostics and biologics (Mesbahi, 2010; Jain et al., 2012; Giasuddin et al., 2013). The wide applicability of Au NPs is due to its simple mechanism of synthesis, convenience to use, and relatively low toxicity in comparison to the other types of nano materials in use (Capek, 2014). Au NPS showed efficient antimicrobial activity against various types of microbes like methicillin-resistant *S. aureus* (MRSA), *Salmonella typhi*, and *Bacillus Calmette-Gu'erin* (Zhao et al., 2010; Lima et al., 2013; Bindhu and Umadevi, 2014). Studies also revealed that

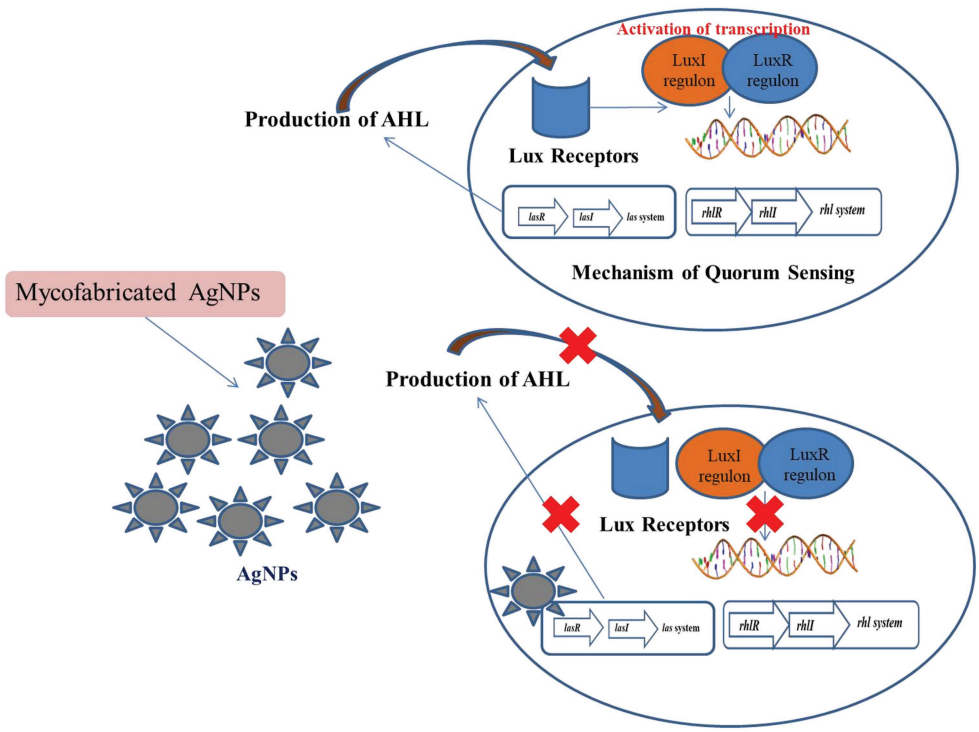

FIGURE 4 | Mechanism of inhibition of QS by myco-fabricated Ag NPs.

acyl homoserine lactone lactonase protein associated with An NP help in inhibiting QS of *Proteus* sp. (Vinoj et al., 2015). These NPs were also able to degrade N-hexanoyl-L-homoserine lactone with the help of N-acyl homoserine lactonase that was present on the surface of the NPs. The enzyme also helps in degrading the moiety associated with acyl homoserine lactone and brings about the conformational changes of the signaling molecule, thus preventing the binding with LuxR transcriptional regulator resulting in the inhibition of QS (Kaufmann et al., 2005; Bai et al., 2008). They were also able to inhibit the metabolic activities and production of EPS, preventing the formation of biofilm and changing the hydrophobicity of the bacterial cells (Samanta et al., 2017). The Au NP produced from the mycelium of *Laccaria fraternal* was responsible for stabilizing the NPs which in turn plays an important role in the reduction of pyocyanin production from *P. aeruginosa* (Samanta et al., 2017).

INHIBITION OF QUORUM SENSING BY MICRO BIOGENIC TITANIUM DIOXIDE NPS

Titanium dioxide NPs possess the ability of inhibiting QS and also have a wide range of activities that includes photo catalysis of organic dyes, usage within the photochromic appliances, gas sensors, dye sensitized solar cells, and antimicrobial activities (Banerjee, 2011). It has been observed that TiO_2NPs in the presence of UV rays produce super-oxides that help in inhibiting the growth of MRSA (Shah et al., 2008). These NPs possess the ability to oxidize the organic substances that are present within the bacterial cells and thus kill the cells (Fujishima et al., 2000; Cho et al., 2005; Shiraishi and Hirai, 2008). Experimental observations indicated that AgCl-TiO_2 NPs was an effective anti-quorum sensing compound against *C. violaceum* (Naik and Kowshik, 2014). It has also been found that the silver of Ag NPs can prevent the synthesis of violacein which can precisely block the mechanism of QS. Moreover, the inhibition of QS was observed in the absence of oxo-octanoyl homoserine lactone by AgCl-TiO_2 NPs.

INHIBITION OF QUORUM SENSING BY MICRO BIOGENIC SILICON OXIDE NPS

The mechanism of QS was also inhibited significantly using SiO_2 NPs which are found naturally in the form of quartz that is present as a major element within minerals, rocks, and sands. These NPs are widely used in biomedicines due to their small particle size and biocompatibility (Malvindi et al., 2012). These NPs are predominantly used in healthcare, chemical, cosmetics, composites, energy microelectronics, aerospace, pharmaceutical, and textile industries (Weiss et al., 2006; Santos et al., 2015). The ROS released by these NPs can also cause damage to DNA, resulting in the death of the cell. Hence, these are regarded as useful substances with antimicrobial activities (Tang and Cheng, 2013). NPs coated with various types of organic components were used to inhibit QS and treat resistant microorganisms by removing signaling molecules from the external environment. Research showed that NPs coated with β-cyclodextrin help in the inhibition of AHL-dependent QS of *V. fischeri* (Miller, 2015). The study showed that the presence of β-cyclodextrin associated with Si-NP helps in taking up the AHL-molecule from the environment and reduction in bio luminescence. It has been further observed that these NPs were also able to down regulate *LuxA* and *LuxR* genes.

INHIBITION OF QUORUM SENSING BY MICRO BIOGENIC ZNO NPS

ZnO NPs are used largely in the field of dentistry (Tomczak et al., 2009). These NPs possess the ability of utilizing proteins from the environment, thus bringing about inhibition of metabolism and cytotoxicity and hindering various cellular processes (Horie et al., 2009). They exhibit a potent antibacterial property by inhibiting bacterial growth and the adherence property of the cells, thus also preventing the formation of biofilm (Yamamoto, 2001; Brayner et al., 2006). Various research works have been performed that demonstrated the strength of ZnO NPs to act as a potent anti-QS agent. The inhibition of the QS mechanism greatly influenced the biofilm formation in a *P. aeruginosa* strain isolated from Cystic fibrosis (CF; García-Lara et al., 2015). These NPs possess the ability of down regulating the QS genes within the Gram-negative bacterial cells. Researchers showed that ZnO NPs were able to inhibit QS in *P. aeruginosa* by down regulating *lasR*. *lasI*, *rhl I*, and *rhl R* (Saleh et al., 2019). Another study showed that ZnO NPs were able to reduce the swimming and swarming motility within *P. aeruginosa* and also showed its efficacy against the *pqs* and *las* system of QS (Khan et al., 2020). ZnO NPs resulted in the efflux of the zinc cation efflux pump of czc operon and various other regulators of transcription such as type III repressor ptrA and porin gene opdT followed by the repression in the production of pyocyanin-associated phz operon. The ZnO NPs also possess the ability of enhancing membrane hydrophobicity in *P. aeruginosa* (Lee et al., 2014).

CONCLUSION

The bacterial cells possess the ability to sense their surrounding population by analyzing the production of auto inducers, known as quorum sensing. This mechanism also helps the bacterial cells to communicate with one another, resulting in the development of biofilm. The mode of action of QS inhibition is mainly *via* inhibition of signal generation, blockage of signal receptors, and disruption of QS signals. Currently, research is focused on finding ways to interrupt the process of bacterial QS using compounds of microbial origin. Microbial biofilm are increasingly causing medical-implant-associated infections. Thus, novel treatment strategies are urgently required for device-associated biofilms infections. The use of nano materials has emerged as a promising approach in preventing biofilm formation by destroying the exopolysaccharides (EPS) of the biofilm matrix and killing the bacteria. Key factors responsible for using

nanomaterials for biofilm treatment are their low cytotoxicity and novel mechanisms of action. Nanoparticles' toxicity strongly depends on their physicochemical properties such as shape, size, surface chemistry, structure, agglomeration state, and cell types in contact with the nano materials (Tran et al., 2020).

The few disadvantages involving microbial nanoparticle synthesis are the tedious purification steps and poor understanding of the mechanisms. Additionally, controlling the shape, size, and mono dispersity in the solution phase is a matter of concern. An important challenge is scaling up the production level processing for industrial applications. This includes addressing a few important issues such as selection of ideal bacteria depending on growth rate, enzyme activities, and biochemical pathways, selection of the biocatalyst state (bacterial enzymes) either of whole cells, crude enzymes, or purified enzymes that could increase the rate of reaction, and optimal conditions for cell growth and enzyme activity. Optimization is also needed for higher biomass synthesis, optimal reaction conditions for better removal of unwanted residual nutrients and metabolites, better extraction and purification processes (freeze-thawing, heating processes, and osmotic shock) of the nanoparticles, and better stabilization of the produced NPs without aggregation (Iravani, 2014).

Microbiologically-synthesized nanoparticles have emerged as a new agent that can be used to either down regulate the operon associated with quorum sensing proteins, or to enhance quorum-quenching activity to prevent biofilm formation. Although QS inhibition shows good potential for treatment of infections, further development and research are necessary to fully understand the mechanisms of action and suitability for clinical applications. Nanomaterial-based treatment methods are expected to continue developing more sophisticated or more complex mechanisms of destroying the EPS and killing the bacteria, although the need for future developments to prevent recurrence after biofilm treatment is still needed.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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frontiers in Microbiology

MINI REVIEW
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A Mini-Review on Lichen-Based Nanoparticles and Their Applications as Antimicrobial Agents

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Biological entities such as green plants, fungi, and lichens are now a days persistently explored for the synthesis of nanoparticles. Lichen-based nanoparticles are also becoming increasingly popular owing to their biocompatibility, eco-friendliness, and cost-effectiveness. The lichen-based metal nanomaterials, particularly synthesized using green chemistry approaches, have turned out to be great substitutes to conventional antimicrobial therapies. Many scientific reports established the significant antimicrobial properties exhibited by the lichen nanoparticles. Therefore, the present mini-review summarizes an overview of lichen-based nanomaterials, their synthesis, their applications, and the molecular mechanism of their potential as broad spectrum antimicrobial agents for biomedical applications.

Keywords: lichens, antimicrobial, nanoparticles, green synthesis, applications

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INTRODUCTION

Microbial pathogenesis is the cause of morbidity and mortality of millions across the globe annually. Soon after the discovery of the antibiotics, they were widely considered as an effective remedy against pathogens and rightly remained so, till the emergence of antibiotic resistance among the microorganisms (Martínez, 2008). However, the recent advancements in nanotechnology led to the development of nanoparticles that have established as potent broad-spectrum antimicrobial agents (Wang et al., 2017). The biosynthesis of nanoparticles through green synthesis method involves bioreduction of metals or metal oxide to their elemental forms with size ranging from 1 to 100 nm. Therefore, this process is gaining considerable attention for its eco-friendliness and cost-effectiveness (Mie et al., 2014; Hussain et al., 2016).

Lichens, the composite organisms that result from a symbiotic association between fungi and algae possess several bioactive compounds (Kambar et al., 2014) and as such have been researched thoroughly and are well known for their bioactivity against many pathogens. Lately, researchers have been exploring the possibilities of using lichens for synthesizing nanoparticles and further utilizing them as antimicrobial agents (Mie et al., 2014).

Many reports are available on the synthesis of nanoparticles from different types of lichens, namely, *Parmeliopsis ambigua*, *Punctelia subrudecta*, *Evernia mesomorpha*, and *Xanthoparmelia plitti* (Dasari et al., 2013); *Parmotrema praesorediosum* (Mie et al., 2014); *Cetraria islandica* (Yıldız et al., 2014; Baláž et al., 2020); *Ramalina dumeticola* (Din et al., 2015); *Acroscyphus* sp. and *Sticta* sp. (Debnath et al., 2016); *Parmelia perlata* (Leela and Anchana Devi, 2017); *Usnea longissima* (Siddiqi et al., 2018); *Parmotrema tinctorum* (Khandel et al., 2018); *Parmelia sulcata* (Gandhi et al., 2019); *Protoparmeliopsis muralis* (Alavi et al., 2019); *Ramalina sinensis* (Safarkar et al., 2020);

Cladonia rangiferina (Devasena et al., 2014; Rai and Gupta, 2019); *Pseudevernia furfuracea* and *Lobaria pulmonaria* (Goga et al., 2020); *Xanthoria elegans*, *Usnea antarctica*, and *Leptogium puberulum* (Baláž et al., 2020); and *Lecanora muralis* (Abdullah et al., 2020).

Nanoparticles derived from metals and their oxides such as silver, gold, titanium, cadmium, iron, zinc, and copper have reportedly been synthesized using many lichens (Mie et al., 2014; Çıplak et al., 2018; Bhat, 2018; Alavi et al., 2019; Gandhi et al., 2019). Many of these lichen-based nanoparticles have been reported to exhibit antimicrobial bioactivity against several bacteria and fungi, which could be attributed to their ability to disintegrate the microbial membrane, oxidation of various cellular components, and generation of hydroxyl radicals (Ruparelia et al., 2008; Marambio-Jones and Hoek, 2010). Therefore, the present review highlights the investigation about the utility of lichens as biological laboratories for the sustainable production of antimicrobial metallic nanoparticles.

LICHEN-DERIVED NANOPARTICLES: METHODOLOGIES AND APPROACHES

The biosynthesis of lichen-derived nanoparticles is gaining popularity these days: as the process does not involve use of any toxic chemicals, therefore, they can be safely used as pharmaceuticals (Kowalski et al., 2011). Researchers around the globe have been following different methodologies such as biomechanical and chemical solid-state synthesis for the synthesis of lichen-based nanoparticles (Baláž et al., 2020). Mie et al. (2014) reported the synthesis of silver nanoparticles by the reduction of silver nitrate using aqueous extract of the lichen *Parmotrema praesorediosum* as a reductant as well as a stabilizer. Nanoparticles were characterized by using ultraviolet (UV)–visible spectroscopy, electron microscopy, energy-dispersive spectroscopy (EDS), and X-ray diffraction (XRD) technique. The cubic structured nanoparticles exhibited an average particle size of 19 nm. Devasena et al. (2014) synthesized magnesium nanoparticles from *Cladonia rangiferina* with an average size of 23 nm. They used light scattering and UV spectroscopy for characterization of the nanoparticles. Din et al. (2015) successfully synthesized silver nanoparticles by the reduction of silver nitrate with the aqueous extract of the lichen *Ramalina dumeticola*. The synthesis of silver nanoparticles in the solution was confirmed by UV–visible spectroscopy at 433 nm. Their physical appearance was characterized by transmission electron microscopy (TEM) and XRD techniques, revealing a cubic shape with an average size of 13 nm. Debnath et al. (2016) reported the biogenic synthesis of gold nanoparticles from *Acroscyphus* sp. *and Sticta* sp. without the addition of any reducing and stabilizing agent. They were quasi-spherical and prismatic in shapes and characterized by UV–visible, Fourier transform infrared (FT-IR) spectroscopy, powder XRD, and TEM. Çıplak et al. (2018) prepared the lichen-reduced graphene oxide (LrGO) bimetallic nanoparticles nanocomposites (LrGO–AgAu) by using the one-pot approach with *Cetraria islandica*. The characterization of nanoparticles, so formed, was carried out using techniques such as TEM, scanning electron microscopy (SEM), XRD, and FT-IR.

Baláž et al. (2020) reported the solid-state mechanochemical synthesis of silver nanoparticles using lichens *Xanthoria elegans*, *C. islandica*, *Usnea antarctica*, and *Leptogium puberulum.* The method involved milling of lichen sample and silver nitrate together in a pulverisette. The milling process was accompanied by recording of XRD pattern, and after the process of milling was complete, the samples were stored in desiccators, and XRD patterns were recorded. TEM analysis and selected area diffraction (SAD) confirmed the formation of silver nanoparticles. Abdullah et al. (2020) used one-pot green synthesis method for the green synthesis of $ZnO/TiO_2/SiO_2$ and Fe_3O_4/SiO_2 nanoparticle composites using the lichen *Lecanora muralis*. XRD, SEM, EDS, and elemental mapping techniques revealed the fabrication of biosynthesized nanostructure. Safarkar et al. (2020) reported the synthesis of iron oxide nanoparticles from the extract of *Ramalina sinensis* by co-precipitation method. They confirmed the synthesis of nanoparticles by UV spectrophotometer, XRD, FT-IR, and field emission SEM–energy-dispersive X-ray spectrometry (FESEM-EDX). They reported the synthesis of spherical iron oxide nanoparticles with particle size ranging from 31.74 to 53.91 nm, which were observed using FESEM. The visible UV spectra obtained for the iron oxide nanoparticles showed peak in the range of 280–320 nm. The nanoparticles exhibited effective antimicrobial properties against *Staphylococcus aureus* and *Pseudomonas aeruginosa.* Goga et al. (2020) used *Pseudevernia furfuracea* and *Lobaria pulmonaria* to synthesize silver nanoparticles with an average size of 10 nm (while a few reached 100 nm) by using solid-state mechanochemical synthesis.

ANTIMICROBIAL NATURE OF LICHEN-DERIVED NANOPARTICLES

Lately, researchers have been making attempts to explore and report antimicrobial properties of the different types of lichen-based nanoparticles (**Table 1**). Mie et al. (2014) reported the antimicrobial activity of *Parmotrema praesorediosum*-derived silver nanoparticles against eight types of pathogenic bacteria including gram-positive and gram-negative bacteria. Their results showed that silver nanoparticles synthesized using *P. praesorediosum* have significant antibacterial activity against gram-negative bacteria. Siddiqi et al. (2018) reported antibacterial activity of *Usnea longissima*-derived silver nanoparticles against six gram-positive (*Staphylococcus aureus*, *Streptococcus mutans*, *Streptococcus pyrogenes*, *Streptococcus viridans*, *Corynebacterium diphtheriae*, and *Corynebacterium xerosis*) and three gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*). The nanoparticles exhibited significant bioactivity against *E. coli* and *K. pneumoniae*, but *S. mutans*, *C. diphtheriae*, and *P. aeruginosa* displayed resistance against them. Baláž et al. (2020) reported that silver

TABLE 1 | Characteristics and antimicrobial activity of Lichen Nanoparticles synthesized by different researchers.

S. No	Lichen	Type of NPs	Shape of NPs	Size of NPs (nm)	Activity exhibited against	References
1.	*Parmotrema pseudotinctorum* and *Ramalina hossei*	Ag NPs	Circular	100	Gram-negative bacteria: 1. *Salmonella typhi* 2. *Escherichia coli*	Kumar et al., 2010
2.	*Parmotrema praesorediosum*	Ag NPs	Cubical	19	Gram-positive bacteria: 1. *Staphylococcus epidermidis* 2. *Staphylococcus aureus* 3. *Bacillus subtilis* 4. *Streptococcus faecalis* Gram-negative bacteria: 1. *Proteus vulgaris* 2. *Pseudomonas aeruginosa* 3. *Serratia marcescens* 4. *Salmonella typhi*	Mie et al., 2014
3.	*Ramalina dumeticola*	Ag NPs	Cubical	13	Gram-positive bacteria: 1. *Staphylococcus epidermidis* 2. *Bacillus subtilis* 3. *Streptococcus faecalis* Gram-negative bacteria: 1. *Proteus vulgaris* 2. *Pseudomonas aeruginosa* 3. *Serratia marcescens* 4. *Salmonella typhi*	Din et al., 2015
4.	*Parmotrema clavuliferum*	Ag NPs	Spherical	106	Gram-positive bacteria: 1. *Bacillus subtilis* 2. *Streptococcus faecalis* 3. *Staphylococcus aureus* Gram-negative bacteria: 1. *Pseudomonas aeruginosa*	Alqahtani et al., 2017
5.	*Parmelia perlata*	Ag NPs	Spherical	–	Gram-positive bacteria: 1. *Staphylococcus aureus* 2. *Streptococcus spp.* Gram-negative bacteria: 1. *Escherichia coli* 2. *Klebsiella pneumoniae* 3. *Salmonella spp.* 4. *Pseudomonas aeruginosa* Fungi: 1. *Aspergillus niger* 2. *Candida albicans*	Leela and Anchana Devi, 2017
6.	*Usnea longissima*	Ag NPs	Spherical	9.40–11.23	Gram-positive bacteria: 1. *Staphylococcus aureus* 2. *Streptococcus mutans* 3. *Streptococcus pyrogenes* 4. *Streptococcus viridans* 5. *Corynebacterium xerosis* 6. *Corynebacterium diphtheriae* Gram-negative bacteria: 1. *Escherichia coli* 2. *Klebsiella pneumoniae* 3. *Pseudomonas aeruginosa*	Siddiqi et al., 2018

(Continued)

TABLE 1 | Continued

S. No	Lichen	Type of NPs	Shape of NPs	Size of NPs (nm)	Activity exhibited against	References
7.	*Protoparmeliopsis muralis*	Ag NPs Cu NPs	Spherical	Ag NPs – 44.87 Cu NPs – 34.38	Gram-positive bacteria: 1. *Staphylococcus aureus* Gram-negative bacteria: 1. *Escherichia coli* 2. *Pseudomonas aeruginosa*	Alavi et al., 2019
8.	*Heterodermia boryi Parmotrema stuppeum*	Ag NPs	Cubic	27.91–37.21 27.69–36.00	Gram-positive bacteria: 1. *Staphylococcus aureus* 2. *Viridans streptococci* Gram-negative bacteria: 1. *Acinetobacter baumannii* 2. *Escherichia coli* 3. *Klebsiella pneumoniae* 4. *Pseudomonas aeruginosa*	Senthil et al., 2019
9.	*Flavopunctelia flaventior* and *Xanthoria parietina*	Ag NPs	Spherical	69–145	Gram-positive bacteria: 1. *Staphylococcus aureus* Gram-negative bacteria: 1. *Escherichia coli* 2. *Pseudomonas aeruginosa*	Alqahtani et al., 2020
10.	*Xanthoria elegans, Cetraria islandica, Usnea antarctica,* and *Leptogium puberulum*	Ag NPs	Bimodal	5–100	Gram-positive bacteria: 1. *Staphylococcus aureus* Gram-negative bacteria: 1. *Escherichia coli*	Baláž et al., 2020
11.	*Pseudevernia furfuracea* and *Lobaria pulmonaria*	Ag NPs	Bimodal	Majority smaller – 10 Few reaching – 100	Gram-positive bacteria: 1. *Staphylococcus aureus* 2. *Listeria monocytogenes* 3. *Bacillus cereus* Gram-negative bacteria: 1. *Escherichia coli* 2. *Pseudomonas aeruginosa* 3. *Salmonella enterica*	Goga et al., 2020
12.	*Ramalina sinensis*	FeO NPs	Spherical	31.74 – 53.91	Gram-positive bacteria: 1. *Staphylococcus aureus* Gram-negative bacteria: 1. *Pseudomonas aeruginosa*	Safarkar et al., 2020

NPs, Nanoparticles.

nanoparticles produced using *Xanthoria elegans*, *Cetraria islandica*, *Usnea antarctica*, and *Leptogium puberulum* were excellent antibacterial agents against *E. coli* and *S. aureus*. Alavi et al. (2019) observed that *Protoparmeliopsis muralis*-driven metal (Ag and Cu) and metal oxide (TiO_2, ZnO, and Fe_3O_4) nanoparticles exhibited antibacterial, antibiofilm, antiquorum sensing, and antioxidant abilities against multidrug-resistant bacterium *S. aureus* and reference bacteria *E. coli* and *P. aeruginosa*. Abdullah et al. (2020) examined *Lecanora muralis*-driven nanocomposites of Fe_3O_4/SiO_2 and $ZnO/TiO_2/SiO_2$ for their antimicrobial and antifungal properties and reported that they exhibited good bioactivity against three species of pathogenic bacteria (*S. aureus*, *E. coli*, and *Pseudomonas* spp.) and five species of fungi (*Candida albicans*, *Candida* spp., *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus*).

MOLECULAR MECHANISM OF ANTIMICROBIAL PROPERTIES OF LICHEN-BASED NANOPARTICLES

The antimicrobial properties of lichen nanomaterials corroborate their ability to disintegrate microbial cellular barriers (cell wall and membranes), which enable them to penetrate the cytoplasm and disintegrate cellular components and genetic material, which eventually halt their metabolic function (**Figure 1**; Slavin et al., 2017). However, possible mechanisms

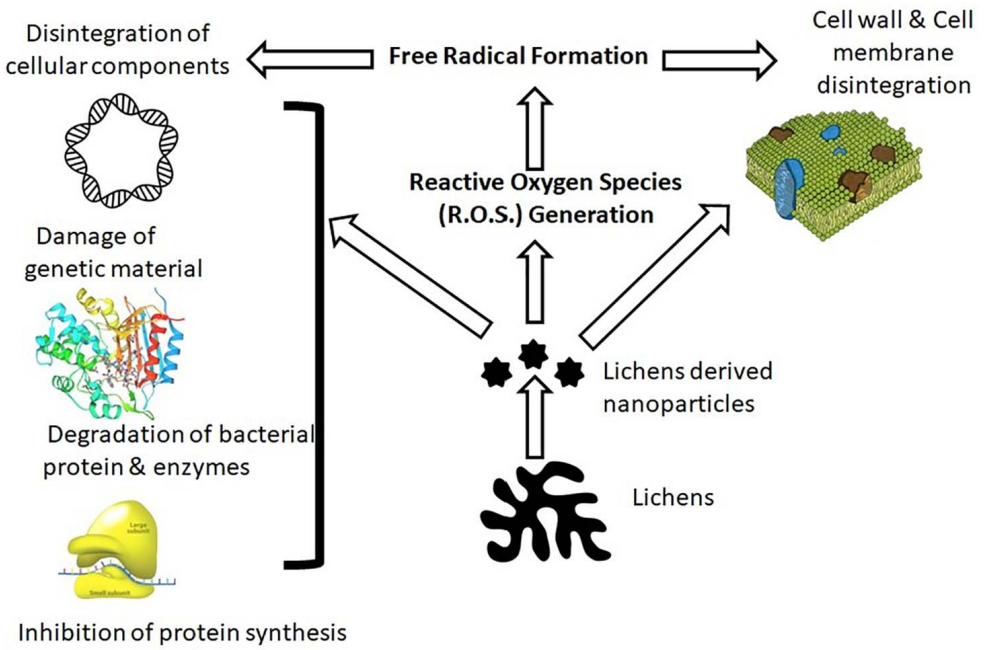

FIGURE 1 | Mechanism of action of lichen nanoparticles on bacteria.

of antibacterial activity of lichen nanoparticles have been proposed such as (i) interference during cell wall synthesis, (ii) cellular stress by reactive oxygen species (ROS), (iii) interference in protein synthesis, (iv) disruption of transcription process, (v) disruption of primary metabolic pathways, (vi) inculcation with genetic material, and (vii) alteration in cell signaling process (Dhand et al., 2016). However, studies highlight that the antimicrobial efficacy and molecular mechanism of lichen nanomaterials depend on (i) type of nanomaterial, (ii) shape and size, (iii) microbial membrane composition, and (iv) physicochemical condition (pH, temperature, presence of co-ions, biofilm formation, etc.) (Sánchez-López et al., 2020).

Siddiqi et al. (2018) demonstrated the antimicrobial property of *Usnea longissima*-driven silver nanoparticles through the denaturation of ribosomes that leads to the inactivation of enzymes and proteins, which ultimately stops their metabolic function and results in bacterial apoptosis. Alavi et al. (2019) critically investigated *Protoparmeliopsis muralis* lichen aqueous extract-assisted green synthesis of silver, copper, titanium oxide, zinc oxide, and iron oxide nanoparticles and their associated antibacterial properties. Total antioxidant capacity (TAC) and 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) antioxidant assay were used to determine the antioxidant property of *P. muralis* lichen. Results clearly indicated that the copper and silver nanoparticles show superior antioxidant and antimicrobial properties over other nanoparticles. Alqahtani et al. (2020) reported that *Xanthoria parietina*- and *Flavopunctelia flaventior*-based silver nanoparticles exhibited greater antibacterial activity against gram-negative bacteria as compared with gram-positive bacteria. This could be attributed to greater penetration of nanoparticles in gram-negative bacteria than that in gram-positive because of a thinner layer of peptidoglycan in the cell wall. Safarkar et al. (2020) reported antimicrobial properties of iron oxide nanoparticle synthesis from *Ramalina sinensis* extract. A study highlights potential antimicrobial efficacy of synthesized nanoparticles against gram-positive and gram-negative bacteria. Electrostatic interaction of positively charged iron nanomaterial and negatively charged bacterial cells may lead to oxidation of bacterial membranes by iron ions, inducing oxidative stress in microbial cells. Production of ROS in stressed microbial cell may further trigger free radical formation. Synthesized free radicals can degenerate various cellular components and may lead to cell death.

CONCLUSION

Lichen-mediated nanoparticles are reported as stable, cost-effective, and biocompatible, which make them an ideal candidate for antimicrobial agents. Owing to their unique physical and chemical properties, they exhibit efficacy against a wide spectrum of pathogenic microorganisms such as gram-positive and gram-negative strains of bacteria and some species of fungi. Cost-effectiveness and cellular toxicity are some key concerns that are required to be critically investigated before exploring their antimicrobial candidature widely in pharmaceuticals. The environmental fate of engineered lichen nanomaterials is another big challenge for the sustainable usage of nanotechnology for biological and environmental applications. Therefore, their green synthesis not only can reduce cost of

production but also can enhance the associated biocompatibility for living beings.

AUTHOR CONTRIBUTIONS

MB prepared the description plan of this review article. RR, SS, and BS carried out the manuscript writing and figure charting. All authors in the manuscript have contributed substantially in the writing of the manuscript and therefore approve it for publication.

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REVIEW
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The Emerging Trend of Bio-Engineering Approaches for Microbial Nanomaterial Synthesis and Its Applications

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Micro-organisms colonized the world before the multi-cellular organisms evolved. With the advent of microscopy, their existence became evident to the mankind and also the vast processes they regulate, that are in direct interest of the human beings. One such process that intrigued the researchers is the ability to grow in presence of toxic metals. The process seemed to be simple with the metal ions being sequestrated into the inclusion bodies or cell surfaces enabling the conversion into nontoxic nanostructures. However, the discovery of genome sequencing techniques highlighted the genetic makeup of these microbes as a quintessential aspect of these phenomena. The findings of metal resistance genes (MRG) in these microbes showed a rather complex regulation of these processes. Since most of these MRGs are plasmid encoded they can be transferred horizontally. With the discovery of nanoparticles and their many applications from polymer chemistry to drug delivery, the demand for innovative techniques of nanoparticle synthesis increased dramatically. It is now established that microbial synthesis of nanoparticles provides numerous advantages over the existing chemical methods. However, it is the explicit use of biotechnology, molecular biology, metabolic engineering, synthetic biology, and genetic engineering tools that revolutionized the world of microbial nanotechnology. Detailed study of the micro and even nanolevel assembly of microbial life also intrigued biologists and engineers to generate molecular motors that mimic bacterial flagellar motor. In this review, we highlight the importance and tremendous hidden potential of bio-engineering tools in exploiting the area of microbial nanoparticle synthesis. We also highlight the application oriented specific modulations that can be done in the stages involved in the synthesis of these nanoparticles. Finally, the role of these nanoparticles in the natural ecosystem is also addressed.

Keywords: nanoparticles, genetic engineering, bacteria, viruses, bacteriophages

INTRODUCTION

Nanotechnology is the branch of science that supports the designing and manipulation of organic and inorganic matter to the nanoscale levels (1–100 nm; Hussain and Hussain, 2015; Danish and Hussain, 2019). A large variety of nanoparticles (NPs) have found place in different sectors of the economy. However, these NPs are produced under extreme physico-chemical conditions, which pose a threat to the environment. Therefore, in order to prevent the associated toxicity, the green approaches for NPs synthesis using biological systems are emphasized.

The microbial bioprocessing is recently explored as an attractive alternative to chemical and physical fabrication of NPs. Microbial synthesis of NPs is an integration of nanotechnology with microbial biotechnology. Bacteria, archaebacteria, fungi, yeast, molds, microalgae, and viruses are being explored for synthesis of bioactive nanostructures with numerous industrial applications (Hulkoti and Taranath, 2014). The NPs produced by microbial biosynthesis and bioprocessing are mostly sustainable, eco-friendly, and cost-effective. However, the process of biosynthesis is time consuming and it is difficult to control the shape, size, and dispersity of the NPs. Several strategies have come up to overcome these limitations such as appropriate strain selection, development of genetically engineered microbes, optimization of microbial cultivation and extraction techniques, and combination approaches such as photo-biological methods (Bao et al., 2003; Mohammadian et al., 2007). A comparison between biological and non-biological synthesis of NPs is presented in **Figure 1**.

Specific microbial interactions with their surroundings lead to the production of bioactive NPs. The microbes residing in industrial and mining effluents have been found to recover metals from the discharged waste and converting them into nanostructures. Similarly, metal chelation in the form of NPs represents antagonistic interactions between rhizosphere associated microbes and pathogenic microbes (Gouda et al., 2019). The marine microbes are capable of forming exotic nanostructures by effective internalization of minerals from rich salty water by reduction/precipitation of toxic metal ions into non-toxic metallic nanoclusters to cause metal detoxification. The microbes are regarded as highly efficient eco-friendly nanofactories (Pimprikar et al., 2009; Li et al., 2011; Senapati et al., 2012; Gnanamoorthy et al., 2014; Manivasagan et al., 2016; Sánchez-López et al., 2020).

Metallic, non-metallic, and metal-oxide NPs are produced by the microbes, intracellularly or extracellularly, *via* enzymatic reduction process (Manivasagan et al., 2016). Marine bacteria,

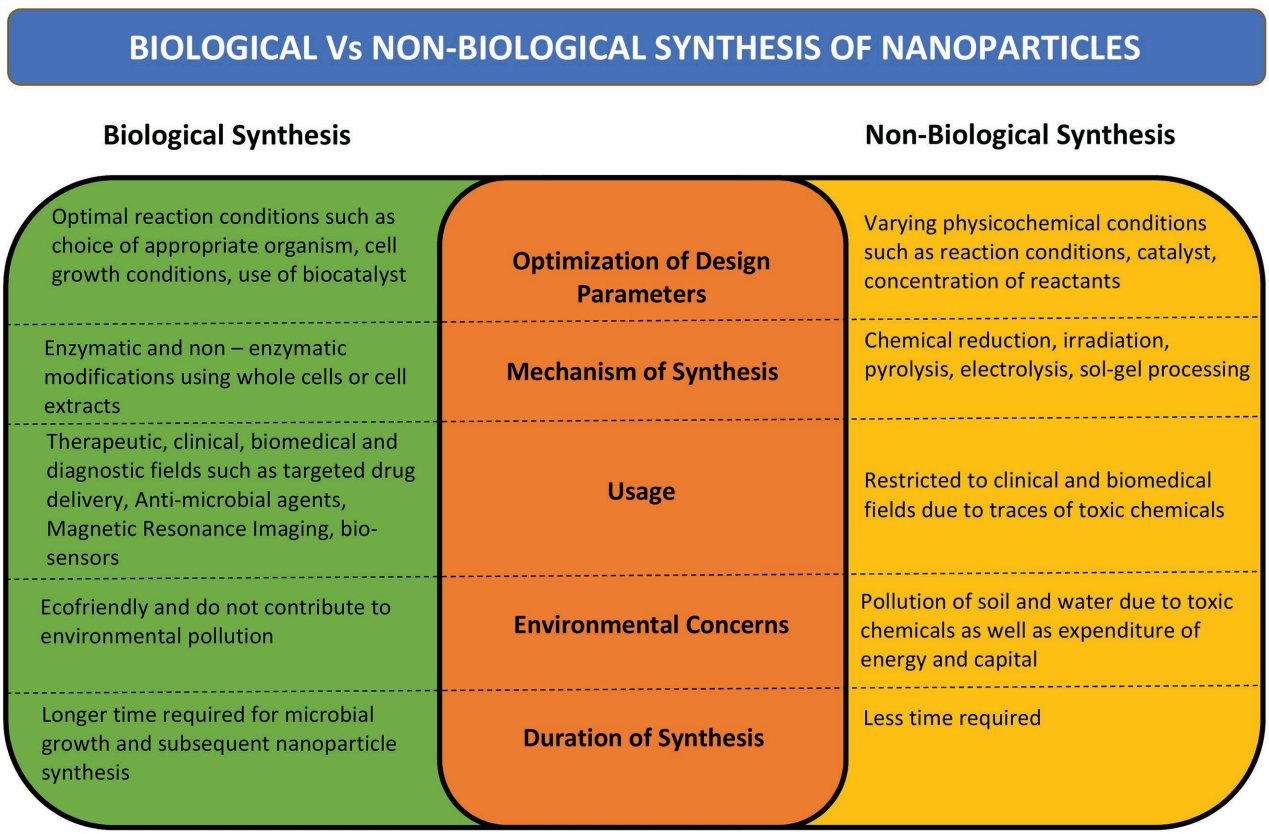

FIGURE 1 | Comparison between biological and non-biological methods of nanoparticle (NP) synthesis. Comparison has been done on the basis of mechanism of synthesis, design parameters, time required for synthesis, its desired uses, and effect on environment.

fungi, and microalgae have been found to synthesize metalic NPs by intracellular or extracellular pathways. The mechanism of microbial synthesis of NPs involves the reduction of positively charged metal ions trapped in the cytoplasm or on the cell wall to fine nuclei by the negatively charged biomolecules that helps in forming the nanostructures (Golinska et al., 2014). Several fungal and algal species have been observed to produce gold (Au) and silver (Ag) NPs when exposed to metal salts in the external medium. Around 38 species of brown algae, 23 species of red algae, 49 species of green algae, and 21 species of blue-green algae are known to produce nanoparticles with wide variety of applications (Chaudhary et al., 2020). Similarly, around 30 species of fungi producing Au and Ag nanoparticles have been observed (Khan et al., 2017). The site of NPs synthesis is specific to the species and may be produced intracellularly either on the surface of mycelia/plasma membrane (such as *Rhodococcus* spp., *Tetraselmis kochinensis*) or below the cell wall surface (*Verticillium* spp.; Mukherjee et al., 2001; Ahmad et al., 2003). Similarly, the extracellular synthesis of metallic nanoclusters involves the role of surface proteins or enzyme secretion. The role of extracellular secretion of nicotinamide adenine dinucleotide phosphate α-NADPH dependent nitrate reductase enzyme is well-documented in case of fungus *Fusarium oxysporum* and bacteria *Rhodopseudomonas* (Khandel and Shahi, 2018). Extracellular biosynthesis of Ag NPs of size 10–15 nm produced by *Escherichia coli* VM1 has anti-cancer potential (Maharani et al., 2016), while the zinc sulphide (ZnS) NPs produced by *Desulforibrio caledoiensis*, has photo-catalytic applications (Qi et al., 2013). Recently, lignin peroxidase enzyme has been reported to be associated with the synthesis of Au and selenium (Se) NPs from *Acinetobacter* spp. SW30 (Wadhwani et al., 2018). The stable Se nanorods of size ~200 nm have been prepared using *Pseudomonas alcaliphila* (Zhang et al., 2011). Different species of *Cyanobacteria* such as *Spirulina*, *Anabaena*, and *Calothrix* form Au, Ag, platinum (Pt), and palladium (Pd) NPs of different size. Amorphous Se NPs (10–80 nm) are formed by *Nostoc linckia* by selenite reduction involving thiol groups of cyanobacterial proteins (Rai et al., 2019). Besides bacteria, the enzymes present on cell surfaces of yeasts and molds can efficiently synthesize monodispersed metal-oxide NPs with well-defined morphology. Zhou et al. (2009) synthesized mesoporous magnetite (Fe_3O_4) particles using yeast cells. *Saccharomyces cerevisae* have been found to produce ~20 nm antimony trioxide (Sb_2O_3) and titanium dioxide (TiO_2) NPs. Other examples include zinc oxide (ZnO) NPs by *Aspergillus fumigatus* and *Candida albicans* (Zikalala et al., 2018). Microalgae have been reported to synthesize metal-oxide NPs by polysaccharides present in their cell walls. ZnO NPs are prepared by many species of algae such as *Sargassum muticum*, *Chlamydomonas reinhardtii*, and *Gracilaria gracilis* (Mahdavi et al., 2013). The mechanism of NP synthesis using microbial cells is shown in **Figure 2**.

Apart from NPs, the microbes are also capable of synthesizing unique nanostructures. Recently, the biosynthesis of 1-D

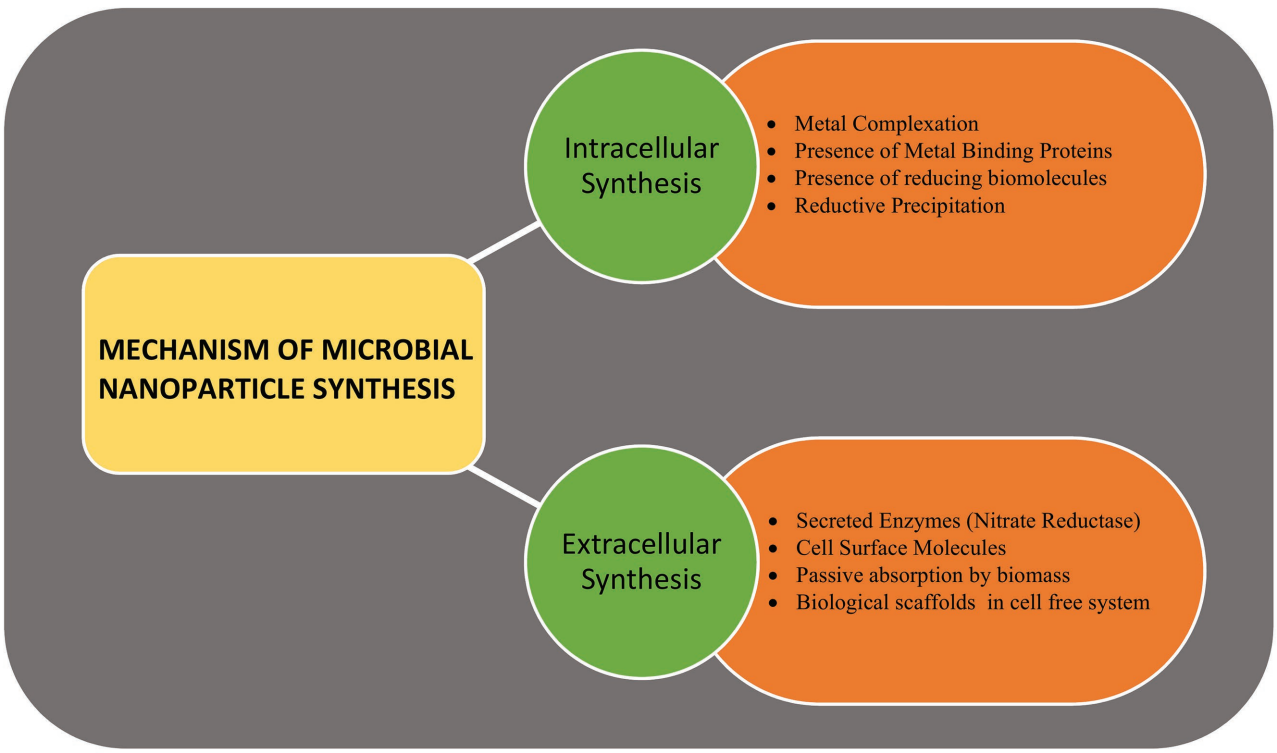

FIGURE 2 | The mechanism of microbial nanoparticle synthesis. The intracellular synthesis includes various enzymes, reducing molecules, chelating agents, and metal binding proteins present within the cell, while the extracellular synthesis involves secreted enzymes, surface enzymes, proteins, and reducing agents.

nanowires has generated considerable attention due to remarkable physico-chemical properties. Microbial nanowires refer to the filamentous appendages of metal-reducing bacteria in the genus *Geobacter*, which produces the conductive Type IV pili (T4P; Reguera, 2018). These nanowires play important role in the bioenergy strategies involving the transport of respiratory electrons to extracellular electron acceptors and, therefore, aids in species electron exchange (Malvankar et al., 2011; Kotloski and Gralnick, 2013). The microbial nanowire based electron transfer mechanism is one of the most significant systems in the microbial fuel cells (Lan et al., 2018), which are potential alternative to harvest energy from organic wastes by anaerobic digestion (Logan and Rabaey, 2012) and the nanodevices (Chen et al., 2010). This remarkable capacity of microbial nanowires is attributed to the assembly of micrometer-long polymers of the hexa-heme cytochrome OmcS in its nanowires (Wang et al., 2019). Bacterial biosynthesis of nanocellulose has opened up several avenues in biomedical research. It is present in the form of chains of 20–100 nm nanofibers in the exopolysachharides of bacterial cells (Klemm et al., 2011; Sivakumar et al., 2014). The critical issue of non-biodegradable nature of nanocellulose has been overcome by periodate oxidation to form dialdehyde nanocellulose (Li et al., 2009). The bio-cellulose derived from bacterial nanocellulose through culture cultivation finds broad applications in biomedical engineering such as stem cells/muscle cells based tissue engineering scaffolds (Lv et al., 2016), urethral reconstruction by nanocellulose seeded lingual keratinocytes (Huang et al., 2015), and antimicrobial wound dressings (Kim et al., 2015). The nanomaterials synthesized by microbes are not only environment friendly but also have a well-defined chemical composition, size, and morphology that makes them a promising candidate for potential applications such as drug delivery, bio- and environmental sensors, antimicrobial agents, and imaging. The applications of NPs synthesized by microbes are depicted in **Figure 3**.

However, there remains major drawback in large scale application of biological synthesis of nanomaterials such as heterogeneity in size, shape, and lesser control over the physicochemical properties. Genetic engineering in combination with molecular biology and biotechnology approaches provide a highly innovative and powerful tool toward the revolutionary path of tailor made and application oriented fabrication of various nanostructures. This review article highlights the recent advances in microbial synthesis of nanomaterials and the impact of

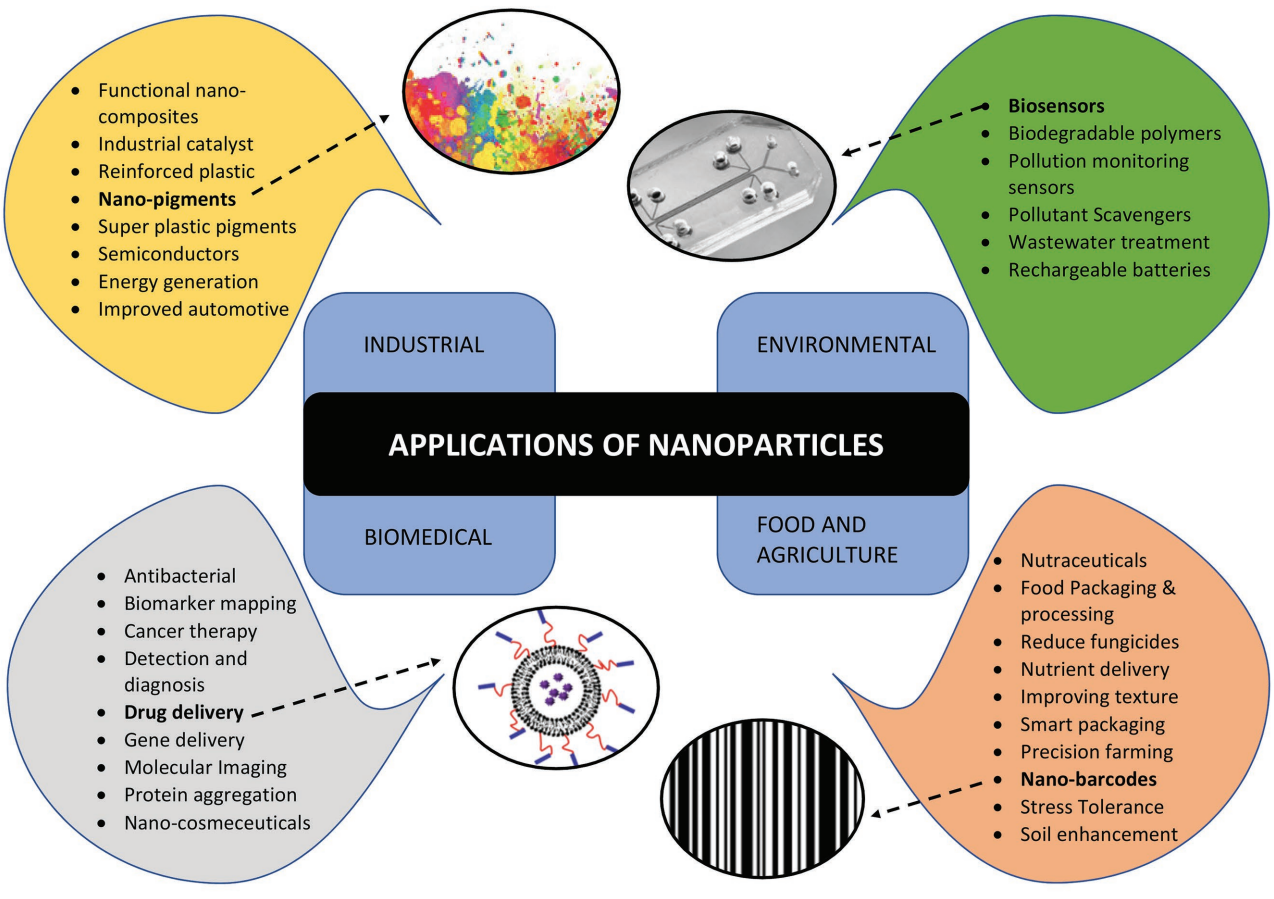

FIGURE 3 | Applications of nanoparticles in various areas such as industries, environment conservation, biomedical diagnostics and therapeutics, food and agriculture highlighting various sub areas of each.

bio-engineering approaches in directing tailor made synthesis of NPs for diverse applications. It also highlights the hidden potential of polymicrobial communities or biofilms in both synthesizing and stabilizing the NPs. Additionally, the review also highlights the use of less common microbes such as protozoa and archaea in the synthesis of NPs. Finally, the review emphasizes on the effect of these NPs on the ecosystem and the necessity of regulatory bodies to closely monitor the usage and disposal of such NPs from the industries and research laboratories. Thus, it provides a detailed compilation of various aspects of nanobiotechnology which has not been covered elsewhere.

BACTERIAL SYNTHESIS OF NPs

Bacteria are prokaryotic microorganisms which are found in the different kinds of environmental conditions such as in the varying range of salinity, temperatures, alkaline, and acidic environments. They are unicellular, forming 50% of the biomass of the aquatic habitats. NPs synthesized using bacteria have been implicated in the fabrication of new materials for biomedical and health care purposes (Schrofel et al., 2014; Fariq et al., 2017). This approach of NP synthesis is more reliable, eco-friendly, and non-toxic (Mohanpuria et al., 2008).

Magnetotactic bacteria are capable of synthesizing the magnetite nanocrystals *via* phospholipid membrane bound vesicles called magnetosomes (Li et al., 2007). The metal ions are transported into the magnetosome vesicles and reduced by the reductase enzymes on cell surface followed by transportation into the phospholipid membrane (Philipse and Maas, 2002). However, the number of such NPs is very limited. Therefore, the researchers use another strategy of inducing the microbes to synthesize different metal oxide NPs during bioremediation of metal ion toxicity (Jayaseelan et al., 2012). Bacteria-induced ZnO and TiO_2 NPs have been synthesized using *Rhodococcus* spp. and *Lactobacillus* cell culture solution, respectively (Jha et al., 2009; Kundu et al., 2014). *Pseudomonas aeruginosa* SM1 has been found to synthesize NPs from various metal ions without the need for growth media, stabilizing agent, pH optimization, and presence of electron donor. This strain can synthesize the NPs at both intracellular locations [cobalt (CO) and lithium (Li)] and extracellular locations [silver, palladium, iron, rhodium, nickel, ruthenium, and platinum (Ag, Pd, Fe, Rh, Ni, Ru, and Pt)] in crystalline as well as amorphous state at room temperature (Srivastava and Constanti, 2012). Other researchers reported the intracellular synthesis of the microscopic Au, Ag, and Au-Ag alloy crystals when *Lactobacillus* strain is mixed with high concentrations of each metal ion. The bacteria produced these NPs intracellularly, and the cells were able to maintain their viability even after crystal growth. Transmission electron microscopy (TEM) was used to examine crystallites of 100–300 nm covering the periplasmic space of the bacteria (Nair and Pradeep, 2002).

pH plays an important role in determining the size and shape of the NPs. The bacterium *Shewanella algae* was used for the production of Au NPs by using H_2 as an electron donor under different pH conditions (Konishi et al., 2007). Au NPs of 10–20 nm were synthesized in the intermembrane space of *S. algae* cells at pH 7, whereas large sized NPs 50–500 nm were precipitated out of the cell. However, this species has also been reported as marine pathogen from squamous cell carcinoma patient (Sumathi et al., 2014). In a similar study, the bacteria *Rhodopseudomonas capsulate* was used to synthesize Au NPs of different shapes and sizes under a range of pH 4–7 (He et al., 2007). So, these studies indicate the pH specific control over the size and deposition locations of Au NPs. Spherical shaped NPs from 10 to 20 nm were formed at diluted concentration of tetrachloroaurate ($AuCl_4$) at pH 6. However, Au nanowires were produced at increasing concentrations of $AuCl_4$ at the constant pH. It was observed that when pH changed to 4, both triangular and spherical shaped NPs were formed at diluted concentrations of salt (Husseiny et al., 2007). The types of nanomaterials used for the purpose of bioremediation, the nature of interactions between NPs and metal(s), and the factors affecting these interactions are highlighted in **Figure 4**.

When two metals are combined together, they form a single bimetallic nanoparticle which provides the potential physical stability and exceptional magnetic, optical, and catalytic properties in comparison to single metallic particles. For instance, it is believed that if Pt is combined with a noble metal, it enhances the catalytic activity of the Pt group metal. Therefore, this integration is useful for different noble applications. However, very few evidences are available for such bimetallic NPs.

BIOACCUMULATION OF NPs WITHIN PHYTOPLANKTON AND ITS ROLE IN BIOREMEDIATION

Phytoplankton are photosynthetic components of the aquatic grazer food chain. They are primary food source for zooplankton (Dhanker et al., 2012, 2013). However, chemicals secreted by many phytoplankton species for their self-defense play important role in shaping the population of grazers such as copepods (Dhanker et al., 2015). They can accumulate large levels of heavy metals inside them and can convert them into suitable nanostructures. This ability has found tremendous applications in the area of bioremediation that involves cleaning of polluted sites using various strategies. However, these NPs also cause serious damage to the phytoplankton depending on their concentration, size, shape, and type of metal involved. Therefore, suitable research approaches are needed to use algae for the purpose of bioremediation while keeping them intact and viable.

Algal mineralization has been recently explored in nanotechnology. Nanostructures have been synthesized either using live algal cells, cell free supernatant, or bioactive molecules extracted form cells. Ag NPs have been synthesized using live cells of algae belonging to Chlorophyta, Ochrophyta, Haptophyta, and *Spirulina* (Merin et al., 2010; Mohseniazar et al., 2011; Dahoumane et al., 2012; Rösken et al., 2014). This method has also been applied for the synthesis of bimetal Au-Ag alloy NPs (Dahoumane et al., 2014). In other study, cell free extract of *Euglena* spp. has been applied for the accumulation of Ag NPs (Li et al., 2015b). *Chlorella vulgaris*, when exposed to Ag salts for nearly 4 h, accumulated 1,200–3,300 μg/g dry weight of Ag NPs. Additionally, using the

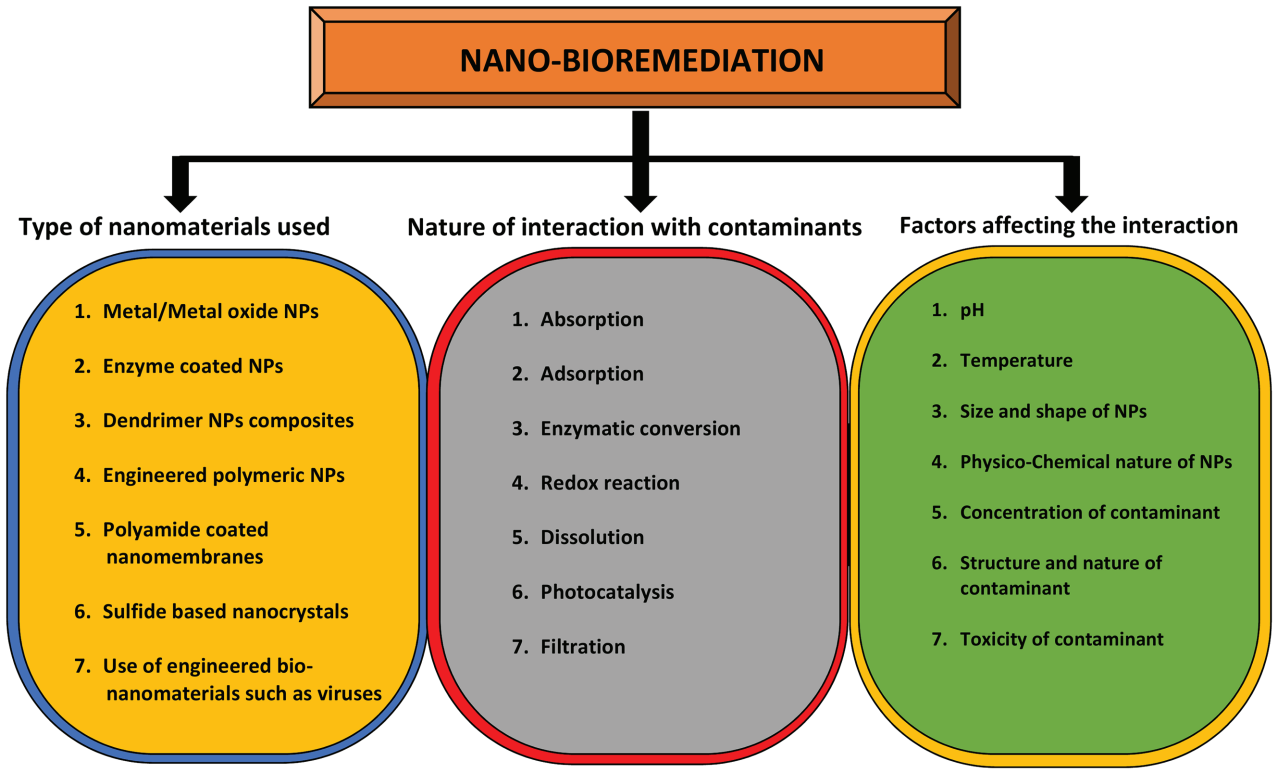

FIGURE 4 | Role of nanomaterials in bioremediation and factors affecting it. The **yellow circle** indicates the types of nanomaterials that can be used for bioremediation purposes while the **gray circle** enlists the types of interactions between nanomaterials and contaminants. The outcome of this interaction depends on various factors as mentioned in **green circle**.

same system, *Raphiodocelis subcapitata* accumulated 45.0 μg/g dry weight of Ag NPs even after exposure for 24 h. This difference in absorption ability is due to exposure time, concentration of Ag ions, reducing conditions, and algal species involved (Ribeiro et al., 2015).

Members of the class Phaeophyceae, Chlorophyceae, Rhodophyceae, and Cyanophyceae have been widely explored for the synthesis of metallic NPs *via* intracellular or extracellular routes. Algae have rich source of antioxidants, pigments, terpenoids, amines, and alkaloids also known as the bioactive compounds that are shown to act as reducing agents favoring the synthesis of metal nanostructures (Asmathunisha and Kathiresan, 2013). The polyols and amides present in *C. vulgaris* have been shown to reduce the Pd salts to accumulate Pd NPs (Arsiya et al., 2017). Similarly, 10 different chemical constituents present in the extracts of *Galaxura elongata* such as glutamic acid, stearic acid among others has been shown to be involved in the synthesis of Au NPs (Abdel-Raouf et al., 2017). The siliceous diatoms have a large surface area and are readily functionalized for potential applications in enzyme immobilization (Gnanamoorthy et al., 2014; Kong et al., 2018). Cells of microalgae are interlocked by a shell of intertwined structures of calcium carbonate ($CaCO_3$), derived from specialized intracellular vesicles and water-soluble acidic polysaccharides, called coccoliths. *Emiliania huxleyi*, is a dominant coccolithophore used as a source of mineralized material for nanotechnology applications such as nano-fluidics (Skeffington and Scheffel, 2018). The coccoliths are characterized by tightly controlled crystal growth and nucleation. Therefore, nanodevices constructed using coccoliths have potential applications in advanced electronics, environmental sensing systems, and drug delivery. Molecules may be selectively encapsulated in hollow funnel and tube shaped nanoscale pores of *Discosphaera tubifera*, *Pontosphaera japonica*, and *Michaelsarsia elegans* (Haywood et al., 2015).

The accumulation of NPs in algae depends on the initial concentration of NPs in the water. It is observed that the absorption process is much faster in the initial stage, but the absorption rate is gradually reduced as it reaches to saturation point (Harja et al., 2015). There is a significant difference in the amount of NPs absorbed by algae from water with a change of pH of the solution. Thus, the range of strong acidic pH increases the absorption possibilities of NPs by algae reasonably (Vijayaraghavan et al., 2011). Other factors are algae size, algal biomass, physicochemical properties, and dose of NPs which influence the absorption capacities of different algal species to NPs (Esmaeili and Beni, 2015).

Due to their capacity to accumulate large amounts of NPs, various types of algae are being used for the process of bioremediation. However, various studies showed that NPs interact with various cellular sites within the algae, to interrupt

with their normal functioning. The interaction of NPs with plasma membrane disrupts the arrangement of its basic components and releases enzyme lactate dehydrogenase into the cell cytoplasm. This may be one of the cell death mechanisms *via* inducing oxidative stress response and disturbing the cell integrity (Bhuvaneshwari et al., 2015). The exposure to TiO_2 NPs induced oxidative stress response pathway in *Anabaena variabilis* damaging the cell membrane (Cherchi et al., 2011). In another study, NPs were found to loosen the bonding between the cellular components and enhancing the membrane permeability, leading to the entry of NPs within the cells (Pal et al., 2007). Furthermore, the damaging effects of NPs have been observed on the chloroplast evident by the disruption of the thylakoid lamellae (Hu et al., 2014). Exposure to the nanotubes in high doses cause swelling in endoplasmic reticulum (Jia et al., 2005). NPs can affect the function of mitochondria which in turn influence the metabolic activities of algal cells (Zhao et al., 2016). Further, NPs cause clumping of the chromatin adjacent to nuclear membrane leading to nuclear dysfunctioning in *Acidophila* (Melegari et al., 2013; Bhuvaneshwari et al., 2015).

Production of reactive oxygen species (ROS) by NPs is another mechanism of toxicity as ROS oxidizes numerous biomolecules such as proteins, lipids, nucleic acids, and carbohydrates leading to loss of function (Larguinho et al., 2014). It also induces gene mutations and oxidative stress response inside the recipient cells while inhibiting cellular enzymatic activities (Melegari et al., 2013). The accumulation of NPs on the surface of algal cells leads to what is known as the shading effect, which perturbs the light absorption capacity of the photosynthetic apparatus (Perreault et al., 2012; Li et al., 2015a; Chen et al., 2018). Aluminium oxide (Al_2O_3) NPs have been found to reduce the content of chlorophyll in *Chlorella* spp. and *Scenedesmus* spp. (Sadiq et al., 2011). It has also been demonstrated that silicon dioxide (SiO_2) NPs affect the photosynthesis process in *Scenedesmus* spp., by reducing the content of chlorophyll a and b without affecting the carotenoid content (Wei et al., 2010).

MYCOGENIC SYNTHESIS OF NPs

Fungi are the eukaryotic heterotrophs with a typical decomposing food habit. They can be unicellular such as yeasts which are shown to synthesize NPs with semiconducting property (Roy et al., 2015; Venkat-Kumar et al., 2019). The multicellular fungi are known as molds which produce filamentous hyphae. The increasing role of fungi in nanobiotechnology has attracted the worldwide attention to synthesize green metallic NPs (Alghuthaymi et al., 2015; Moghaddam et al., 2015). Mycogenic synthesis of NPs is generally preferable due to advantages such as easy handling, less nutritional demands, huge biomass production, better yield, high tolerance, and non-pathogenicity for human use (Dar et al., 2013; Ahluwalia et al., 2014). Extracellular production of fungal metallic NPs has been studied in detail in the last few decades (Castro-Longoria et al., 2011; Devi and Joshi, 2012; Castro et al., 2014; Mishra et al., 2014). Many yeast species have been found to synthesize Ag NPs having antifungal activity (Calvo et al., 2010; Eugenio et al., 2016). The Ag-Au alloy NPs produced by yeast cells have shown promising application in the synthesis of electrochemical sensors for the detection of paracetamol and vanillin (Zheng et al., 2010; Wei, 2017). The Pd NPs synthesized using the extracts of *S. cerevisiae* are shown to be useful in the photo catalytic degradation of azo dye used in textile industries (Sriramulu and Sumathi, 2018). The nitrate reductase enzyme produced by certain yeast and fungi species have been reported for the production of NPs. *Fusarium oxysporium* strains produce Ag NPs by reduction of Ag^+ ions, using species-specific nitrate reductase enzymes (Duran et al., 2005). Fernandez et al. (2016) utilized the nitrate reductase activity present in the cell free supernatant of the culture of *Cryptococcus laurentii* and *Rhodotorula glutinis* to synthesize Ag NPs. They found a direct correlation between the concentration of NPs and the nitrate reductase enzyme activity.

The cell wall of fungi plays an important role in the reduction of metal ions during intracellular production of NPs (Sastry et al., 2003). In brief, the metal ions present in the medium are trapped on the fungal cell surface due to electrostatic attraction by the wall enzymes, followed by the enzymatic reduction leading to the formation of NPs. The psychrotrophic marine strain of the *Yarrowia lipolytica* was analyzed for the production of cell-associated Ag and Au NPs in the presence of metallic salts (Agnihotri et al., 2009). However, the extraction of cell-associated NPs becomes difficult. Therefore, the cell associated biopolymer melanin was isolated from the cell free culture of *Y. lipolytica* and employed for the synthesis of highly stable free form of Ag NPs having antibacterial activity (Apte et al., 2013). The proteins present in the fungal extract get adsorbed on the surface, thereby enhancing the colloidal stability of the Ag NPs (Du et al., 2015). Ag NPs synthesized by *R. glutinis* and *Rhodotorula mucilaginosa* were found effective in degrading the highly toxic chemical pollutants such as methylene blue (MB) and 4-nitrophenol (4-NP; Vidhu and Philip, 2014; Cunha et al., 2018).

The recent advancement in biological tools and techniques has been used by the researchers for the synthesis of improved metallic NPs. The engineered fungal and yeast cells prove to be more advantageous compared to the conventional physicochemical methods being eco-friendly, less toxic, cost effective, and production of monodisperse NPs. Recombinant fungi and yeast cells have been utilized for the biosynthesis of intracellular metallic NPs that are highly dispersed, stable, and safe (Siddiqi and Husen, 2016). Genetically modified metal resistant *Pichia pastoris* exhibiting the overexpression of *Mucor racemosus* cytochrome b5 reductase enzyme (Cyb5R) was successfully used as a reduction system for the synthesis and biosorption of intracellular Ag and Se nanoparticles (Elahian et al., 2017).

PROTOZOANS AS CELLULAR FACTORIES FOR NANOMATERIAL SYNTHESIS

In recent times, synthesis of NPs utilizing microbes have been explored to a great extent but little is known about

the use of protozoans as bio factories. Very few studies were reported so far showing the potential of protozoa in synthesizing metallic NPs. For instance, *Leishmania* sp. had been used for the synthesis of Ag and Au NPs. These NPs were found to be within the range of 10–100 and 50–100 nm scale, respectively (Ramezani et al., 2012). Currently, Ag NPs are being synthesized utilizing *Pseudomonas* strain related with the antarctic psychrophilic protozoon *Euplotes focardii* (John et al., 2020). In another study, *Tetrahymena thermophila* SB210 was used for *in vivo* synthesis of nano-Se within the range of 50–500 nm scale (Cui et al., 2016). Recently, calcite skeletal structures of marine protozoa foraminifera have been used for the synthesis of magnetic nanocomposites. This is, the first report of bionic synthesis of nanocomposites using the natural biomineralization pathway (Magnabosco et al., 2019). Other studies have reported the biosynthesis of QDs by *Tetrahymena pyriformis*. The synthesized nanomaterial was found to be around 8.27 nm in diameter and emitted yellow fluorescence, characteristic of metal ion Cd^{2+} (Cui et al., 2019). Furthermore, cell-free exudates of the ciliated protozoan *T. thermophila* were used to convert silver nitrate ($AgNO_3$) to Ag NPs under illumination with fluorescent tubes at ambient temperature (Juganson et al., 2013).

ARCHAEA FOR THE SYNTHESIS OF NPs

Archaea are the single celled prokaryotes inhabiting in a broader range of habitats. They include both extremophiles and non-extremophiles living in moderate conditions as well as in presence of extremes of pH, temperature, and salt concentration. Thus, they inhabit various places such as soil, deep oceans, marshlands, animal intestine, hydrothermal vents, hot water springs, and dead sea (DeLong and Pace, 2001).

Heavy metal tolerance has been exhibited by many archaeal species such as *Sulfolobus Solfataricus* (Schelert et al., 2004, 2006), *Thermoplasma acidophilum* (Ruepp et al., 2000), *Ferroplasma acidarmanus* (Baker-Austin et al., 2007), and *Halobacterium* sp. (Ng et al., 2000). However, many of the extremophilic archaeal species are difficult to grow in laboratory due to limitations in mimicking the natural conditions in which they live. Recently, two halophilic archaea, *Haloferax* sp. and *Halogeometricum* sp. isolated from solar saltern have been shown to synthesize Ag and Se NPs, respectively. The mechanism of NP synthesis involves both intracellular and extracellular reduction of metal ions. These NPs show remarkable uniformity in size indicated by polydispersity indices and have antibacterial activity against variety of pathogens (Abdollahnia et al., 2020). In another study, *Halococcus salifodinae* BK3, a haloarchaea was used for the synthesis of Ag NPs using $AgNO_3$ salts. This intracellular mode of NP synthesis showed the role of NADPH-dependent nitrate reductase in metal tolerance, its reduction and synthesis of NPs (Srivastava et al., 2013). The similar group later showed the synthesis of Se NPs from sodium selenite (Na_2SeO_3) using another isolate *H. salifodinae* BK18. The mechanism of NP synthesis is similar to the one involved in the synthesis of Ag NPs using BK3 isolate (Srivastava et al., 2014). Another study involved the use of *Haloferax volcanii* in the synthesis of Au and Ag NPs with better antibacterial and catalytic properties (Costa et al., 2020). *Metallosphaera sedula*, an extreme thermoacidophilic archaeon which oxidizes metals during respiration have been used to synthesize tungsten nanostructures. These nanoscale metallo-organic complexes are formed between archaeal cells and tungsten polyoxometalate on which the archaea are grown. This process is accompanied with the accumulation of intracellular tungsten NPs consisting of cluster of atoms (Milojevic et al., 2019). The hyperthermophilic archaea, Thermococcales living in the hydrothermal deep sea vents produce Fe_3S_4 nanocrystals extracellularly using iron phosphate as the precursor. This process implicates a mechanism of carbon dioxide (CO_2) homeostasis in hydrothermal ecosystems as greigite is the major catalysts for CO_2 reduction (Gorlas et al., 2018). Another group of researchers used thermos-acidophilic archaea, *Sulfolobus tokadaii* for the reduction of Pd (II) to Pd (0) NPs in a redox reaction (Kitjanukit et al., 2019). In a latest study, mass scale production of superparamagnetic iron oxide (Fe_2O_3) NPs has been achieved using *Halobiforma* sp. N1 with better properties suited for localized hyperthermia therapy used in cancer treatment (Salem et al., 2021).

The self-assembly of the archaeal surface layer (S-layer) has been an area of extensive research. Using the S-layer from *Sulfolobus acidocaldarius* as a template, Pt NPs encapsulated within the dendrimers can be synthesized with excellent topochemical properties (Mark et al., 2006). The ferritin protein system of *Pyrococcus furiosus*, a hyperthermophilic archaeon encapsulates Ag NPs and have rather specific binding and nucleation sites for Ag(I), not observed in ferritin templates from other microbial systems (Kasyutich et al., 2010). The same ferritin template from *P. furiosus* has been recently implicated in the synthesis of Au and Pd NPs with detergent modified enzymatic activities (Peskova et al., 2019). This protein based template represents an excellent platform for the bio fabrication of metallic NPs. In a rather interesting approach, the cells of *S. acidocaldarius* possessing only the outermost S-layer, termed as the cell ghosts, were successfully used for the fabrication of Au NPs. These NPs consisted exclusively of Au (0) NPs rather than a mixture of different oxidation states of Au metal with unusually strong paramagnetic properties (Selenska-Pobell et al., 2011).

VIRUSES AS SELF-ASSEMBLING NANOCONSTRUCTS

The ability of biological molecules such as proteins, viruses, and DNA to self-assemble in a solution is a promising approach for predesigned engineering nanostructures. These engineered nanostructures self-assemble to form functional nanoconstructs and are used in biomedicine field for the targeted drug delivery, vaccine preparation, gene therapy, bioimaging, tissue engineering, and specific cell targeting (Keum et al., 2011; Wu et al., 2013).

Viruses are nanosized entities consisting of a capsid, a protein shell enclosing a viral genome (Roos et al., 2010). They represent an intracellular self-assembling nanoconstruct and, therefore, have the potential to be used for the synthesis of engineered NPs. Several virus encoded proteins form stable nanoparticle configurations that self-assemble in infected host cells to wrap up the viral genetic material as a pre-imperative for propagation. However, non-replicating and non-infectious self-assembled viral nanoconstructs as prefabricated nano-scaffolds have been formed if scaffold proteins are assembled in the absence of viral genome (Lopez-Sagaseta et al., 2016).

This property of viral capsid to self-assemble around nucleic acid under physiological conditions, allows for alteration and modification in their structure to desirable nano-construct form. The basic principles involved in this process include alterations in the surface charge, electrostatic interactions, chemical conjugation, and covalent attachment by genetic manipulations (Pokorski and Steinmetz, 2011). The self-assembled viral nanoconstructs enter the host cell, multiply there by efficiently delivering their genetic material using the host intracellular machinery to produce progeny viruses. This property of virus allows for their use in the medical fields such as gene therapy but pathogenicity of animal viruses limits their use (Makkonen et al., 2015). Interestingly, bacteriophages and plant viruses such as tobacco mosaic virus (TMV), cowpea chlorotic mottle virus (CCMV), red clover necrotic mosaic virus (RCNMV), bacteriophage MS2, and *Salmonella typhimuriam* bacteriophage P22 are being focused more as they are safe to be used in humans (Wu et al., 2013).

Over the past decades, advancements in nanotechnology have allowed for the fabrication of nano-scale devices and their utilization in the biomedical field (Li and Wang, 2014; Lee et al., 2016). Viruses as self-assembling nanoconstructs open up the new opportunities for the development of energy storage devices, biosensors, and drug delivery systems. They allow target-specific drug delivery by encapsulating DNA/RNA, antigens, drugs, and enzymes. More recently, viral nanoconstructs have been used to develop light-harvesting systems (Yokoi et al., 2010). Furthermore, viral nanoconstructs enable target-specific delivery of antigens and amplification of the immune responses. Several structural proteins derived from different viruses served as the templates for nanoconstructs to deliver vaccine candidates such as core and surface antigens of Hepatitis B Virus (HBV), *Human Parvovirus* B19, *Papillomavirus*, *Bluetongue Virus*, TMV, *Picorna Virus*, etc. These subunit vaccine candidates were designed in such a way that they potentially mimic structural repetitiveness of the natural host-pathogen surface interactions, thereby providing improved antigen stability and immunogenicity. Several preclinical vaccine trials based on this strategy may be applicable against infectious diseases such as influenza, malaria, hepatitis, rabies, and AIDS (Lopez-Sagaseta et al., 2016).

Other group of researchers illustrated the precise self-assembly of NPs into ordered nanostructures directed by TMV coat protein (Zhang et al., 2019). Matsuura et al. (2020) prepared ribonuclease-decorated artificial virus-like capsid by the self-assembly of β-annulus-S-peptide. These constructs were created by the interaction between S-peptide moiety and S-protein. The recombinant TMV coat protein monomers with a reactive cysteine residue were developed to attach three thiol-reactive chromophores to viral structure and an efficient energy transfer was observed and recorded using fluorescence spectroscopy (Miller et al., 2007). Besides, bacteriophage MS2 contains translational repression (TR) operator protein that binds to its RNA stem-loop. Modification of the protein with the drug such as ricin A and 5-fluorouridine allows the protein to diffuse inside the viral nanoconstructs and bind steadily to the capsid to achieve targeted therapy (Wu et al., 1995). Recently, bacteriophage M13 and its relatives are mostly used to design genetically engineered viruses, which find their place in the development of phage-based nanosensors, fabrication of nanomaterial, nanofibers, and tissue regeneration (Pires et al., 2016). The recombinant phage tail sheath protein, gp053 isolated from *E. coli* infects *Myovirus* vB_EcoM_FV3 (FV3) and self-assemble to form stable polysheaths with potential applications in different fields of nanosciences (Šimoliunas et al., 2019). An optical nano-construct was designed by deleting the genome of Brome Mosaic Virus (BMV) and doping with indocyanine green (ICG), an FDA approved near-infrared (NIR) chromophore that allows site specific deep tissue optical imaging (Jung et al., 2011).

Although, engineering of the self-assembled nanoconstructs is a challenging task. The different strategies involved in nanoconstruct manipulation involve rational construction through conventional recombinant DNA technologies and microbial protein production. C3-symmetric molecular design of peptides and their characteristic self-assembly into virus-like nanostructures is a novel strategy. Through this strategy, trigonal conjugates of b-sheet-forming peptides, trigonal conjugates of glutathione, and a viral b-annulus peptide fragment were formed (Matsuura, 2012). However, these assemblies involve weak interactions. Thus, measurements of the self-assembly kinetics of individual viral capsids around their RNA genome was identified by using interferometric scattering microscopy. The results indicated that the self-assembly proceeds by nucleation, followed by monotonic growth (Garmann et al., 2019). Beside, nanoconstruct designing depends on the physical principles of virus assembly related to packaging, encapsulation, and capsid modification. Furthermore, several factors, such as pH, charge on capsid protein, and the effect of amino acids, also play an important role (Stella and Turvilee, 2018; Chaudhary and Yadav, 2019).

SYNTHESIS OF NPs BY POLYMICROBIAL COMMUNITIES

Most of the microbes in their natural habitats do not exists in pure culture and are bound to get surrounded by other types of micro-organisms. In this scenario, these microbes must adapt themselves to co-inhabit with others to form communities that are referred to as "polymicrobial communities." From time to time, these communities undergo dynamic changes in terms of the proportion of the individual microbial type due to the

intrinsic and extrinsic factors. However, it is the net outcome of this "collaboration" that determines the longevity of these communities (Kim et al., 2020).

The complex interplay between the co-habiting partners of these communities is very intriguing. Many times, this crosstalk is facilitated through secretion of various bioactive molecules either directly into the extracellular milieu or *via* membrane vesicles. Majority of infectious diseases involve the formation of polymicrobial communities that are difficult to eradicate completely with the help of current treatment regime. The polymicrobial nature of biofilms underlying the pathogenesis of cystic fibrosis has been revealed using an integrated approach of morphological, biochemical, and molecular methods. Using a combination of multiple techniques such as plate count, q-PCR, and fluorescent *in situ* hybridization using peptide nucleic acid probes (PNA-FISH), it was observed that these biofilms consists of a combination of *P. aeruginosa*, *Inquilinus limosus*, and *Dolosigranulum pigrum*. The combination of these species within the biofilms varied under stresses of oxygen concentration and presence of antibiotics (Lopes et al., 2018). Such kind of communities can also exist on artificial solid supports such as catheters, pacemakers, etc. In another study, the biofilms of mine drainage systems precipitating ZnS was found to be consisting mainly of sulfate reducing bacteria belonging to the family Desulfobacteriaceae along with other genera including the *Cytophaga/Flexibacter/Bacteroides* (CFB group), *Planctomycetales*, *Spirochaetales*, *Clostridia*, and green non-sulfur bacteria. The bacteria belonging to family Desulfobacteriaceae predominated the older and mature biofilms that are ZnS rich, whereas fresh and ZnS poor biofilms have a more diverse proportion of individual communities (Labrenz et al., 2000). Thus, it is essential to understand the complex dynamics of these polymicrobial communities for better control over them. These tiny communities need special attention from the clinical point of view, at the same time, they can be exploited for beneficial purposes.

Majority of these polymicrobial communities exists in the form of biofilms. A biofilm is a three-dimensional (3D) niche in which single or multiple bacterial species can co-exist within the framework formed by the extra cellular polysaccharides (EPS) secreted by its habitants. EPS can consist of xanthan, dextran, succinoglycan, hyaluronic acid, alginate, and several other polymeric substances, depending on the type of microbes involved in biofilm formation. Xanthan gum is produced by *Myxococcus xanthus*, whereas dextran is produced by *Leuconostoc*, *Lactobacillus*, and *Streptococcus* genera. Gellan and curdlan based EPS are produced by *Sphingomonas* spp. and *Alcaligenes faecalis*. Cellulose based EPS is a characteristic of *Agrobacterium*, *Azotobacter*, *Rhizobium*, *Salmonella*, etc., while Levan is a major EPS component in the biofilms of *Mycobacterium*, *Pseudomonas*, *Corynebacterium*, and *Bacillus*. Succinoglycan is another type of polysaccharide observed within the biofilms of *Alcaligenes*, *Pseudomonas*, and *Agrobacterium* (Glenn et al., 2007; Flemming and Wingender, 2010; Freitas et al., 2011; Donot et al., 2012; Mishra and Jha, 2013; Casettari et al., 2015; Habibi and Khosravi-Darani, 2017; Moussa et al., 2017). Recent types of bacterial EPS are FucoPol and GalactoPol with the former being produced by Enterobacter A47 and the later by *Pseudomonas oleovorans* aNRRL B-14682. Both these EPSs are formed by their respective bacteria while using glycerol as the sole source of carbon (Freitas et al., 2009; Ferreira et al., 2014).

Biofilm provide a safer niche for its inhabitants due to its inherent resistance to antimicrobial agents, various mechanisms for neutralizing toxic metals from the surroundings, better protection from host immune responses and other hostile conditions that becomes difficult for planktonic bacteria to manage. The cells within the biofilms of *P. aeruginosa* were found between 2 and 600 times more resistant to the heavy metals such as copper (Cu), lead (Pb), and zinc (Zn) than free swimming cells (Teitzel and Parsek, 2003). The resistance to toxic metals and other antimicrobial agents is acquired through multiple ways such as sequestration of positively charged metals by negatively charged species in the biofilm EPS such as phosphate, sulfate, carboxyl groups etc. (Hunt, 1986). Additionally, majority of antimicrobial agents are effective against actively metabolizing cells and their efficacy is reduced against stationary cells. Since biofilm is a 3D structure with multiple cellular layers, it contains layers of metabolically active, intermediate, and dormant cells. These dormant cells often are found to persist within the deepest layers of biofilm where the nutrients and oxygen are in scarcity. These dormant cells are responsible for reforming the mature biofilm after the initial onslaught of antimicrobial agent and thus establish recurring infections (Spoering and Lewis, 2001). The proteome of EPS within the biofilms of *Shewanella* spp. have been shown to contain redox proteins that play essential role in the immobilization of uranium (U; Cao et al., 2011). The same findings have been reported by other research groups using various micro-organisms such as *Synechococcus elongates*, *Acidithiobacillus ferrooxidans*, *M. xanthus*, and *Pseudomonas stutzeri* DSM 5190 (Macaskie et al., 2000; Merroun et al., 2003; Jroundi et al., 2007; Merroun and Selenska-Pobell, 2008; Acharya et al., 2009). *E. coli* which is genetically engineered for enhanced EPS production has been found to possess greater resistance toward the toxicity of Ag NPs. The production of EPS in *E. coli* is controlled by capsule synthesis (cps) operon that is positively regulated by *rcsA* gene. *Escherichia coli* overexpressing *rcsA* cloned in pSB1A2 overproducing colonic acid based EPS was found to exhibit better resistance to the activity of Ag NPs. Addition of exogenous xanthan based EPS to bacteria that lacked *rcsA* also confers the similar advantage by increasing the aggregation of NPs and also reducing the surface area of bacterial cells exposed to NPs (Joshi et al., 2012). Although mainly consisting of polysaccharides, these biofilm EPS also contains many of essential organic and inorganic components which play crucial role in metal immobilization, thus proving to be a better alternative over commercially available polysaccharides.

Biofilms also provide some advantages for the production of NPs compared to planktonic bacteria such as larger surface area, higher biomass accumulations that allows for hassle free, efficient, economic, and large scale synthesis of NPs with minimal requirement for precursor molecules. The biological synthesis of NPs requires metal ions and the agent to reduce them to

NPs. These biofilms provide an array of natural reducing molecules such as proteins, lipids, and other aromatic compounds which are essential for the nanoparticle synthesis. A biofilm of metal reducing bacteria such as *Geobacter sufurreducens* have been shown to provide a better reducing environment for metal ions and thus are efficient in synthesizing NPs than their planktonic counterparts. Also, the rate of extracellular reduction of Pd (II) to Pd (0) NPs was found to be affected by the nature of the electron donor and was significantly enhanced by the addition of external reducing agents (Pat-Espadas et al., 2013a,b; Yates et al., 2013). Thus, biofilms can be manipulated to have better efficiency in synthesizing NPs at various levels.

Sulfur reducing bacteria (SRB) has been used for many years for bioremediation of metal polluted soils and water bodies. Majority of studies involving SRB have been performed using *Shewanella* spp., *Desulfovibrio* spp., and *Geobacter* spp. (Ayangbenro et al., 2018). These bacteria can also be used for the bioremediation of toxic metals from sewage plants as these bacteria grow well on organic resources (De Lima et al., 2001). The naturally occurring biofilms of these bacteria can precipitate several toxic metals such as cadmium (Cd), Co, chromium (Cr), Cu, manganese (Mn), Ni, and Zn as insoluble sulfides (White et al., 1998). Synthesis of sphalerite (ZnS) NPs has been shown within the naturally occurring biofilms of aerotolerant sulfate reducing bacteria from the family, *Desulfobactericiae*. The concentration of sphalerite within these biofilms is 10^6 times higher than in the surrounding water indicating the predominant mechanism of controlling the metal levels in the groundwater and wetlands. These ZnS NPs can be as very fine in size ranging from 2 to 5 nm and also accumulates 0.01% by weight of arsenic (As) and 0.004% by weight of Se (Labrenz and Banfield, 2004). Thus, biofilms provide safe and inert niche for the nanoparticle synthesis in which the rate of synthesis can be controlled.

Recently, EPS purified from such biofilms has been used for the synthesis of metal NPs having wide variety of applications. Xanthan gum is effective in the synthesis of Ag and Au NPs with better catalytic and antibacterial properties. It also acts as drug carrier for doxorubicin hydrochloride against human lung cancer cell lines (Xu et al., 2014). Au NPs stabilized using dextran sulfate have shown better antitumor effects against carcinoma in the mouse model and better bactericidal properties against many Gram-negative and few Gram-positive pathogens (Cakic et al., 2016). Moreover, Ag NPs coated with dextran polysaccharide isolated from *Leuconostoc mesenteroids* T3 have better sensitivity and selectivity toward detection of cysteine in aqueous solutions (Davidovic et al., 2017). Similarly, purified carboxylic curdlan has been used for stabilizing Se and Zn NPs having improved antibacterial and antitumor activity (Yan et al., 2018). A combination of gellan and alginate based EPS matrix can be used as a stabilizing and catalyst system for Pd NPs (Cacchi et al., 2012). This strategy of using a combination of various EPS materials can be applied for the synthesis of other NPs as well. Moreover, the EPS production can be tailor made using genetic, molecular, and other biotechnology tools. Succinoglycan, levan, and cellulose based EPS have been shown to act as reducing and/or stabilizing agents for the synthesis of metallic NPs (Galvez et al., 2018; Gonzalez-Escarcega et al., 2018). The means by which biofilms are crucial in synthesizing as well as stabilizing nanoparticles are depicted in **Figure 5**.

Overall, approximately 150 representative bacterial species have been used in various studies for synthesis of NPs, whereas in case of fungi, about 80 species have been used for this purpose (Sastry et al., 2003; Korbekandi et al., 2009; Li et al., 2011; Iravani, 2014; Kitching et al., 2015; Moghaddam et al., 2015; Siddiqi and Husen, 2016; Sehgal et al., 2018; Gahlawat and Choudhary, 2019; Grasso et al., 2019). Similarly, around 130 species of various classes of algae have been used for the nanomaterial synthesis (Khan et al., 2017; Chaudhary et al., 2020). While the majority of the research has been done bacteria, fungi, and yeasts, the hidden potential of protozoa and archaea for nanomaterial synthesis is yet to be explored as very few species from each of them have been used for the synthesis of NPs. In addition, microbial biofilms also have tremendous potential for the synthesis and stabilization of NPs.

IMPACT OF BIO-ENGINEERING APPROACHES ON MICROBIAL NANOMATERIAL SYNTHESIS

In natural ecosystem, microbes encounter numerous metals in close vicinity. Some of them die owing to the toxic nature of these metals while others persist which are termed as the metal resistant micro-organisms. Most commonly, this resistance occurs *via* interaction of cationic metal ions with anionic cellular components, such as cell membrane, proteins, and DNA, and subsequent reduction, hydrolysis, or oxidation leads to the formation of metal, metal oxide, or other types of NPs. Many of the metal resistant micro-organisms have been used successfully for the nanoparticle synthesis. However, there remain major drawbacks associated with their implication which includes lack of homogeneity in terms of size and shape of these NPs and issues concerned with scaling up of this process in the industries. This demands the use of novel approaches involving biotechnology, molecular biology, and genetics to address these issues. The use of such engineered NPs has found applications in diverse areas ranging from cosmetics to medicine (Raj et al., 2012; Valavanidis and Vlachogianni, 2016). Genetic engineering allows for the tailor made synthesis of NPs using various microbes that are better suited for different applications. Various genetic engineering approaches used for the nanomaterial synthesis and assembly have been summarized in **Figure 6**.

Use of Engineered Biological Scaffolds

The use of biological scaffold system has been used over the years to facilitate the biomineralization of metal ions leading to synthesis of nanomaterials. Expressing a recombinant virus scaffold system in bacteria has been shown to provide an endogenous system that can have a direct control over the size, shape, and phase of NPs during the nucleation stage. This has enabled the use of this virus-based toolkit to direct the synthesis of magnetic and semiconducting

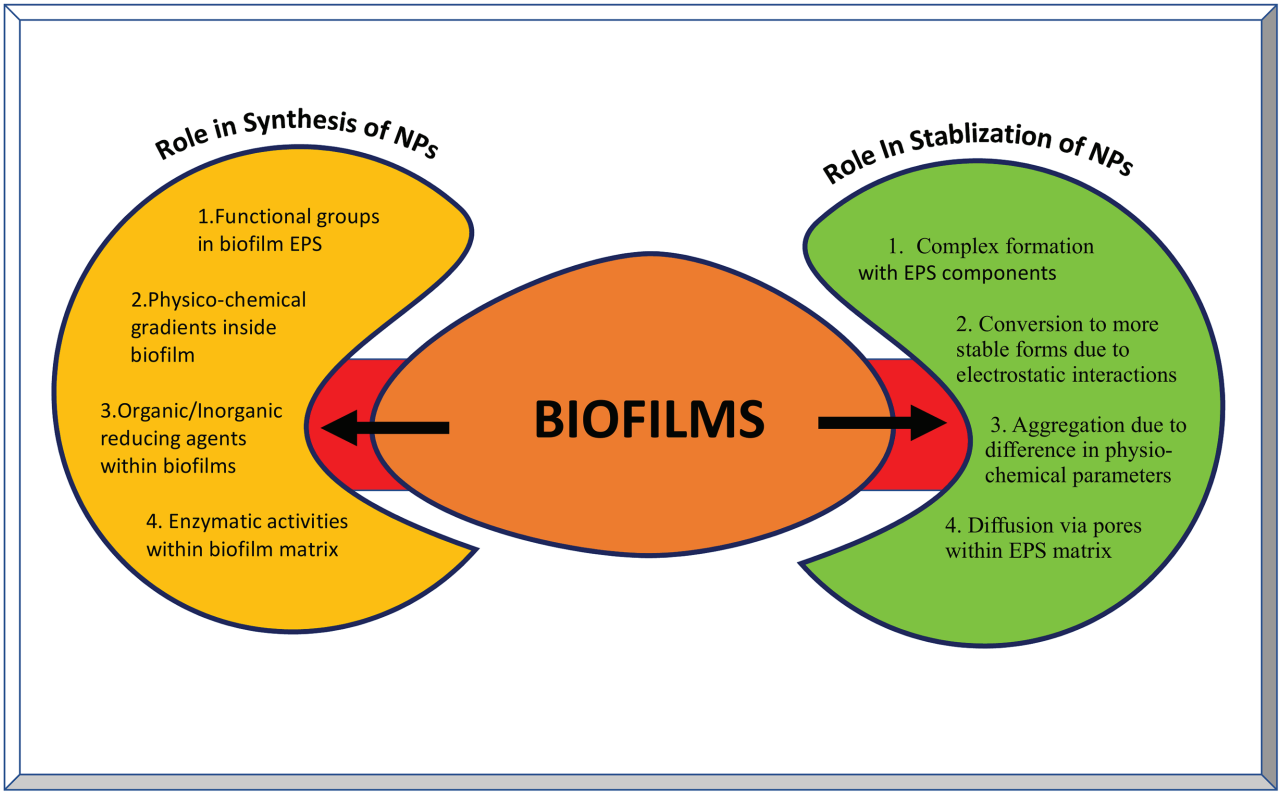

FIGURE 5 | Role of biofilms in the synthesis and stabilization of nanoparticles. The **left yellow panel** indicates various factors contributing to the NP synthesis inside biofilms, while the **right green panel** indicates various outcomes of NPs-biofilm interaction leading to stabilization of NPs..

nanostructures. Phage display method has been used to identify phage proteins having substrate specificity toward NPs, control over its nucleation, and inherent ability to orient themselves as per the symmetry of phage capsid (Whaley et al., 2000; Lee et al., 2002; Mao et al., 2003). Expressing a genetically modified M13 Phage scaffold harboring peptides controlling the properties of nanostructures directs the synthesis of tailor made semiconducting and magnetic nanowires inside hosts. Since these proteins are genetically encoded and contained within capsid, multiple copies of it can be produced upon infection of a host bacterium (Mao et al., 2004). In another study, expressing recombinant noninfectious p22 viral cage proteins into a host, allows for the biomineralization of Fe_2O_3 NPs. While the inner capsid layer proteins initiate the nucleation of NPs, the outer shell proteins regulate the size of the NPs by providing a physical constrain. Additionally, homogeneity in nanoparticle size can be achieved by expressing polyanionic peptides that interact with capsid. The assembly of this viral cage can be easily altered using chemical, molecular, or genetic ways, thus giving a new level of control over the area of nanoparticle synthesis (Reichhardt et al., 2011).

In addition to the protein scaffold, expression of cell free DNA scaffold can be used to direct the assembly of cellular biosynthetic machinery. This DNA scaffold can then be used toward the synthesis of numerous metabolic products (Conrado et al., 2012). The DNA scaffold also directs the nucleation of metal NPs based on electrostatic interactions. The circular plasmid DNA from *Bacillus* spp. form stable complexes with Ag ions using charge-charge interactions. The negatively charged sugar phosphate backbone of plasmid DNA interacts with the positively charged Ag ions leading to stabilization and reduction into Ag nanoassemblies. The DNA-Ag ions complex formation is confirmed by measuring the absorbance of the solution at 420 nm, characteristic of Ag NPs. The control solution lacking the plasmid DNA but with Ag ions failed to give the characteristic absorbance confirming the role of plasmid DNA in reducing Ag ions to form NPs. This process is accelerated using the method of photo irradiation (Liu et al., 2012). Since plasmids can be isolated and purified from many bacteria on large scale, this method provides a promising future for the directed fabrication of nanomaterials.

Expression of Metal Binding Proteins

Additionally, expression of metal binding proteins with affinity for heavy metals in foreign host has been proved to be effective for heavy metal removal. The first of this kind of study was performed with recombinant *E. coli* expressing phytochelatin synthase gene from *Schizosaccharomyces pombe* in addition to

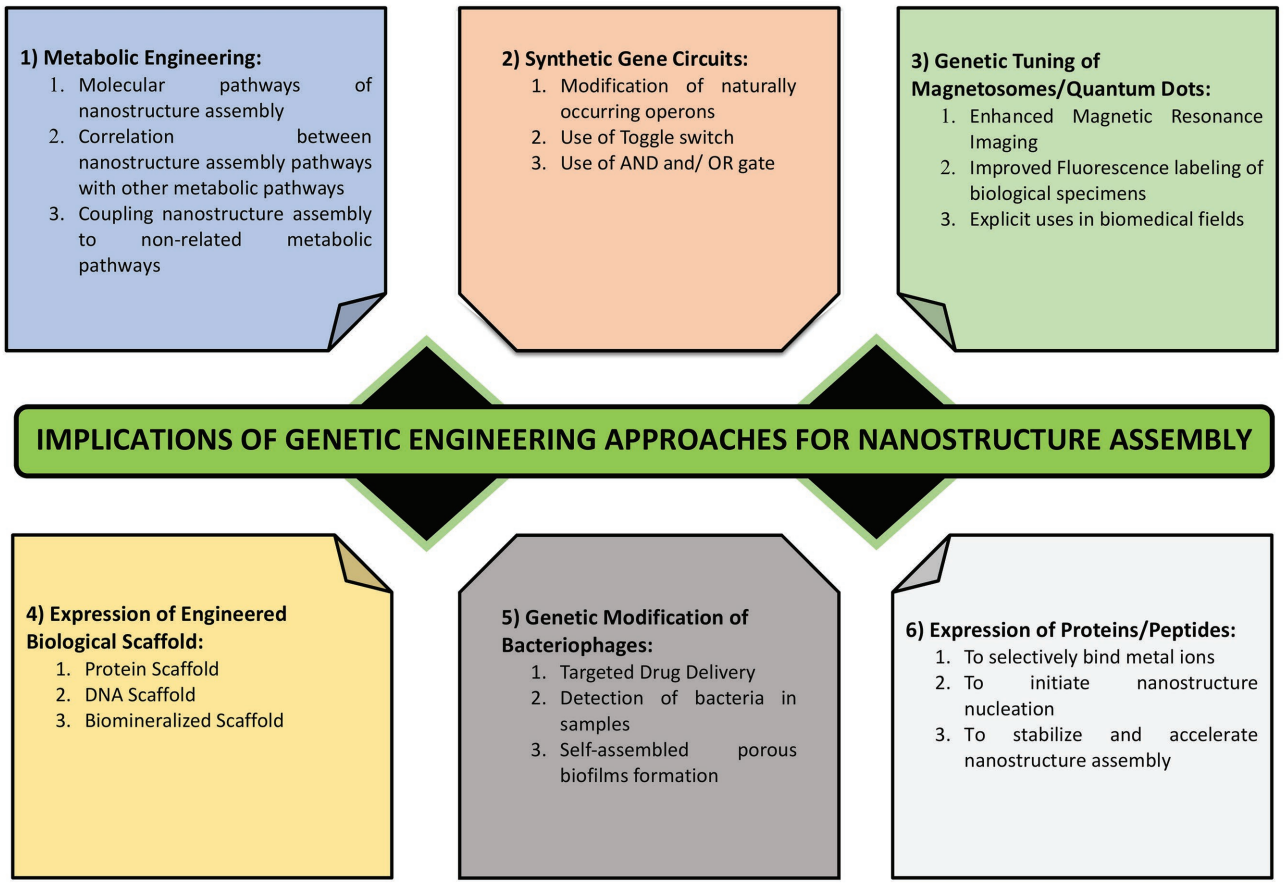

FIGURE 6 | Various approaches for engineering the process of nanostructure synthesis and assembly. It highlights the importance of genetic tuning of cellular structures such as magnetosomes, metabolic engineering, metabolic coupling, expression of metal binding proteins and those involved in metal reduction and complexation, use of synthetic regulated gene circuits, and the use of cell free scaffolds.

modified γ-glutamylcysteine synthetase which succeded in producing Cd nanocrystals (Kang et al., 2007). γ-Glutamylcysteine synthetase acts as a catalyst to the synthesis of glutathione which is a precursor of phycochelatin. Phycochelatin is a metal binding protein that acts as the capping agent for the nanostructures. Recombinant *E. coli* harboring genes for phycochelatin synthase from *Arabidopsis thaliana* and metallothionein from *Pseudomonas putida* produces NPs of various metals such as semi conducting, alkali earth, magnetic, para magnetic, noble, and rare earth fluorides. It was shown that by changing the concentration of metal ions, NPs of desired size could be obtained. Using the same system of recombinant *E. coli*, another group of researchers have been successful in synthesizing around 60 different types of nanomaterials that include 34 elements from the periodic table. Thus, recombinant *E. coli* expressing metal binding proteins can be used as a cellular factory for the synthesis of diverse NPs (Park et al., 2010; Choi et al., 2018).

Mammalian cells expressing recombinant protein that sequester iron NPs have made it easy for their MRI. The use of genetically engineered mammalian cells expressing recombinant protein system encapsulin/cargo from *Quasibacillus thermotolerans* along with encapsulin from *M. xanthus* provides a highly efficient genetic reporter system. Encapsulin is a family of iron sequestering proteins naturally that occurs in bacteria and archea. Upon expression in HEK293T cells, this encapsulin protein system self-assemble into nanospheres having icosahedral symmetry that further sequesters and encapsulates ferritin like proteins into it. The mammalian cells harboring this sequestered cargo protein enables its multiplexed gene reporter imaging using the conventional transmission electron microscopy (Sigmund et al., 2019). In magnetotactic bacteria, *magA* gene encodes for a protein involved in iron sequesteration and transport into the cells. Expressing this gene into mouse neuroblastoma cells N2A, causes iron loading and its conversion into NPs by cellular enzymes. This stabilized nanoparticle now provides a contrast signal system during the MRI that can be easily made nonfunctional with a single point mutation (Goldhawk et al., 2009).

Fabrication of Magnetosomes

Till date, importance of individual genes in the synthesis of NPs has been studied using either gene knockdown or knock

in approach. In the gene knockdown approach, the expression of a gene product is silenced using siRNA/miRNA and while in gene knock in approach, a gene or cluster of genes is introduced into a cell lacking it. In both cases, the impact of gene silencing or gene introduction on the rate of nanoparticle synthesis, properties of resulting NPs and their efficiency/suitability for various applications is observed (Das et al., 2016; Chen et al., 2019). Magnetosomes are the very finely ordered nanostructures found in magnetotactic bacteria that are membrane bound. These bacteria that are generally found in deep oceans use magnetosomes to align along the earth's gravitational field. Many researchers are trying to elucidate the mechanistic pathway underlying the synthesis of these tiny magnetic structures as they can be exploited for biotechnology and nanotechnology purposes. However, they are limited owing to the fact that these bacteria are difficult to isolate from the deep ocean samples and also difficult to handle under laboratory conditions due to their fastidious nature (Stoller et al., 2020). Furthermore, the synthesis of magnetosomes is a very tidy process controlled by a complex set of genetic components (Jogler and Schuler, 2009). In 2001, a group of researchers observed a large cluster of genes conserved in several species of magnetotactic bacteria to be encoding proteins directly involved in the magnetosome formation (Grunberg et al., 2001). Later, the role of this conserved genetic loci termed as Magnetosome Island (MAI) was eludicated by studying the effect of deletion of individual genes from the island on the magnetization property (Murat et al., 2010). Earlier, it was shown that an acidic protein encoded by *mamJ* aligns the magnetosomes along a filament like structure and deletion of these genes affects the orientation of magnetosomes along earth's magnetic field (Scheffel et al., 2006). In a breakthrough study, Kolinko et al. (2014) showed that the ability to mineralize these magnetic nanocrystals can be transferred to a heterologous host such as *E. coli via* transfer of a set of genes. The *mamAB* operon in *Magnetospirillum gryphiswaldense* encodes for proteins that are involved in the formation of magnetosome membrane, transport of iron into magnetosomes, crystallization of magnetite (Fe_3O_4) NPs and their orderly arrangement, and positioning inside the magnetosomes. The smaller operons, namely *mamGFDC*, *mms6*, and *mamXY*, play accessory roles in this process of biomineralization. Using a phage vector, a set of 29 genes from these four operons was stitched together in an expression cassette and introduced into photosynthetic bacterium *Rhodospirillum rubrum*. This study opened a new era of tailor made optimized synthesis of magnetic nanostructures in recombinant host of interest using synthetic biology approaches. Another study shows the importance of redox control mechanism along with carbon metabolism and iron supply in inducing synthetic bio magnetization in model organism *S. cerevisiae*. Screening of knockout mutants for inducing magnetization identified TCO89, a component of target of rapamycin complex 1 (TORC1) along with several genes for carbon metabolism in yeast as essential in inducing the bio magnetization (Nishida and Silver, 2012).

Recently, a group of researchers achieved genetic control over the physico-chemical properties of Fe_2O_3 NPs in *Magnetospirillum magneticum* AMB1. By fine tuning of ribosome binding sites, constitutive promoters, and use of inducible genetic system over a wide range, the size, shape, surface properties, and chain length of Fe_3O_4 NPs can be controlled (Furubayashi et al., 2020). This process is much more complicated than it appears due to multidimensional complexity associated with gene expression systems.

Synthetic Gene Circuits

Recently, synthetic gene circuits are being designed and expressed to have a better control over the synthesis and properties of NPs made. For constructing a gene expression circuit, all the molecular components need to be assembled, the information of which is encoded in DNA itself. DNA binding enzymes can decode this information along with other enzymes that can catalyze the chemical reactions leading to metal binding. Some proteins contain region that bind metal ions and reduce them with the help of enzymes. Thus, multiple structural and enzymatic components are encoded by this synthetic gene circuits regulating the nanoparticle synthesis (Rice and Ruder, 2013). According to the central dogma of biology, DNA is transcribed into RNA by RNA polymerase and this RNA then binds to ribosomes to be translated into functional proteins. In the transcription step, binding of RNA polymerase to the promoter of specific DNA sequence results in the synthesis of complementary RNA sequence. This step requires precision and high specificity of RNA polymerase as any deviation from this will result in the expression of unwanted gene(s). Two types of proteins, activators, and repressors each having affinity for DNA decides the fate of this step. Activators can catalyze the binding of RNA polymerase to DNA promoter, while repressors can prevent this binding by itself binding to DNA. Similarly, in the second step, the sequence of RNA transcribed influences its binding to ribosomes. Using genetic engineering approaches, these sequences can be altered in precise and specified manner leading to control over gene expression. In 19th century, continuous efforts were made in modifying and optimizing the naturally occurring promoters to provide better control over the gene expression events. Several of bacterial and viral promoters were modified that responded to activators *AraC* and repressors *lacI* and *tetR* (Lutz and Bujard, 1997). The first synthetic promoter toggle designed. In 19th century consisted of two mutually repressing gene operons. When both the operons repress each other equally, the gene circuit is said to be bistable. This ability of repressing each other depends on many variables such as affinity and binding strength of DNA and RNA polymerases to DNA promoters, as well as the binding strength of ribosomes and its corresponding binding sites in mRNA. By altering the bases of each of these regions, the toggle switch can be turned ON or OFF even in the absence of inducer such as tetracycline and lactose (Gardner et al., 2000).

Another group of researchers designed AND gate in bacteria that consisted of genetically engineered RNA polymerase with a genetic defect in the genetic code that blocks its complete translation. Providing one input, for example, Arabinose results in partial translation of the protein while another input, example salicyclate results in restoration of this genetic defect to

induce the expression of wild type full length RNA polymerase (Anderson et al., 2007). Using this approach, the fermentation timings could be controlled using genetically engineered strains of *S. cerevisiae* expressing synthetic timers (Ellis et al., 2009).

Recently, synthetic genetic circuits have been used to induce the bio sensing ability inside the biofilms. Biofilms provide a tremendous platform for the synthesis of nanostructures which can be controlled using synthetic gene circuits. Curli fibers are amyloid nanofibers synthesized by many species of *Enterobacteriae* and are responsible for community type behavior inside biofilms (Tursi and Tukel, 2018). The curli fiber consists of two subunits CsgA, the major subunit of the developing curli fibers, and CsgB, the minor curli subunit. The function of CsgB is to regulate the nucleation of CsgA on the cell wall of bacteria and its further assembly into nanofibers (Barnhart and Chapman, 2006). These fibers can provide a conductive surface which can be used to synthesize nanomaterials. Therefore, attempts are being made to increase metal binding capacity of these nanofibers so that they can accelerate the selective synthesis of NPs inside the biofilms. Recently, the gene sequence encoding CsgA was fused with another sequences encoding for short peptides. This synthetic gene circuit now encodes for modified curli nanofibers with specific binding affinity for precursor metal ions. These modified curli nanofibers now act as template to direct the synthesis of other metal nanostructures inside biofilms (Olmez et al., 2019).

The synthetic gene circuit has also been used to detect the cellular toxicity of nanomaterials. A synthetic gene circuit consisting of four heat shock promoter regions along with a gene sequence coding for reporter protein acts as the biosensor for the nanoparticle induce toxicity (Saltepe et al., 2019). Such synthetic biosensor circuit based on use of HSP system can be applied to assess the toxicity of other types of nanomaterials as well.

Genetically Engineered Bacteriophages

Viruses are at the crossroads of living and non-living as they possess the genetic material necessary for all the living organisms but lack the machinery to make functional proteins. For this purpose, they rely on their host hence are referred to as obligate intracellular parasites. Upon injection of viral nucleic acid into host, multiple copies of it are produced using cellular polymerases. This is followed by transcription and translation of structural and functional viral proteins. The most important step of virus life cycle is the accurate assembly of viral capsid enclosing the nucleic acid to give rise to a functional virion. This process occurs *via* self-assembly of structural proteins into capsid having a defined symmetry (Koonin and Starokadomskyy, 2016). For long time, scientists are intrigued with this tremendous ability of viruses to self-assemble into nanomolecular assemblies and, thus, it has remained a topic for research over the years. Recently, researchers are using this ability of viral capsid to self-assemble for inducing the synthesis of nanomaterials having exotic applications.

The self-assembled nanoassembly of viruses has found applications as filters, sensors, photonics, and bio mimetics. Using the genetically engineered M13 bacteriophage, a nanoporous self-assembled biofilm structure is formed that filters selective ions from the sodium chloride (NaCl) solution. This self-assembled biofilm is multilayered with a pore diameter of 150–200 nm and a depth of 15–20 nm. It consists of alternating units of M13 phage along with polydiallyldimethylammonium chloride (PDDA) formed by pulling in and out method. The role of PDDA is to reduce the surface roughness of M13 phage allowing, thus facilitating the smooth assembly of biofilm. Using genetic engineering tools, negative charge of the bacteriophage is increased by inducing the expression of glumatic acid. Using this biofilm, Na^{2+} ions are trapped in phage layers, while Cl^{-} ions are trapped in PDDA layers (Devaraj et al., 2018). This method provides an eco-friendly, inexpensive, and energy efficient approach for selective fabrication of nanoassemblies for diverse applications. M13 bacteriophages have a small size and thus small genome and have a unique self-assembling property that leads to the formation of variety of nanostructures (Sawada and Serizawa, 2018).

Over last many years, bacteriophages have attracted attention of researchers worldwide due to their potential use as antimicrobial agent. Many research groups have successfully used this method to reduce bacterial burdens in different settings owing to the high degree of specificity displayed by phages toward their host bacterium. However, there are certain limitations on the *in vivo* usage of this therapy due to the poor control over the replication and spread of phages post clearance of bacterial infection and also the chances of facilitating horizontal gene exchange *via* the process of transduction (Principi et al., 2019; Brives and Pourraz, 2020). This problem can be overcome by coupling phages to Au nanorods, thereafter called as phanorods that can be destroyed upon photothermal heating after its use. The chimeric phages expressing increased specificity, specifically target the bacterial cells. Subsequent photothermal ablation leads to destruction of both host cells as well as bacterial cells. The Au nanorods conjugated phages can be excited using near infra-red light. Upon excitation, they emit energy *via* a process of non-radioactive decay which leads to the generation of heat in targeted bacterial cells leading to their destruction (Peng et al., 2020).

The nucleation and size of nanostructures has been shown to be controlled by peptides. Therefore, bacteriophages expressing these peptides upon exposure to the chemical precursor molecules initiate the accumulation and crystallization of corresponding nanostructures on the phage capsid (Karimi et al., 2016). The specificity displayed by bacteriophages toward host bacteria is executed through the highly specific protein-protein interaction between phages and bacteria. Therefore, expressing this phage protein rather than using the whole phage seems to provide an alternative, at least, for few applications. The tail fibers and spikes of phages express receptor binding proteins (RBPs) by which they bind to complementary cell wall proteins of their host bacterium (Dunne et al., 2019). Expressing these RBPs has found to be useful for the detection of some of the human pathogens such as *Salmonella*, *Shigella*, and *Pseudomonas* spp. (Schmidt et al., 2016; He et al., 2018; Kunstmann et al., 2018).

Since a long time, TMV has been used for application oriented synthesis of NPs. These viruses can be modified to flank metal binding proteins/peptides to direct the controlled synthesis of Au NPs of uniform size and crystalline shape. Two short amino acid motifs, GASL and SEKL, were found to stimulate the synthesis Ag nanoplates which are much bigger in size than other nanostructures. It was observed that repeating these sequences in the metal binding peptide being displayed on the phage capsid accelerates this process upon incubation with Ag salts (Love et al., 2015). These peptides may act as the biological catalyst for the synthesis of these nanostructures. Use of reduced aromatic amino acids such as tryptophan in combination with these repeating sequences further speed up the process of Ag nanoplate formation (Tan et al., 2010). Genetically modified phages can be used for reduction of metals into nanostructures even in the absence of reducing chemical agents. Using reducing biological compounds such as dipeptide consisting of dual cysteine residues, modified TMV was shown to synthesize Pd NPs at temperatures above 50°C (Lim et al., 2010).

Genetic Tuning of Quantum Dots

Quantum dots (QDs) are luminiscent NPs that has revolutionized the field of nanotechnology because of its unparalleled importance in biomedical fields and diagnostics. They are made up of semiconducting material that has unique electronic and optical characteristics and can also transfer electrons. A typical QD consists of a core made of semiconducting material, a shell made of metallic layer such as ZnS to enhance the optical properties and a cap to increase the solvent accessibility. Several types of QDs have been synthesized by now are made up of hetero nano-structures such as CdS, PbSe, CdTe, ZnS, and PbS. These QDs range in size from 1 to 10 nm and exhibit quantum effect owing to the quantum confinement.

The breakthrough study for the biosynthesis of Cds QDs was performed in 1989 using yeasts species such as *S. pombe* and *Candida glabrata*. These species accumulated CdS crystallites in the presence of Cd salts. A short peptide was used to control the nucleation and the growth of these nanocrystals. The nanocrystals synthesized by this green approach were uniform in size (monodisperse) compared to those synthesized chemically (Dameron et al., 1989). This approach was later used in multiple micro-organisms enabling the efficient synthesis of QDs. Using genetically engineered *E. coli* expressing a binding peptide, CdS nanocrystals were synthesized that are more compatible for bio imaging and labeling (Mi et al., 2011). In a similar study, *gshA* gene involved in glutathione biosynthesis was over expressed in *E. coli*. Upon exposure to $CdCl_2$ and K_2TeO_3 salts, these engineered *E. coli* cells accumulated increased levels of CdTe hetero nanostructures compared to the wild type bacteria. Overexpression of *gshA* gene increases the cellular content of reduced thiol compounds leading to reduction of metals ions (Monras et al., 2012).

In addition to the genetic control over QD synthesis, a novel approach involves coupling the QD synthetic pathways to non-related biochemical reaction. This novel approach has been demonstrated successfully for the synthesis of CdSe QDs using yeast as a model organism. The biosynthesis of CdSe QDs usually occurs at higher temperature (300°) using the toxic solvents (Seo and Kim, 2007; Ratnesh and Mehata, 2015). By using the biogenic approach, the reaction temperature can be reduced significantly also providing the control over the photoluminiscent properties of CdSe nanocrystals. Upon exposure, yeast cells take up the selenite and convert it into glutathione selenotrisulfide with the help of reduced glutathione (GSH) and GSH related enzymes such as NADPH and glutathione reductase. Since this conversion depends on growth phase, exposing the stationary phase yeast cells to selenite salts maximizes its conversion into organoselenium compounds such as selenocysteine and selenomethionine. After this, co-incubating these seleniumized yeast cells to Cd salts at appropriate time leads to accumulation to CdSe QDs which can be easily observed using fluorescence microscopy. Thus, coupling metabolic pathways in space and time can be used as an efficient strategy to exert control over the synthesis of QDs (Cui et al., 2009). The importance of glutathione metabolic pathway was highlighted by studies involving deletion of several genes of these pathways. Deletion of *gsh1* and *gsh2* genes controlling the first and second stages of glutathione biosynthetic pathway, respectively, lead to the decrease in the fluorescence intensity of intracellular CdSe QDs. Addition of $CdCl_2$ to selenumized yeast cells showed 8-fold increase in the expression of *gsh1* gene using RT-PCR which further highlighted its role in CdSe biosynthetic pathway. Deletion of another gene, *glr* which increases the level of oxidized glutathione (a chemical analog of glutathione) also cannot restore the reduced ability of yeast cells to synthesize CdSe nanocrystals. However, addition of exogenous glutathione restored this ability to a great extent (Li et al., 2013). This study strengthened the role of glutathione synthesis pathway in the intracellular formation of CdSe QDs. The route involving the intracellular formation of CdSe QDs has also been applied toward the directional synthesis of other hetero nanostructures such as Au NPs, Au-Ag alloy NPs, Au clusters, PbSe nanocubes, and Ag_2Se QDs (Cui et al., 2010, 2012; Zhang et al., 2011; Gu et al., 2012). This implies the significant importance of this biosynthetic route in tailored biogenesis of nanostructures in other microorganisms.

CONCLUSION

The review represents the impact of a combination of genetic engineering, biotechnology, microbiology, molecular biology, synthetic biology, and metabolic engineering approaches on the tailor made NP synthesis to have better functional properties. With the increasing demand of these nanostructures, technological advancements have been made to facilitate the customized application oriented synthesis of NPs. However, the increasing usage of these nanostructures also poses a bigger risk of harming the ecosystem which in long run would have unimaginable detrimental effects. Therefore, a balance needs to be maintained between the ecosystem maintenance and technological advancements.

FUTURE PROSPECTS AND CHALLENGES

Beyond this review highlighting the advancements in the field of microbial nanotechnology, further research is essential for the widespread applications of nanomedicine while preserving the ecosystem. The concept of controlled drug release at target sites, bio distribution of these drugs and their intended effects at the tissue/cellular level, as well as theoretical mathematical prediction models yet need to be improved. Many studies in nanomedicine field focus on biomedical and formulation studies that appear in the early stages of biomedical applications. Therefore, it is essential to implement these approaches using *in vivo* models to further enhance its feasibility toward human welfare. To date, biological synthesis of metal NPs has been performed primarily at the laboratory scale. Hence, industrial scale adaptation is necessary for mass production. With appropriate optimized conditions and suitable micro-organisms, these "bio-nano-factories" can produce stable NPs with well-defined shapes, structures, and morphologies. Appropriate business strategies should result in the creation of a non-toxic biological system capable of producing metal NPs which will be another milestone toward sustainable development. Vaccines containing NPs have generated much interest in recent years, and a wide variety of NPs have been developed and used as delivery vehicles or immune enhancers. This approach has not only improved the antigen stability, antigen processing, and immunogenicity, but also leads to targeted delivery and slow release of antigens. In addition, NPs are not only used as antigens of interest but also as adjuvants in vaccine preparations. Till date, the available literature on synthesis of NPs shows heterogeneity in size with some actually measuring in nanometers while others measured in submicrons (more than 100 nm). Therefore, in depth understanding of the factors that govern the size and shape of NPs is essential to achieve consistent homogeneity. Other parameters which need more attention are the drug loading and release capacity of these NPs.

Nowadays, *de novo* protein engineering and *in silico* techniques have developed rapidly and can play an important role in supramolecular nanomaterial engineering for specific applications. Several challenges remain, including the difficulty of synthesizing non-aggregating NPs that have coherent and desirable properties, a fundamental lack of understanding of how the physical properties of NPs affect their bio-distribution and orientation, and how these properties affect their interactions with the biological system at different levels from cell to the tissue and organ. Other state-of-the-art techniques, such as computational design, material genomes, and artificial intelligence, can be integrated to discover more effective and translational NPs based on bioengineering strategies.

With better control over nanomaterials synthesis, researchers can make the nanomaterial world more amazing. However, current synthesis technology remains bottleneck that prevents in-depth exploration of the properties and applications of nanomaterials. Therefore, there is a lot of scope for improvement. There has been great enthusiasm for the simple approach toward the development of nano-robots (and nano devices) acting in tissue diagnosis, drug delivery, combating deadly virus like *SARS*, *Ebola*, and *Covid-19*, and repair mechanisms with complete external control mechanisms. This is not yet a reality and is still a future investigation that perhaps humanity can achieve in the very near future.

However, along with its benefits, the potential risk of nanomedicine toward both humans and the environment also needs long-term studies. Since nanomedicine has revolutionized the field of drug discovery and its administration in biological systems, the need for the regulation over its usage in healthcare and environmental systems is also increasing. Therefore, the appropriate acute or chronic toxicity effects of new nanomaterials on humans and the environment should be analyzed appropriately. Finally, the disposal of such nanomaterials into environment should be dealt with strict guidelines and regulations.

AUTHOR CONTRIBUTIONS

RD, TH, PT, and SK wrote the manuscript. SK and TH conceived the idea. SK compiled the manuscript. KS made the illustrations. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GLOSSARY

Ag	Silver
Ag_2Se	Silver selenide
AIDS	Acquired immunodeficiency syndrome
Al_2O_3	Aluminium oxide
Au	Gold
AuCl4	Tetrachloroaurate
BMV	Brome mosaic virus
$CaCO_3$	Calcium carbonate
CCMV	Cowpea chlorotic mottle virus
$CdCl_2$	Cadmium chloride
CdS	Cadmium sulfate
CdSe	Cadmium selenide
CdTe	Cadmium telluride
CFB	*Cytophaga/flexibacter/bacteroides*
Co	Cobalt
CO_2	Carbon dioxide
COVID-19	Coronavirus disease 2019
Cr	Chromium
Cu	Copper
Cyb5R	Cytochrome b5 reductase enzyme
DNA	Deoxyribose nucleic acid
EPS	Extra cellular polysaccharides
Fe	Iron
Fe_2O_3	Iron oxide
Fe_3O_4	Ferrosoferric oxide/magnetite
Fe_3S_4	Greigite
FISH-PAN	Fluorescent *in situ* hybridization using peptide nucleic acid probes
GSH	Glutathione
HBV	Hepatitis B virus
ICG	Indocyanine green
K_2TeO_3	Potassium tellurite
Li	Lithium
MAI	Magnetosome Island
MB	Methylene blue
Mn	Manganese
MRG	Metal resistance genes
MRI	Magnetic resonance imaging
Na_2SeO_3	Sodium selenite
NaCl	Sodium chloride
Ni	Nickel
NIR	Near-infrared
4-NP	4-Nitrophenol
NPs	Nanoparticles
PbS	Lead sulfide
PbSe	Lead selenide
Pd	Palladium
PDDA	Polydiallyldimethylammonium chloride
Pt	Platinum
QDs	Quantum dots
RBPs	Receptor binding proteins
RCNMV	Red clover necrotic mosaic virus
Rh	Rhodium
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RT-PCR	Real time polymerase chain reaction
Ru	Ruthenium
S-layer	Surface layer
SARS	Severe acute respiratory syndrome
Sb_2O_3	Antimony trioxide
Se	Selenium
SiO_2	Silicon dioxide
SRB	Sulfur reducing bacteria
TR	Translational repression
T4P	Type IV pili

(Continued)

Ag	Silver
TEM	Transmission electron microscopy
TiO_2	Titanium dioxide
TMV	Tobacco mossaic virus
TORC1	Target of rapamycin complex 1
TR	Translational repression
U	Uranium
ZnO	Zinc oxide
ZnS	Zinc sulphide

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Mechanistic Aspects of Microbe-Mediated Nanoparticle Synthesis

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In recent times, nanoparticles (NPs) have found increasing interest owing to their size, large surface areas, distinctive structures, and unique properties, making them suitable for various industrial and biomedical applications. Biogenic synthesis of NPs using microbes is a recent trend and a greener approach than physical and chemical methods of synthesis, which demand higher costs, greater energy consumption, and complex reaction conditions and ensue hazardous environmental impact. Several microorganisms are known to trap metals *in situ* and convert them into elemental NPs forms. They are found to accumulate inside and outside of the cell as well as in the periplasmic space. Despite the toxicity of NPs, the driving factor for the production of NPs inside microorganisms remains unelucidated. Several reports suggest that nanotization is a way of stress response and biodefense mechanism for the microbe, which involves metal excretion/accumulation across membranes, enzymatic action, efflux pump systems, binding at peptides, and precipitation. Moreover, genes also play an important role for microbial nanoparticle biosynthesis. The resistance of microbial cells to metal ions during inward and outward transportation leads to precipitation. Accordingly, it becomes pertinent to understand the interaction of the metal ions with proteins, DNA, organelles, membranes, and their subsequent cellular uptake. The elucidation of the mechanism also allows us to control the shape, size, and monodispersity of the NPs to develop large-scale production according to the required application. This article reviews different means in microbial synthesis of NPs focusing on understanding the cellular, biochemical, and molecular mechanisms of nanotization of metals.

Keywords: nanoparticles, synthesis mechanism, microbes, metal nanotization, biomaterials, therapeutic

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INTRODUCTION

Nanoparticles (NPs) are particles with dimensions between 1 and 100 nm that may have different chemical and physical properties relative to their bulk-metal counterpart in addition to the large surface-to-mass ratio (Sardar et al., 2014). The physical and chemical properties of NPs can be differing by their elemental composition, larger specific surface area, and composition of the

coating agents (Ahmad et al., 2013a; Sadaf et al., 2020). NPs possess unique features such as mechanical properties (Mishra et al., 2015; Gao et al., 2020), antimicrobial capabilities (Ahmad et al., 2014a, 2015; Abdulla et al., 2021), drug delivery capacities (Ahmad et al., 2021), optical properties (Albrecht et al., 2018), and catalytic capabilities (Mishra et al., 2016; Liu and Liu, 2017; Perwez et al., 2017; Ghosh et al., 2018a,b) and act as artificial chaperones (Ahmad et al., 2014b; Ghosh et al., 2019).

There are various approaches to synthesize nanomaterials, namely, chemical, physical, and biological methods. In general, the chemical and physical methods are preferred routes by the industries, but their disadvantages overshadow their performance. They are usually expensive, consume enormous amounts of time and energy, have complicated procedures, and generate toxic by-products (Castro et al., 2014; Ngoepe et al., 2020). Biogenic NPs are therefore an alternative with the potential to be an eco-friendly and cost-effective method for NP synthesis (Mishra et al., 2013a; Khatoon et al., 2015; Mazumder et al., 2016; Kim et al., 2018; Jacob et al., 2020). In relation to the manufacture of NPs, the word "biogenic" encompasses a range of methodology used for the NP synthesis by either plant extracts or microbes by reduction of metal ions into NPs through their inherent NP manufacturing capabilities (Capeness et al., 2019; Castillo-Henriquez et al., 2020). Bacterial growth properties and genetic modifications render them potent for biogenic NP manufacture as well as industrial applications, particularly when combined with their ability to catch metals, such as those found as environmental pollutants (Nancharaiah et al., 2016).

Interactions between inorganic matter and biological entities have been responsible for geochemical cycles and the maintenance of life on this planet for millions of years. Many species during evolution rely on minerals of different sizes and shapes for a broad range of functions, including physical support, defense from foreign agents, and navigation (Wang and Nilsen-Hamilton, 2013). Biomineralization requires the absorption and modulation of ions from the atmosphere into highly ordered structures, activities that are subject to strict biological regulation (Mann, 2001). A solid-phase organic matrix comprising polysaccharides, phospholipids, and mostly proteins is needed to generate higher-order inorganic structures (Addadi and Weiner, 1985, 2014; Weiner and Dove, 2003). The processes of inorganic structure formation, nucleation, crystal growth, and developing minerals of particular size as well as shape are involved. Harsh conditions may be required to form minerals in the environment. To overcome these situations, organisms provide an offshore account in which specific biological systems help with specific membrane pumps to produce a saturating level of a specific ion (Weiner and Dove, 2003). During mineral formation, the organic matrix plays a major role. First of all, negatively charged residues pull and concentrate positive ions from solution. This contributes to ion saturation at particular points to initiate the nucleation. Nucleation involves a reduction in the free energy and formation of nano-size particles. As a result, the organic matrix decreases the free energy and stabilizes the ions to create a solid stable particle that will be growing into a crystal. Also, the organic matrix plays an important role in the crystal growth and formation of definite particle size. Earlier research has shown that diverse proteins can directly interact with the mineral surface for the formation of solid structure (Hunter, 1996; Mann, 2001; Addadi and Weiner, 2014; Nudelman et al., 2018). A specific organelle called magnetosome, which contains nano-magnetic particles synthesized by magnetotactic bacteria (MTB), is a good model to understand NP formation (Lower and Bazylinski, 2013). The magnetosome is composed of well-defined nano-magnetic particles in a chain or chains that are enclosed by a membrane layer and oriented as per the cell axis (Yamamoto et al., 2010). This magnetosome is often exploited to carry drugs or other loads as a delivery vehicle in cancer treatments (Vargas et al., 2018).

As is evident, several metals such as gold, silver, copper, cadmium, zinc, tellurium, platinum, titanium, and palladium are found to be synthesized through microbial routes, which are often harvested for industrial or biomedical applications. This mini review covers the microbial route to synthesize the various nanomaterials, focusing on the mechanistic aspects of nanotization.

MICROBIAL-MEDIATED SYNTHESIS OF NANOPARTICLES

Microorganisms such as bacteria, fungi, yeast, and algae are often favored for NP synthesis due to simpler cultivation, rapid growth rate, and their capacity to grow at atmospheric pH, temperature, and pressure conditions. Different biological agents behave differently with different metal solutions in order to form NPs (Fariq et al., 2017; Saravanan et al., 2020; Ghosh et al., 2021). Metal ions are initially trapped on the surface of the cell followed by the reduction of metal ions to NPs with the presence of enzymes synthesized by the microbes. The NP synthesis process is depicted in **Figure 1**. The microbial-mediated synthesis of NPs and their possible application is summarized in **Table 1**.

Bacterial-Mediated Synthesis of Nanoparticles

Bacteria that reduce metals are found to be environmentally friendly catalysts for bioremediation as well as material synthesis. In general, through the microbial respiration processes, genus *Shewanella* has been found to synthesize diverse metal oxides (Kim et al., 2018). Electrons can be moved from reduced organic to oxidized inorganic compounds through microbial dissimilatory anaerobic respiration, thus promoting the formation of crystal along with bioremediation processes. It is well documented that the genus *Shewanella* is able to assist the oxidation of organic acids as electron donors and reduction of inorganic metals as electron acceptors (Heidelberg et al., 2002; Harris et al., 2018). Bacterial nanowires and flavins are extracellularly excreted by the genus *Shewanella* by bioreduction process (Marsili et al., 2008; El-Naggar et al., 2010; Beblawy et al., 2018). Few researchers have documented biosynthesis of copper NPs through biosorptive process with dead *Rhodotorula mucilaginosa* biomass. The synthesized NPs were spherical in form and were considered to be a good method for NP synthesis for simultaneous pollutant remediation.

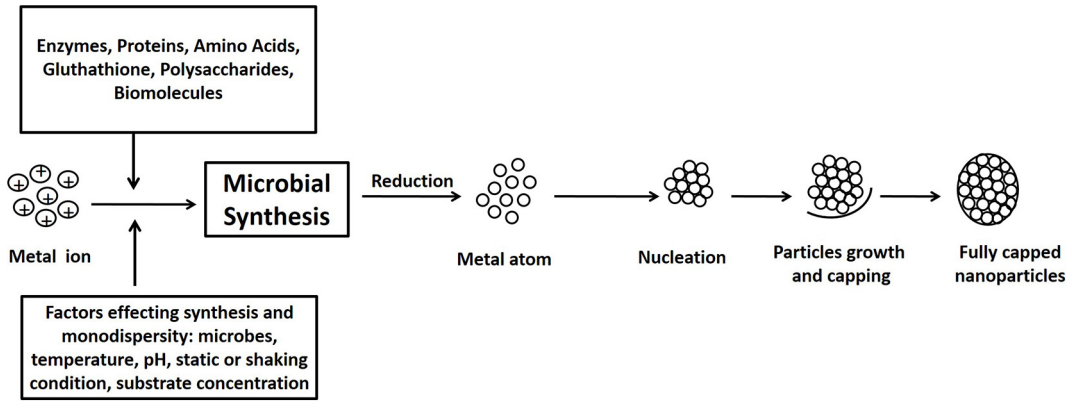

FIGURE 1 | Schematic diagram of mechanisms of nanoparticle synthesis by microbes: the pathway of nanoparticle synthesis by microbes involves metal capture, enzymatic reduction, and capping. Several biomolecules such as proteins, amino acids, and polysaccharides found in the microbial extracts help in the stabilization of the nanoparticles.

Another analysis involving *Clostridium pasteurianum* metallic molybdenum NP synthesis has also been published (Salvadori et al., 2014; Nordmeier et al., 2018). Ag NPs were synthesized by *Shewanella oneidensis* MR-1 with antibacterial activity (Suresh et al., 2010). Another report showed that Cu NPs were synthesized through bioreduction of Cu(II) by *S. oneidensis* MR-1 (Kimber et al., 2018). *Shewanella loihica* PV-4 and *S. oneidensis* MR-1 have the ability to produce Pd NPs with higher catalytic activities (Wang W. et al., 2018; Xiong et al., 2018). *S. oneidensis* MR-1 have properties to utilize toxic soluble tellurite as electron acceptor leading to Te nanorod formation. Also, needle-shaped crystalline Te nanorods were formed both intracellularly and extracellularly (Kim et al., 2012, 2013). Gold- and tellurite-containing nanostructures were biosynthesized in aerobic and anaerobic conditions by crude extracts from *Enterobacter cloacae* MF01 (Contreras et al., 2018). In another study, the investigators explored the formation biogenic selenium nanostructures by gram-negative bacteria under aerobic conditions (Piacenza et al., 2018). Studies have also revealed the importance of different volatile sulfur compounds (VSCs) in the biosynthesis of CdS quantum dots (QDs) by *Pseudomonas fragi* GC01 (Gallardo Benavente et al., 2019). Also, similar studies showed ruthenium and ruthenium-palladium NPs synthesized by *Escherichia coli* cells (Macaskie et al., 2019) and mercury NPs synthesized by *Enterobacter* sp. (Sinha and Khare, 2011).

Fungus-Mediated Synthesis of Nanoparticles

Fungal NP synthesis is favored over other microbial synthesis methods due to the high resistance of fungal mycelial mesh to higher flow and agitation in bioreactors (Saravanan et al., 2020). Chitin was found to be the key ingredient in the fungal cell wall system that is involved in heavy metal complexation, resulting in synthesis of NPs (Wang L. et al., 2018). Due to several bioactive metabolites, strong aggregation, and increased efficiency, fungi are more resourceful than bacteria in the biosynthesis of NPs (Castro-Longoria et al., 2011; Alghuthaymi et al., 2015; Saravanan et al., 2020). In Au NP biosynthesis, many filamentous fungi have been reported to be capable. This research employed diverse approaches in order to biosynthesize Au NPs. The authors proposed that the NPs could be stabilized by fungal secreted compounds and media materials (Molnar et al., 2018; Guilger-Casagrande and De Lima, 2019). Formulation of silver NPs from *Penicillium chrysogenum* NG85 and *Fusarium chlamydosporum* NG30 was successful. Ag NPs were prepared using cell-free filtrate obtained from the autolyzed biomass. The involvement of enzymes and proteins in the cell-free filtrate was responsible for the formation of NPs in which the enzymes mediated the reduction of silver ions to silver atoms and the stabilization of silver atoms by capping materials was carried out by proteins (Khalil et al., 2019). *Phomopsis liquidambaris* extracellular filtrate isolated from healthy *Salacia chinensis* leaves contains proteins that could reduce and serve as a capping agent, thereby stabilizing the formulation of Ag NPs that demonstrated bactericidal activity against pathogens (Seetharaman et al., 2018). Filtered biomass extract of *Aspergillus tamarii*, *Aspergillus niger*, and *Penicillium ochrochloron* could act as a potential fungal nanofactories for the green and eco-friendly production (Devi and Joshi, 2015). An endophytic fungus *Periconium* sp. isolated from leaves of *Balanites aegyptiaca* mediated the synthesis of zinc NPs (Ganesan et al., 2020). The synthesis of copper oxide NPs from endogenous fungi has been accompanied by a similar method. Copper oxide NPs were synthesized using *Trichoderma asperellum* water extract and copper nitrate solution (Saravanakumar et al., 2019). *P. chrysogenum* provided a particular pigment that facilitated the synthesis of NPs (El-Sayyad et al., 2018).

Mechanistic Aspect of Metal Nanoparticle Toxicity on Microbes

Nanoparticles have been synthesized from many metals, including gold, silver, copper, nickel, cobalt, zinc, and titanium inside microorganisms. These metal and metal oxide nanomaterials comprise a large segment of the growing nanotechnology market. Increasing use of metallic nanomaterials

TABLE 1 | Nanoparticles synthesized by microbe and their possible application.

Microbial strain	Nanoparticles	Size in nm	Application	References
Micrococcus lylae	TiO_2	13.58 ± 0.04	Degradation of dye	Fulekar et al., 2018
Cellulosimicrobium sp.	TiO_2	15.76 ± 0.03	Degradation of dye	Fulekar et al., 2018
Micrococcus aloeverae	TiO_2	17.31 ± 0.02	Degradation of dye	Fulekar et al., 2018
Chlorella pyrenoidosa	TiO_2	50	Dye degradation	Sharma et al., 2018
Bacillus mycoides	TiO_2	40–60	Construction of green solar cells	Ordenes-Aenishanslins et al., 2014
Lactobacillus sp.	TiO_2	50–100	Antibacterial activity, immobilization, and refolding of enzyme	Ahmad et al., 2013a, 2014a
Aspergillus flavus	TiO_2	62–74	Antimicrobial activity	Rajakumar et al., 2012
Marinospirillum alkaliphilum	Ag	30–70	Antimicrobial effect and dye removal	Nazari and Kashi, 2021
Escherichia coli	Ag	5–50	Antimicrobial activity	Saeed et al., 2020
Pseudoduganella eburnean	Ag	8–24	Antimicrobial activity	Huq, 2020
Sphingobium sp. MAH-11^T	Ag	7–22	Antibacterial activity	Akter and Huq, 2020
Bacillus subtilis	Ag	3–20	Antibacterial activity	Alsamhary, 2020
Lactobacillus plantarum TA4	Ag	14.0 ± 4.7	Antibacterial and Antioxidant activity	Mohd Yusof et al., 2020
Padina sp.	Ag	25–60	Antibacterial activity	Bhuyar et al., 2020
Chaetomorpha linum	Ag	70–80	Efficient anticancer agent	Acharya et al., 2020
Chlorella ellipsoidea	Ag	220.8 ± 31.3	Photophysical, catalytic, and antibacterial activity	Borah et al., 2020
Penicillium oxalicum	Ag	60–80	Antibacterial activity	Feroze et al., 2020
Aspergillus niger	Ag	13.2–646.8	Antifungal effect	Gursoy, 2020
Acinetobacter baumannii	Ag	37–168	Antimicrobial and antibiofilm activities	Shaker and Shaaban, 2017
Thermophilic *Bacillus* sp. AZ1	Ag	9–32	Antimicrobial activity	Deljou and Goudarzi, 2016
Actinomycetes	Ag	10–20	Antibacterial	Abdeen et al., 2014
Verticillium sp.	Ag	25 ± 12	Antimicrobial activity	Mukherjee et al., 2001
Pseudomonas stutzeri AG259	Ag	200	Deal with the metal toxicity stress in the environment	Klaus et al., 1999
Spirulina platensis	Au	15.60–77.13	Antiviral activity	El-Sheekh et al., 2020
Sargassum cymosum	Au	7–20		Costa et al., 2020
Cladosporium sp.	Au	5–10	Photodegradation, *in vitro* anticancer activity, and *in vivo* antitumor studies	Munawer et al., 2020
Morchella esculenta	Au	16.51	Antimicrobial activity and cytotoxic activity	Acay, 2020
Micrococcus yunnanensis	Au	53.8	Antibacterial and anticancer	Jafari et al., 2018
B. subtilis	Au	20–25	Catalytic degradation of dye	Srinath et al., 2018
Shewanella loihica	Au	2–15	Dye degradation	Ahmed et al., 2018
Aspergillus sp.	Au	2.5–6.7	Nitrophenol reduction	Shen et al., 2017
Streptomyces griseoruber	Au	5–50	Catalytic activity for the degradation of methylene blue	Ranjitha and Rai, 2017
Stephanopyxis turris	Au	10–30		Pytlik et al., 2017
Galaxaura elongate	Au	3.85–77	Antibacterial	Abdel-Raouf et al., 2017
Cystoseira baccata	Au	8.4	Anticancer	Gonzalez-Ballesteros et al., 2017
Tetraselmis kochinensis	Au	5–35		Senapati et al., 2012
Streptomycetes viridogens HM10	Au	18–20	Antibacterial activity	Balagurunathan et al., 2011
Cordyceps militaris	ZnO	10–15	Photocatalytic degradation of methylene blue dye	Li et al., 2019
A. niger	ZnO	53–69	Antibacterial and dye degradation	Kalpana et al., 2018
Lactobacillus sporogens	ZnO	145.70	Antimicrobial	Mishra et al., 2013b
Aeromonas hydrophila	ZnO	57.7	Antimicrobial activity against *Pseudomonas aeruginosa* and *A. flavus*	Jayaseelan et al., 2012
Candida albicans	CdS	50–60	Bactericidal potential against *Salmonella typhi* and *Staphylococcus aureus*	Kumar et al., 2019
Bacteria strains NS2 and NS6	PbS	40–70	Bioremediation without producing toxic chemicals to the environment	Lok et al., 2006
S. loihica	Pt	1–10	Dye degradation	Ahmed et al., 2018
Penicillium chrysogenum	Pt	5–40	Cytotoxicity	Subramaniyan et al., 2018
S. loihica	Pd	1–12	Dye degradation	Ahmed et al., 2018
S. platensis	Pd	10–20	Adsorbent	Sayadi et al., 2018
S. loihica	Cu	10–16	Antibacterial	Lv et al., 2018
Baker's yeast	Fe_2O_3	2–10	Detection H_2O_2 and glucose	Mishra et al., 2015
Sargassum wightii	ZrO_2	18	Antibacterial	Kumaresan et al., 2018
C. pyrenoidosa	CdSe QD	4–5	Imatinib sensing	Zhang Z. et al., 2018

QD, quantum dot.

is likely to result in the release of these particles into the aqueous environments, thus providing a path to enter the food chain and eventually disturbing the ecological balance. Toxicities associated with NPs in microorganisms are mainly related to their nano-size that causes membrane disorganization, generation of reactive oxygen species (ROS), and, in some cases, oxidative DNA damage and release of the toxic ions (Morones et al., 2005; Niazi and Gu, 2009).

The metal NPs cause adsorption on the cell wall leading to depolarization and increase in its permeability, followed by disintegration of membranes and further penetration into the membrane (Thill et al., 2006; McQuillan et al., 2012; Slavin et al., 2017). Inside microbes, these metallic NPs increase significant production of ROS, which target multiple sites simultaneously like conformational changes in protein, peroxidation of the lipids, and DNA damage, thus leading to membrane disintegration and ultimately may cause cell death (Madl et al., 2014; Slavin et al., 2017).

Purification and Characterization of Monodisperse Nanoparticles

Ensuring monodispersity of NPs is important for biological studies and clinical translation. An important step in understanding the physical properties of NPs is purifying NPs into monodisperse fractions. NPs have been separated by size and form, and certain methods have been created to purify subpopulations of particles after their assembly. Size exclusion chromatography will separate both hard and soft NPs according to their size (Wei and Liu, 1999; Ahmad et al., 2013b; Satzer et al., 2014). Similarly, different density and mass-based methods can separate NPs according to their form (e.g., discoidal from spherical-like NPs) (Johansson et al., 2007; Robertson et al., 2016). There are a variety of techniques that manufacture uniformly appearing nanomaterials with desired properties. The assembly process can yield NPs with several properties simultaneously (Robertson et al., 2016). Characterization methods assess the form, scale, distribution, surface morphology, and surface area of the NPs. Methods to classify NPs are illustrated in **Figure 2**. The visual observation of color change is critical for NPs. Due to the variation in the surface plasmon resonance (SPR) measured by the NPs, color shift is observed (Zhang et al., 2016). SPR allows the presence of the metal to be monitored by UV–Vis spectroscopy, while X-ray diffraction (XRD) can be used to classify metal NPs. Analysis of XRD data will tell about the composition of materials. Apart from controlling the size of the dust, it is used for particle size determination (Reddy et al., 2016). Dynamic light scattering (DLS) is one of the widely used techniques for the determination of NP size. Hydrodynamic radii are determined using the time it takes light to pass around the particle. In colloidal suspensions, DLS helps ensure calculations are more precise (Kumari et al., 2019). Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are other useful techniques for the determination of size, shape, morphology, and aggregation of NPs (Ahmad and Khare, 2018). Particle size, agglomeration, and shape can be determined by atomic force microscopy (AFM) topography imaging (Ahmad and Sardar, 2014). Biomolecules responsible for capping NPs can be observed by Fourier transform infra-red (FTIR) spectroscopy (Menon et al., 2017; Sardar et al., 2018). Inductively coupled plasma mass spectrometry (ICP-MS) can analyze NPs qualitatively and quantitatively. Single or combination methods are used to characterize and isolate monodisperse particles.

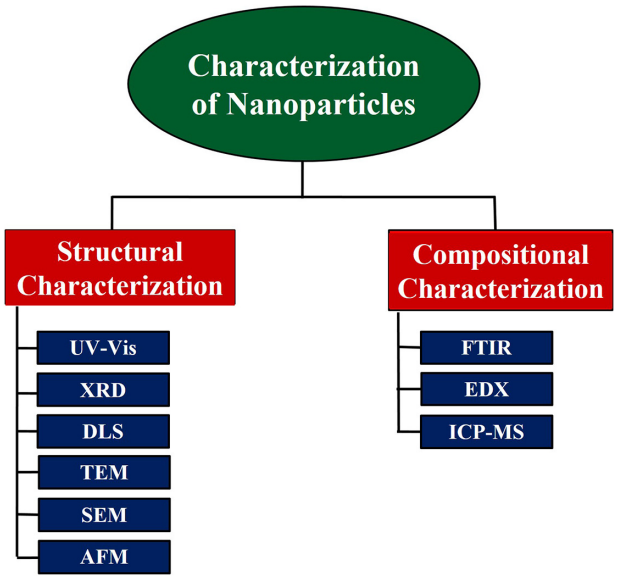

FIGURE 2 | Characterization methods for nanoparticles: several analytical techniques are employed to isolate and characterize monodisperse nanoparticles. UV–Vis, ultraviolet–visible spectroscopy; XRD, X-ray powder diffraction; DLS, dynamic light scattering; TEM, transmission electron microscopy; SEM, scanning electron microscopy; AFM, atomic force microscopy; FTIR, Fourier transform infrared spectroscopy; EDX, energy-dispersive X-ray spectroscopy; ICP-MS, inductively coupled plasma mass spectrometry.

MECHANISMS INVOLVED IN METAL NANOTIZATION

Why do microbes accumulate nanometals? Presence of metals in the environment entails their penetration into cells, disruption of membrane structure, inactivation of enzymes, and production of antimetabolites, which chelate with essential metabolites leading to toxicity or cell death for the microbial cells in the vicinity of the metal particles (Sobolev and Begonia, 2008). This property of metals has also been explored in case of antimicrobial activity against pathogenic strains. As such, microbes try their best to evade the toxicity of the metals by eliminating or reactively changing their properties or accumulating them in forms away for vital organelles. The nanotization of metals by microbes is an important part of geo-cycles and occurs mainly as a stress response resulting in adaptive or defense mechanism for the organism against the metal toxicity. Thus, the microorganisms capable of NP synthesis are often metal resistant in nature, and bacteria genera such as *Pseudomonas* are

reported to grow in high metal concentrations (Iravani, 2014; Luo et al., 2015). The interaction of the anionic cell components with the cationic metal ions leads to the formation of metal, metal oxide, or metal sulfide NPs *via* reduction, chelation, or hydrolysis (Bansal et al., 2005). As detoxification measures, the organism can employ enzymatic reduction, dissimilatory oxidation, precipitation, complexation, or transport *via* efflux systems to remediate the metals from the cell (Arshad, 2017). The broad mechanisms of NP synthesis mainly involve either of the pathways involving enzymes, proteins, exopolysaccharides, and electron shuttle quinines (Gahlawat and Choudhury, 2019). Often external parameters such as temperature and pH play a definite role in NP synthesis with regard to properties such as size as well as concentration (Saklani et al., 2012).

Synthesis through microbial routes gives the distinct advantages of control of shape and size, in addition to being a greener alternative to chemical and physical processes. Compared with other biological synthesis methods such as plants, which may result in decrease in monodispersity due the presence of phytochemicals and yield difference due to seasonal variations, microbial means offer a monodisperse NP synthesis methods, which are reproducible in industrial conditions in bioreactors, without batch variations (Ahmad et al., 2021). Additionally, the small size and biocompatibility of biogenic NPs render them good candidates as drug delivery carriers, antimicrobials, anticancer drugs, and diagnostic agents. The disadvantages, though few, mainly refer to the high cost and technology involved in the development and production process of biogenic NPs. Moreover, some NPs may end up in the environment with polluting as well as disease-causing effects (Parveen et al., 2016). Thus, it is important to assess the toxicity and long-term effects of synthesized NPs before using them in any application.

Enzymatic Action

Enzymes are believed to be the foremost entities involved in the reduction and capping of metals in microbes, through redox reactions occurring in either the intracellular or extracellular space, often acting as the nucleation sites. Broadly, the intracellular route involves metal capture, enzymatic reduction, and capping, while in the extracellular method, secreted or membrane-bound enzymes/proteins are involved. Additionally, shuttle quinones such as anthraquinones, naphthoquinones, and hydroquinones are involved in the process. Mostly NADH-dependent nitrate reductases are reported in fungi to be involved in the reduction process. Fungal species such as *Penicillium brevicompactum*, *Cladosporium cladosporioides*, *Fusarium oxysporum*, *Fusarium semitectum*, and *Fusarium solani* have been reported to use nitrate reductases to produce Ag NPs (Ovais et al., 2018; Meenakshi, 2020). NADH and NADH-dependent reductases in *Pseudomonas aeruginosa* JS-11 were reported for the biogenic reduction of SeO_3^{2-} to insoluble Se^0 NPs (Dwivedi et al., 2013). In a cell-free study, glutathione (GSH), NADPH, and GSH reductase have been utilized to quasi-biosynthesize Ag_2Se QDs with tunable fluorescence (Gu et al., 2012). In *Rhodopseudomonas capsulate*, NADH and NADH-dependent enzymes aided in the conversion of Au ions into Au nanospheres through an electron shuttle mechanism (He et al., 2007). In case of palladium NPs, hydrogenases have been found to play a profound role in reducing Pd(II), with the deposit of Pd(0) NPs depending on the localization of hydrogenases in *Desulfovibrio fructosivorans*. The enzyme serves as the nucleation site, providing electrons to Pd(II) for its reduction (Mikheenko et al., 2008). Hydrogenases have also been reported in the reduction of several other metals such as selenium by *C. pasteurianum*, uranium by *Micrococcus lactyliticus*, and gold by *Shewanella algae* (Iravani, 2014). In case of metal sulfide NPs, the metal and sulfide moieties need to be present in soluble salt form as precursors, and furthermore, sulfide anions and metal cations react with each other to form the metal sulfide NPs, mediated by extracellular or intracellular enzymes. For intracellular reduction, the ions enter the cytoplasm through magnesium or manganese transport chains. For extracellular synthesis, secreted enzymes or those present on the cell membrane are involved (Hosseini and Sarvi, 2015; Fariq et al., 2017). In case of intracellular synthesis, cations are utilized in the capturing metallic ions from the exterior and subsequent reduction inside the cell, followed by accumulation in the cytoplasmic membrane, cell wall, or periplasmic space. Besides the commonly reported reductase, laccase and ligninase have also been reported for the intracellular synthesis route (Ovais et al., 2018).

Proteins and Peptides in Biosynthesis

In addition to the enzymes discussed in the above section, myriad proteins are also found to responsible for NP formation by microbes. Proteins and peptides are also involved in the capping and stabilization of the formed nanometals. Also, for intracellular entry of metals, transport proteins become essential. Especially in case of magnetic NPs, MTB employ magnetosome membrane proteins for biomineralization. Another protein termed MagA, isolated from the strain *Magnetospirillum* sp. AMB-1, was elemental in biogenic magnetic NP synthesis (Matsunaga and Takeyama, 1998). In another instance, for controlled size and shape, a small acidic protein Mms6 isolated from the same strain was utilized to precipitate uniform $CoFe_2O_4$ nanocrystals *in vitro* (Prozorov et al., 2007). In case of smaller peptides, dipeptides, and tripeptides having polar amino groups have shown mediation of assembly of Au NPs in the presence of $HAuCl_4$ as a reducing agent. Gold NP-tripeptide was prepared using a novel tripeptide, harboring a C-terminus tyrosine residue that reduced Au^{3+} to Au NPs. Furthermore, the terminally located free amino group bound Au NPs resulting in stable colloidal Au (Ramesh et al., 2015). In a similar study, yeast strains of *Schizosaccharomyces pombe* and *Candida glabrata* accumulated CdS NPs inside the cell plasma coated with phytochelatins, a peptide known to arrest DNA disruption and cell cycle damage occurring in metal toxicity (Krumov et al., 2007).

Efflux Pump Systems

As toxic metal ions accumulate around a microbial cell and further enter inside the cell membrane, efflux pumps try to eliminate and excrete them into the extracellular space, thus combating metal toxicity. The presence of efflux pump genes,

including a multidrug resistant (MDR) one, is one of the main factors behind a metal-resistant phenotype and has an impact on the nanometal synthesis capacity of the organism. In case of silver, BaeSR, as a two-component signal transduction (TCS) system, is involved in the overexpression of efflux pumps related to metal and antibiotic resistance. Such proteins generally belong to the RND (resistance, nodulation, and cell division) family. Similarly, CusCFBA efflux system has been identified in the *Escherichia coli*, overexpressed in the presence of higher concentration of copper ions (Graves et al., 2015). A lower number of porins such as OmpF or OmpC present on the outer membrane of *E. coli* is also known to be responsible for the efflux of silver ions and hence the resistant phenotype (Salas-Orozco et al., 2019). These efflux pumps are also responsible for antibiotic resistance in bacteria, and one study explored vanillin-coated Au NPs as inhibitors of MexAB-OprM efflux pump components (Arya et al., 2019).

Interaction With Organelles and Biomolecules

The interaction of metals with cells and subsequent nanosynthesis can be elucidated precisely by understanding how they interact with individual organelles and biomolecules. In fact, instead of whole cells, organelles and subcellular components in *ex vivo* conditions have been explored for their capability to synthesize nanometals with controlled dimensions. In one such instance, circular plasmid DNA molecules close to 4-kb size (acting as the reducing agent) were allowed to complex electrostatically with Ag ions, followed by UV irradiation, leading to the formation of Ag NPs, compared with the non-plasmid control (Liu et al., 2012). Isolated porins from the cell membrane of *Mycobacterium smegmatis*, termed as MspA, were docked onto the self-assembled organic thiosulfates and electrodeposited on Au plates. These self-assembled protein layers were further used to deposit Cu NPs with potential applications in transistors (Woerner et al., 2007). Separate classes of studies have also focused on protein self-assemblies into nanostructures. Genetically engineered *Pichia pastoris* has been used to synthesize protein nanostructures composed of blocks to coat DNA used in gene delivery applications (Hernandez-Garcia et al., 2012).

GENETIC AND MOLECULAR BASES OF METAL NANOTIZATION

In the presence of elevated concentrations of heavy metals, bacteria usually respond by expressing specific heavy metal resistance genes (MRGs) for NP production. Since these genes are mostly present in plasmids or transposons, they are easily transferred to the neighboring microbial communities. Several research groups have studied these genes to elucidate the mechanisms behind nanotization. A group worked on estimating the amount of metals bioavailable for the microbial community using quantitative PCR and found that the gene *czcA* (a Cd/Zn/Co efflux pump) was responsible for Cd/Zn/Co bioavailability in microbes (Roosa et al., 2014). A study by yang and their group showed that some of the MRG such as *pcoA*, *merA*, *silC*, and *arsA* genes were present in higher frequencies in MDR bla_{NDM-1}^{-} and $bla_{CTX-M-15}^{-}$ Enterobacteriaceae isolates (Yang et al., 2018). In Northern China near a copper tailing dam area, the following genes were found at the remedial site: copper resistance genes (*copA*, *copB*, *pcoA*, *pcoC*, and *pcoD*), other MRG (*czcA*, *czcC*, and *czcD*), arsenic resistance genes (*arsB* and *arsC*), *nccA* (for nickel), *pbrT* (for lead), and *chrB* (for chromium) (Chen et al., 2019). Some of the genes are present in operons such as s*ilG* gene in the *sil* operon for silver sequestration (Randall et al., 2015). A study has shown that *arsRBCC* operon and *arsC* gene in *Desulfovibrio desulfuricans* G20 helped in regulating arsenic in the microbial environment (Li and Krumholz, 2007). Studies have also found upregulated levels of efflux complexes in the presence of excess heavy metals, such as resistance-nodulation-cell division (RND) transporters, the P-type ATPases, efflux complexes made from membrane fusion protein (MFP) family, or the outer membrane factor (OMF) protein family.

The understanding of the genetics of microbe-mediated NP synthesis has been interestingly used to design genetically engineered microbes with metal-resistant phenotypes, which find applications in NP synthesis as well as remediating the metal-contaminated environment. Such an example was observed in *Escherichia coli* strains expressing PC synthetase of *Schizosaccharomyces pombe*, used for the synthesis of semiconductor CdS nanocrystals. The phytochelatins produced by the action of PC synthase act as a nucleation site for the nanocrystals and stabilize them against aggregation (Kang et al., 2008). Thus, several diverse gene families are reported to be involved in nanotization of metals by microbial strains.

APPLICATIONS OF MICROBIAL NANOPARTICLES

Owing to their nanoscale sizes leading to an increase in the surface/volume ratio, NPs find applications in myriad industrial, environmental, and biomedical applications. TiO_2 NPs from several microbial species such as *Micrococcus lylae*, *Cellulosimicrobium* sp., *Micrococcus aloeverae*, and *Chlorella pyrenoidosa* have been shown to show dye-degradation capability to remediate polluted waste waters (Fulekar et al., 2018). Similarly, Au NPs from *Streptomyces griseoruber* and ZnO NPs from *Cordyceps* have been specifically explored to degrade methylene blue dye *via* catalysis (Ranjitha and Rai, 2017; Li et al., 2019). Toxic compound remediation is also a major environmental application of biogenic NPs where PbS and Au NPs from bacterial and fungal strains have shown promise (Lok et al., 2006; Shen et al., 2017). In electronics, TiO_2 NPs from *Bacillus mycoides* have been applied in the construction of green solar cells (Ordenes-Aenishanslins et al., 2014). Closer dimensions to biomolecules also render these biogenic NPs good candidates for biomedical applications. A major portion of microbial NPs such as Ag, Ag, Se, and Te NPs find applications as antibacterial, antifungal, antiviral, and antibiofilm agents (Abdeen et al., 2014; Zonaro et al., 2015; El-Sheekh et al., 2020; Gursoy, 2020). Biogenic NPs display good penetration across membranes, and blood–tissue and blood–brain barriers,

thus finding applications as anticancer agents and drug delivery vehicles (Gonzalez-Ballesteros et al., 2017). An interesting application had utilized bacterial magnetosomes loaded with doxorubicin and tested on H22 tumor-bearing mice; they displayed higher tumor toxicity than only doxorubicin (Sun et al., 2009). These magnetosomes are also recognized as better MRI contrast agents with higher relaxivity than the conventional ones (Zhang Y. et al., 2018). In biosensing, CdSe QDs from *C. pyrenoidosa* have been exploited for imatinib sensing, while Fe_2O_3 NPs have been used to detect H_2O_2 and glucose (Mishra et al., 2016; Zhang Z. et al., 2018). Thus, it is evident that the applications of microbial NPs are diverse and multifaceted, holding great promise in several fields of research.

CONCLUSION AND FUTURE PERSPECTIVES

Several bacterial, viral, algal, fungal, and yeast species are known to trap metals *in situ* and convert them to elemental NP forms, while remediating their immediate environment in the process. This feature has been further exploited in industrial, environmental, and biomedical applications. However, most metals are toxic to microbial cells; thus, it is widely reported that the synthesis of metals into their elemental nano-forms results as a defense mechanism or stress response for the organism to eliminate, segregate from essential organelles, or reactively change the harmful nature of the metals. Mechanisms such as enzymatic reactions, precipitation, complexation, binding to peptides, and efflux pumps are involved in this process, which act independently or simultaneously for the metal remediation by the cell, resulting in a metal-resistant phenotype, with microbes harboring specific genes for this property. Even though a number of mechanisms have been reported for biogenic nanosynthesis, it is important to extend our studies to other reducing enzymes, catalytic proteins, and stabilizers along with their tandem action in the cell. The role of different classes of enzymes needs to be studied in detail. The precise understanding of pathways and mechanisms involved in the biogenic synthesis allows researchers to modulate existing microbes and engineer metabolic pathways for NP synthesis with controlled size and shapes for varied applications.

AUTHOR CONTRIBUTIONS

SG, RA, and KB conceptualized and prepared the manuscript. MFA and SR helped and addressing the review comments with inputs which were further included in the revised manuscript. All authors have critically reviewed the manuscript.

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REVIEW
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Exploration of Microbial Factories for Synthesis of Nanoparticles – A Sustainable Approach for Bioremediation of Environmental Contaminants

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The nanomaterials synthesis is an intensifying research field due to their wide applications. The high surface-to-volume ratio of nanoparticles and quick interaction capacity with different particles make them as an attractive tool in different areas. Conventional physical and chemical procedures for development of metal nanoparticles become outmoded due to extensive production method, energy expenditure and generation of toxic by-products which causes significant risks to the human health and environment. Hence, there is a growing requirement to search substitute, non-expensive, reliable, biocompatible and environmental friendly methods for development of nanoparticles. The nanoparticles synthesis by microorganisms has gained significant interest due to their potential to synthesize nanoparticles in various sizes, shape and composition with different physico-chemical properties. Microbes can be widely applied for nanoparticles production due to easy handling and processing, requirement of low-cost medium such as agro-wastes, simple scaling up, economic viability with the ability of adsorbing and reducing metal ions into nanoparticles through metabolic processes. Biogenic synthesis of nanoparticles offers clean, non-toxic, environmentally benign and sustainable approach in which renewable materials can be used for metal reduction and nanoparticle stabilization. Nanomaterials synthesized through microbes can be used as a pollution abatement tool as they also contain multiple functional groups that can easily target pollutants for efficient bioremediation and promotes environmental cleanup. The objective of the present review is to highlight the significance of micro-organisms like bacteria, actinomycetes, filamentous fungi, yeast, algae and viruses for nanoparticles synthesis and advantages of microbial approaches for elimination of heavy metals, dyes and wastewater treatment.

Keywords: bioremediation, green synthesis, microbes, nanoparticles, wastewater treatment

INTRODUCTION

The environmental pollution is one of the major problems of society. Water is essential for life and industrial as well as economic growth of nation. The heavy metals, organic compounds, insecticides, fertilizers, industrial effluents, and sewage are the principal environmental contaminants. The disposal of contaminants in water streams and rivers leads to contamination of water resources and adverse effect on aquatic ecosystem (Sharma et al., 2015). The excessive application of synthetic dyes in different industrial activities and use of pesticides in crop fields is responsible for water and soil pollution (Choi et al., 2018; Doshi et al., 2018; Hu et al., 2018). The disposal of untreated effluent in water resources may be due to inefficiency of wastewater treatment plants against some specific pollutants present at low concentration degrade surface water quality and give adverse impact on ecosystem and health of human-beings (Ajaz et al., 2020; Oon et al., 2020). However, contaminants can be used as a resource to fabricate nanoparticles via biogenic route for pollutants deterioration (Huang et al., 2018; Seifan et al., 2018; Mandeep and Shukla, 2020). The environmental attenuation depends on various technologies such as adsorption, chemical reactions, photocatalysis and filtration for contaminants removal from environment. Conventional methods are bound with various limitations such as expensive, energy intensive, generation of hazardous toxic chemicals, requirement of high temperature and pressure and uneconomical method because of their inability to completely purify wastewater and no option to reuse the material (Sharma et al., 2015). Nanoparticles are increasingly applied for the wastewater treatment due to their large surface area, high reactivity and degree of functionalization (Goutam et al., 2018). The treatment of wastewater can be performed by using pure or mixed microbial culture due to the synergistic metabolic action. The periphyton biofilm can be applied for degradation of dyes (Shabbir et al., 2020). The removal of dyes has been reported through the utilization of genetically modified microbes (Kumar et al., 2020). Dong et al. (2019) found that *Enterococcus gallinarum* and *Streptomyces* S27 degraded azo dyes by azoreductase enzyme. Laccase showed significant degradation potential for many dyes (Iark et al., 2019). The laccase degrades dye by non-specific free radical mechanism to form phenolic compounds and there will be no formation of aromatic amines (Chivukula and Renganathan, 1995).

The characteristics and efficiency of nanotechnology-based materials makes them appropriate for treatment of environmental contaminants as they have improved catalysis, high surface area which reflects high activity (Dwevedi, 2019). The degradation of environmental pollutants is challenging with conventional methods due to the complex nature of mixture with less reactivity and more volatility. The recent researches have shown the application of nanomaterials for solving most of the issues related to water quality and its recycling (Uddandarao et al., 2019). The treatment of wastewater and industrial effluent based on nanotechnology can provide water with less toxic substances, heavy metals and other impurities (Zonaro et al., 2017; Salem and Fouda, 2020). El-Kassas et al. (2016) reported the various nanomaterials for the removal of inorganic and organic pollutants.

Nanoparticles have large surface area with surface energy which can easily absorb huge amount of pollutants. They can catalyze chemical reactions with fast speed with less energy intake as compared to huge material, thus check the release of contaminants. Due to the unique surface chemistry of nanomaterials as compared to conventional methods, can target contaminants with their functional groups for remediation. The desired alterations in shape, size, absorptive capacity and chemical components of nanomaterials enhances the performance of nanomaterials can provide significant benefit for treatment of contaminants (Sekoai et al., 2019; Wu et al., 2019). Application of biogenic substances will promote green technology as there will be very less generation of a sludge and it can offer a safe alternative for remediation of environmental pollutants. The interception of green chemistry and nanotechnology has paved a path to green nanotechnology (Anastas and Warner, 1998). The particles in the range from 1 to 100 nm are considered as nanoparticles which may present in an aggregate or free condition. Nanoparticles are basic component of nanotechnology as they are fundamental sources of various nanostructured devices. Nanoparticles are produced either by top-down or bottom-up methods as shown in **Figure 1**. Top-down approach is a process of conversion of large structures into small ones with the help of physical methods. The bottom-up approach utilizes small atoms or molecules to produce nanoparticles by self-assembly or supra-molecular chemistry. The biological mode of nanoparticle synthesis via bottom-up approach has been emerged as novel and green strategy. The biosynthesis of nanoparticles has got recognition due to less toxicity, biocompatibility, energy efficient and eco-friendly nature of the process with less sludge production hence can be used in pharmaceutical industry and biomedical applications (Mohammadlou et al., 2016; Ijaz et al., 2020; Noman et al., 2020; Goutam and Saxena, 2021). Micro-organisms in contaminated environment adapt and modify themselves for the degradation of xenobiotic compounds exhibiting the enormous catabolic activity toward the polluted environment (Hsueh et al., 2017). Biogenic synthesis of metal nanoparticles has received advantages due to their physico-chemical properties and wide applications in biotechnology (Slavin et al., 2017; Goutam et al., 2020). The global generation of metallic nanoparticles is estimated as 13.7 billon United States dollars and it is anticipated to increase 50 billon United States dollars by the year 2026. Main objective of the present review is to provide information on recent developments for the fabrication of functional nanoparticles, their characterization techniques and applications for remediation of pollutants.

FACTORS THAT AFFECTING NANOPARTICLES SYNTHESIS

Different experimental conditions such as pH, temperature, raw materials concentration, size and procedure can affect production and utilization of microbial nanoparticles (Baker et al., 2013).

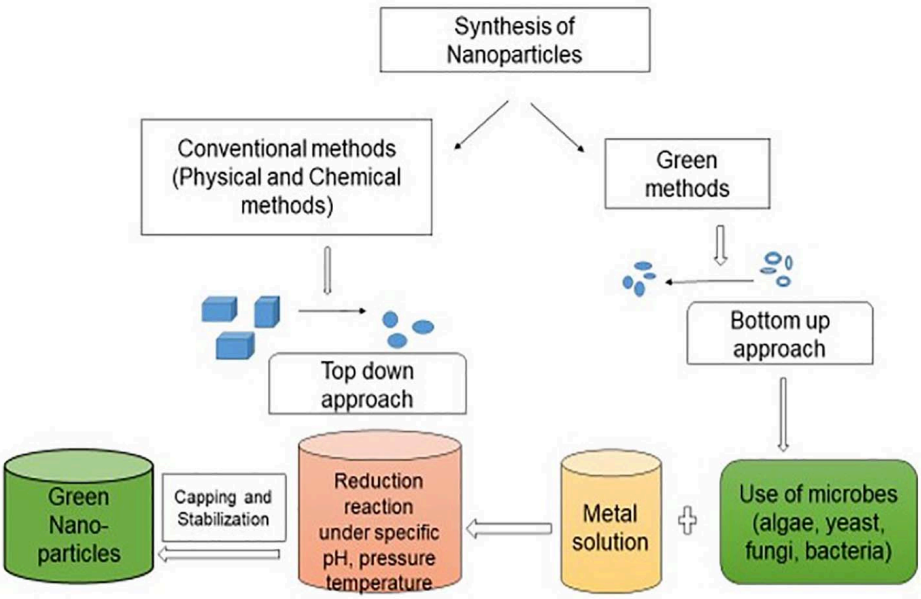

FIGURE 1 | Synthesis of nanoparticles by different methods.

The pH of the medium affects microbial synthesis of nanoparticles. Reports have revealed that pH of solution medium affects size and composition of produced nanoparticles (Patra and Baek, 2014). The temperature is another parameter that influences nanoparticles synthesis in physical, chemical and biological methods. The physical method requires very high temperature (>350°C), whereas chemical methods require less than 350°C temperature. The production of nanoparticles by using green technology generally requires temperature less than 100°C (Rai et al., 2006). The pressure plays a pivotal role in nanoparticles synthesis as it can alter dimension and form of synthesized nanoparticles. Reduction of metal ions with biogenic sources was fast at ambient pressure condition (Tran et al., 2013). The synthesized biogenic nanoparticles quality is significantly affected by exposure period (Darroudi et al., 2011). The shape, size and adsorption capacity of the nanoparticles play a significant function in determination of the nanoparticle properties. The melting point of nanoparticles has been reported to decrease when the size of particles reduces to the nanometer scale. Baer et al. (2013) stated that appearance of nanoparticles influences their chemical properties. The change in the chemical properties has been observed when the individual nanoparticles come in contact with the surface of other nanoparticles. This process promotes the development of tuned nanoparticles. Environmental conditions play a pivotal role in synthesis of nanoparticles. Sarathy et al. (2008) reported conversion of single nanoparticle into core-shell nanoparticle by absorbing materials or reacting with other materials either by oxidation or corrosion. The expenses required for the synthesis of nanoparticles is also an important component. To promote potential applications of nanoparticles, expenses related with their production required to be controlled. Physical method requires expensive equipment whereas chemical method provides high yield in less time but it is expensive method (Ding et al., 2015). The nanoparticles production by biological methods involves low cost and can be applied at large scale (Gour and Jain, 2019).

MICROBIAL SYNTHESIS OF NANOPARTICLES

The green technology is an extensively accepted procedure for bioremediation due to clean, safe, non-toxic effect and environmentally benign method (Mishra et al., 2014; Salvadori, 2019). The production of nanoparticles by microbes is bottom up technique in which most of the reactions are reduction/oxidation. The basic concept of bioremediation is the change of harmful pollutants into less harmful compounds. Nanoparticles produced from microbes can transform pollutants into the compounds with less toxicity, solubility and mobility (Wasi et al., 2008). The metallic nanoparticles produced by biological methods are more stable at room temperature for long duration in comparison to metallic nanoparticles generated via chemical routes (Balakrishnan et al., 2017). The capping of the microbial proteins over the metallic nanoparticle surface provides stability to the biosynthetic procedures. The cost of production of the nanoparticles can be decreased to 1/10th in comparison to the chemical synthesis protocols by applying proper methods. Significant amount of contaminants can be removed with less number of biogenic nanoparticles. The biogenic nanoparticles show large surface area with high catalytic reactivity and they do not assemble due to the presence of capping agents released by microbes. The nanoparticles can be synthesized by microbes either intracellularly or extracellularly. Mishra et al. (2014) stated

that extracellular biosynthesis is popular due to its low cost as it can be done without downstream processing. Microbes absorb precursor metal ions and can produce respective nanoparticles by using detoxification process (Mohseniazar et al., 2011). Microorganisms do not require high energy (Kumari et al., 2017) and there is no need to add capping or stabilizing agents thus application of microbes is cost effective process (Makarov et al., 2014). The synthesis of fine, uniform and functional nanoparticles under normal conditions is a challenging task (Tang et al., 2017). The biogenic sources provide a safe, cost-effective and environmentally benign method to fabricate metal nanoparticles (Ovais et al., 2018). The advantages such as well-defined morphologies, ease of production, scaling and enhanced biocompatibility have been lucrative for scientists to utilize biological resources as nanofactories (Singh et al., 2016). Microorganisms such as virus, fungi, yeast, algae, marine microbes, actinomycetes, bacteria have been widely used for the production of nanoparticles with gold, silver, copper, silicon, iron, nickel, cadmium and lead as described below and listed in **Table 1**.

Filamentous Fungi Mediated Synthesis of Metallic Nanoparticles

The filamentous fungi can be used as a potential source for the nanoparticles synthesis. The mycelium of fungi has high surface area which secretes huge amount of proteins that can participate directly in nanoparticles production (Mohanpuri et al., 2008). The production of nanoparticles by filamentous fungi is considered better due to their capacity to secrete proteins, enzymes and metabolites, simple scaling up and downstream handling, economic feasibility, increased surface area due to presence of mycelia and low-cost requirement for production procedures (Fouda et al., 2018; Spagnoletti et al., 2019). Different filamentous fungi species grow very fast and their maintenance at laboratory conditions is easy (Fouda et al., 2018). The nanoparticles fabrication with nanoscale dimension through fungi shows more monodispersity as compared with those synthesized by bacteria. *Fusarium oxysporum* in the presence of aqueous $AuCl_4^-$ ions with NADH-enzyme-mediated reaction releases reducing agents into the solution for the formation of gold nanoparticles. The synthesized nanoparticles show long-term stability due to the protein binding capacity by linkage of cysteine and lysine residues (Das et al., 2017). The filamentous fungi have high regenerative ability with environmental-benign production for synthesis of metal nanoparticles in significant amount with its commercial feasibility (Bansal et al., 2005). *Aureobasidium pullulans, Aspergillus niger, Cladosporium resinae, Penicillium* species, *Funalia trogii, Ganoderma lucidum, Rhizopus arrhizus* and *Trametes versicolor* absorbed heavy metals from polluted sites which was used for nanoparticles production (Say et al., 2003). Salvadori et al. (2013) reported uptake of Cu(II) by *Hypocrea lixii* dead biomass and production of copper nanoparticles. The same microorganism was able to produce NiO nanoparticles both extra and intracellularly (Salvadori et al., 2015).

Fusarium oxysporum exhibited extracellular synthesis of Au–Ag nanoparticles when treated with equimolar mixture of tetrachloroaurate ion and silver nitrate (Senapati et al., 2005) and in the presence of hexachloroplatinic acid it can produce platinum nanoparticles (Riddin et al., 2006). *Aspergillus flavus* synthesized silver nanoparticles (9 nm size) as it can reduce silver ions due to presence of sil genes in their plasmid (Vigneshwaran et al., 2007). Salvadori et al. (2014) stated that *Aspergillus aculeatus* dead biomass was reported to produce NiO nanoparticles (5.89 nm size) which were organized in form of film. Due to the presence of metabolites, fungi are better resource for synthesis of nanoparticles in comparison to bacteria (Singh et al., 2016). Zhang et al. (2011) found biosynthesis of gold nanoparticles in vacuoles of filamentous fungi and they also explained the functions of fungal proteins for capping of gold nanoparticles. Filamentous fungi are known as better candidate for metallic nanoparticles synthesis due to the presence of different enzymes in their cells and simple handling procedures (Khandel and Shahi, 2018). Filamentous fungi show metal uptake capacities and it can be easily cultured in huge amount by solid substrate fermentation. *Verticillium* species produced gold nanoparticles intracellularly after the exposure to chloroauric acid solution. Gericke and Pinches (2006) found the synthesis of gold nanoparticles by *Verticillium luteoalbum*. There was no effect of age on the shape of the gold nanoparticles but number of nanoparticles was reduced significantly with the use of old cells. The biomass of *Fusarium oxysporum* was used for generation of silver nanoparticles (Karbasian et al., 2008). Saxena et al. (2014) stated that genetic modification methods can be applied to enhance properties of nanoparticles.

Yeast Mediated Synthesis of Metallic Nanoparticles

Most of the yeast genera can accumulate significant amount of heavy metals. The detoxification mechanism in yeast cells takes place by glutathione, metallothioneins and phytochelatins. Dameron et al. (1989) called yeast cells as semiconductor crystals or quantum semiconductor crystals as they have the ability to synthesize semiconductor nanoparticles such as cadmium and lead sulfide. *Pichia jadinii* synthesized gold nanoparticles in which gold ions were reduced by the enzymes present in cytoplasm or cell wall of yeast (Gericke and Pinches, 2006). The particles were not clumped together due to the peptide coating and exhibited very high stability as compared to nanoparticles synthesized by chemical methods. The quantum crystallites were produced by *Candida glabrata* and *Schizosaccharomyces pombe* when they were grown in cadmium salts (Williams et al., 1996). The gold nanoparticles were generated by *Yarrowia lipolytica* both extracellularly and intracellularly (Pimprikar et al., 2009). In *Yarrowia lipolytica,* nickel and cadmium in less concentration caused significant accumulation of metal-binding proteins (Strouhal et al., 2003). It not only resists heavy metals and also helps in hydrocarbons degradation (Bankar et al., 2009). *Yarrowia lipolytica* can be used for the synthesis of metallic nanoparticles as well as treatment of environmental contaminants such as heavy metals. The

TABLE 1 | Biological synthesis of metal nanoparticles using different microbes.

S. no.	Sources	Type of nanoparticles	Synthesis methods	Experimental conditions	Characterizations	Morphology	Size (nm)	References
Filamentous fungi								
1.	*Aspergillus niger*	Silver	Extracellular	T: 25°C; t: 72 h	TEM, ESI	Spherical	20	Gade et al. (2008)
2.	*Fusarium solani*	Silver	Extracellular	T: 25°C; t: 24 h	TEM, FTIR	Spherical	5–35	Ingle et al. (2009)
3.	*Pleurotus sajor-caju*	Silver	Extracellular	T: 25°C; t: 72 h; pH 6	SEM	Spherical	5–50	Nithya and Ragunathan (2009)
4.	*Coriolus versicolor*	Silver	Extracellular Intracellular	T: Room; pH 10	FTIR, TEM, XRD	Spherical	25–75	Sanghi and Verma (2009)
5.	*Penicillium fellutanum*	Silver	Extracellular	T: 5°C; t: 24 h; pH 6	TEM	Globular	5–25	Kathiresan et al. (2009)
6.	*Trichoderma viride*	Silver	Extracellular	T: 27°C; t: 48 h; pH 7.2	TEM, FTIR	Spherical	5–40	Fayaz et al. (2010)
7.	*Epicoccum nigrum*	Silver	Extracellular	T: 55°C; pH 12	XRD, TEM	Spherical	1–22	Qian et al. (2013)
8.	*Guignardia mangiferae*	Silver	Extracellular	T: 25°C; t: 12 h	HR-TEM, SAED, XRD	Spherical	5–30	Balakumaran et al. (2015)
9.	*Fusarium oxysporum*	Silver	Extracellular	T: 50°C; pH 6	FTIR, TEM	Spherical	5–13	Husseiny et al. (2015)
10.	*Arthroderma fulvum*	Silver	Cell filtrate	T: 55°C; t: 12 h; pH 10	XRD, TEM	Spherical	15.5	Xue et al. (2016)
11.	*Colletotrichum* sp. ALF2-6	Silver	Cell free extract	T: 50–80°C; alkaline pH	FTIR, XRD, TEM	Myriad	5–60	Azmath et al. (2016)
12.	*Duddingtonia flagans*	Silver	Extracellular	T: 60°C; pH 10	DLS, TEM	Quasi-spherical	30–409	Costa Silva et al. (2017)
13.	*Fusarium oxysporum*	Silver	Cell-free filtrate	T: 28°C	DLS, SEM	Spherical	24	Hamedi et al. (2017)
14.	*Aspergillus oryzae* MTCC no. 1846	Silver	Cell filtrate	T: 90°C; pH 10	XRD, TEM, FTIR	Spherical	7–27	Phanjom and Ahmed (2017)
15.	*Fusarium keratoplasticum*	Silver	Culture filtrate	T: 35°C; t: 48 h	XRD, FTIR	Spherical	6–36	Mohmed et al. (2017)
16.	*Rhizopus stolonifera*	Gold	Culture filtrate	T: 40°C; 48 h	XRD, TEM, FTIR	Spherical	9.47	AbdelRahim et al. (2017)
17.	*Trichoderma longibrachaitum*	Silver	Culture filtrate	T: 28°C; t: 72 h	FTIR, TEM	Spherical	10	Elamawi et al. (2018)
18.	*Penicillium oxalicum* GRS-1	Silver	Extracellular	T: 60°C; pH 7	XRD, FESEM	Spherical	10–40	Rose et al. (2019)
19.	*Aspergillus fumigatus* BTCB10	Silver	Cell-free filtrate	T: 25°C; pH 6	ATR-FTIR, XRD, SEM	Spherical	322.8	Shahzad et al. (2019)
Yeast								
1.	*Candida glabrata*	CdS	Intra and extracellular	pH 3.5; 40,000 g	TEM	Hexamer	20 Å, 29 Å	Dameron et al. (1989)
2.	*Pichia jadinii*	Au	Intracellular	T: 28°C; t: 24 to 72 h	TEM	Various	–	Gericke and Pinches (2006)
3.	*Yarrowia lipolytica NCIM3589*	Au	Cell wall	T: 30°C; t: 72 h	SEM TEM	Particles and plates	15	Agnihotri et al. (2009)
4.	*Saccharomyces cerevisiae*	TiO_2	Extracellular	T: 60°C, t: 10–20 min	X-ray, TEM	*Spherical*	12	Jha et al. (2009)
5.	*Saccharomyces cerevisiae*	Au	Cell wall cytoplasm	t: 15 min to 72 h	TEM	Spherical	15	Sen et al. (2011)
6.	*Candida albicans*	Au	Cell-free extract	T: 25°C; pH 7	TEM	Spherical	5	Ahmad et al. (2013)
7.	*Rhodotorula mucilaginosa*	Ni/NiO	*Extracellular*	T: 30°C; pH 4; t: 60 min	AFM, XPS, FTIR	*Spherical*	5.5	Salvadori et al. (2016)
8.	*Chlorococcum humicola*	Silver	Cell extract	T: Room	FTIR, TEM, SEM	Spherical	16	Jena et al. (2013)
9.	*Aphanothece* sp.	Silver	Cell extract	T: Room	EDX, SEM	Spherical	44–79	Sudha et al. (2013)
10.	*Sargassum muticum*	Silver	Cell extract	T: Room	FTIR, XRD, TEM	Spherical	5–15	Azizi et al. (2013)
11.	*Caulerpa racemosa*	Silver	Cell extract	T: Room	TEM, XRD	Spherical Triangular	5–25	Kathiraven et al. (2014)

(Continued)

TABLE 1 | Continued

S. no.	Sources	Type of nanoparticles	Synthesis methods	Experimental conditions	Characterizations	Morphology	Size (nm)	References
12.	*Bifurcaria bifurcata*	Copper oxide	Cell extract	T: 100–120°C	FTIR, XRD, TEM	Crystalline	5–45	Abboud et al. (2014)
13.	*Sargassum longifolium*	Silver	Cell extract	T: Room	TEM, SEM	Spherical	40–85	Rajeshkumar et al. (2014)
14.	*Sargassum bovinum*	Palladium	Cell extract	T: 60°C	TEM, XRD, EDX	Octahedral	5–10	Momeni and Nabipour (2015)
15.	*Sargassum tenerrimum*	Gold	Cell extract	T: Room	HRTEM, FTIR	Rounded	5–45	Ramakrishna et al. (2016)
16.	*Sargassum ilicifolium*	Aluminum oxide	Cell extract	T: 25°C; t: 24 h; pH 4	TEM, SEM	Hexagon	35	Koopi and Buazar (2018)
Bacteria								
1.	*Lactobacillus* species	Titanium	Cell culture	pH 2–4	XRD, TEM	Spherical	40–60	Prasad et al. (2007)
2.	*Pseudomonas Putida* NCIM 2650	Silver	Extracellular	T: 37.5°C; t: 48 h; pH 6	FTIR, SEM	Spherical	70	Thamilselvi and Radha (2013)
3.	*Serratia nematodiphila*	Silver	Extracellular	T: 35°C; t: 24 h	TEM, XRD	Crystalline	10–31	Malarkodi et al. (2013)
4.	*Escherichia coli* (DH5a)	Silver	Extracellular	t: 15 min	TEM	Spherical	10–100	Ghorbani (2013)
5.	*Bacillus* strain CS11	Silver	Extracellular	T: Room	TEM	Globular	42–92	Das et al. (2014)
6.	*Bacillus methylotrophicus*	Silver	Extracellular	T: 28°C, t: 24 h	TEM, EDX	Spherical	10–30	Wang et al. (2016)
7.	*Novosphingobium* species	Silver	Extracellular	T: 25°C; t: 48 h	XRD, TEM	Spherical Crystalline	8–25	Du et al. (2016)
8.	*Pseudomonas fluorescens* CA 417	Silver	Extracellular	T: 80°C; pH 8	FTIR, XRD, EDS, TEM	Cubic Spherical Oval	10–60	Syed et al. (2016)
9.	*Bacillus amyloliquefaciens*	Titanium dioxide	Cell culture	T: 37°C; t: 72 h	FTIR, TEM, XRD	Spherical	22–97	Khan and Fulekar (2016)
10.	*Brevibacillus formosus*	Gold	Cell culture	T: 37°C; t: 24 h	FTIR, TEM, DLS	Spherical	5–12	Srinath et al. (2017)
11.	*Pseudomonas* sp. ef1	Silver	Cell culture	T: 22°C; t: 24 h	SEM, TEM, EDS	Spherical	50	John et al. (2020)
Actinomycetes								
1.	*Streptomyces hygroscopicus*	Gold	Intracellular	T: 35°C; 72 h	TEM	Spherical	10–20	Waghmare et al. (2014)
2.	*Streptomyces kasugaensis* NH28 strain	Silver	Cell filtrate	T: 27°C; t: 72 h	TEM, FTIR	Rounded	4.2–65	Składanowski et al. (2016)
3.	*Streptomyces capillispiralis*	Copper	Extracellular	T: 35°C; t: 6 h	TEM, XRD	Spherical	3.6–59	Hassan et al. (2018)
4.	*Streptomyces* species	Silver	Extracellular	T: 35°C; pH 8	TEM, FTIR	Spherical	2.3–85	El-Gamal et al. (2018)
Marine microbes								
1.	*Sargassum wightii*	Gold	Extracellular	t: 12 h	XRD, TEM	Spherical	8–12	Singaravelu et al. (2007)
2.	*Fucus vesiculosus*	Gold	Extracellular	pH 7; t: 8 h	XRD, TEM	Spherical	20–50	Mata et al. (2009)
3.	*Pichia capsulata*	Silver	Culture filtrate	pH 6; T: 5°C; t: 24 h	TEM	–	50–100	Manivannan et al. (2010)
4.	*Rhodosporidium diobovatum*	Lead	Intracellular	T: 25°C; t: 96 h	XRD	Spherical	2–5	Seshadri et al. (2011)
5.	*Gelidiella acerosa*	Silver	Extracellular	t: 48 h at 120 g $AgNO_3$	SEM, XRD, TEM	Spherical	22	Vivek et al. (2011)
6.	*Ulva fasciata*	Silver	Extracellular	T: 100°C; t: 4 h	FTIR, SEM, TEM	Spherical	28–41	Rajesh et al. (2012)
Virus								
1.	Tobacco mosaic virus	CdS, PbS, SiO_2, and Fe_2O_3	Surface	$CdCl_2$ Pb (NO_3)	TEM	Nano-tubes	10–40	Shenton et al. (1999)
2.	M13 bacteriophage	ZnS, CdS	Inorganic synthesis	T: 0–25°C; t: 24 h	HRTEM STEM	ND	560 × 20 nm quantum dot nano-wires	Mao et al. (2003)
3.	Tobacco mosaic virus	Gold	–	t: 20 min	TEM	Spherical	5	Kobayashi et al. (2012)

reduction of gold nanoparticles on the cell wall of dead cells of *Saccharomyces cerevisiae* significantly decreased the production cost of nanoparticles. The synthesis of cadmium nanoparticles by *Candida glabrata* and *Schizosaccharomyces pombe* has been reported by Dameron et al. (1989). *Rhodosporidium diobovatum* has been used for production of stable lead sulfide nanoparticles intracellularly (Seshadri et al., 2011). Soliman et al. (2018) described the synthesis of silver nanoparticles by *Candida albicans, Saccharomyces boulardii and Candida utilis*. Lian et al. (2019) reported use of *Magnusiomyces ingens* LHF1 for generation of stable selenium nanoparticles. Two patents were granted to Benedito Correa and his team members for synthesis of copper nanoparticles and use of fungal species for remediation of wastewater and industrial scale synthesis of copper nanoparticles was obtained in an inexpensive and eco-friendly manner. The patents were processes described to be used to bioremediate the copper tailings pond located at Sossego mine owned by the Company Vale SA, Canaã dos Carajás, Pará, Brazilian Amazonia region. Briefly, the processes consist of using the dead biomasses of the yeast *Rhodotorula mucilaginosa*, and of the filamentous fungi *Hypocrea lixii* and *Trichoderma koningiopsis* in aqueous solution containing copper, to removal of the metal, and concomitant synthesis of metallic copper nanoparticles, under conditions of physico-chemical parameters determined as optimal for carrying out the process. Obtaining as a final product, nanoparticles of metallic copper, in addition to promoting the uptake of the polluting transition metal (copper) from the impacted area. Being a low cost and ecofriendly process. The copper removal capacities and concomitant transformation into metallic copper NPs for *Rhodotorula mucilaginosa*, *Hypocrea lixii*, and *Trichoderma koningiopsis* were, respectively: 26.2 mg g^{-1}, 19.0 mg g^{-1} and 21.1 mg g^{-1} (Correa et al., 2014a,b). Salvadori et al. (2016) explained the production of magnetic spherical nanoparticles of nickel or nickel oxide by dead organic matrix of *Rhodotorula mucilaginosa*. This technique can be of commercial importance due to the induction of magnetic metallic nanoparticles from liquid waste containing toxic metals which may results in detoxification of effluents and safe environmental release. Yeast mediated synthesis data of metallic nanoparticles are summarized in **Table 1**.

Algae Mediated Synthesis of Metallic Nanoparticles

The algae are aquatic oxygenic photoautotrophs which can be used in production of nanoparticles (Castro et al., 2013). *Chlorella vulgaris*, *Dunaliella salina*, and *Nannochloropsis oculata* can produce silver nanoparticles of less than 15 nm size inside the cells within 48 h (Mohseniazar et al., 2011). The bio reduction ability of algae reflected significant potential in green synthesis of various metal oxide nanoparticles such as gold, silver, platinum, palladium, copper oxide and zinc oxide (Konishi et al., 2007; Xie et al., 2007; Oza et al., 2012; Momeni and Nabipour, 2015). Algae can produce complex inorganic nanomaterials both intracellularly and extracellularly (Sau and Murphy, 2004). The gold nanoparticles can be synthesized intracellularly in *Rhizoclonium fontinale* and extracellularly in *Lyngbya majuscula* and *Spirulina subsalsa* (Chakraborty et al., 2009). The metal ions can be attached to the cell surface via electrostatic interactions between ions and negatively charged carboxylate groups. Later, ions can be reduced by enzymes which lead to nuclei formation and grow with reduction of metal ions (Parial et al., 2012). Accumulation of gold (9–20 nm size) was reported in *Chlorella vulgaris* dried cell suspension (Hosea et al., 1986). *P. boryanum* in aqueous $AuCl_3$ solution showed the deposition of gold (I)–sulfide nanoparticles at the cell wall. Cyanobacteria shows reduction of gold (III)–chloride to metallic gold with the formation of an intermediate Au (I) and gold (I)–sulfide (Lengke et al., 2006). **Table 1** highlights the algae mediated synthesis of metallic nanoparticles.

Bacteria Mediated Synthesis of Metallic Nanoparticles

The bacteria are known as potential bio-resources for generation of nanoparticles such as gold, silver, platinum, palladium, titanium, titanium dioxide, magnetite cadmium sulfide and others as listed in **Table 1**. Bacteria are important microbes for fabrication of nanoparticles due to their adaptability to adverse environmental conditions (Wang et al., 2017). Garole et al. (2018) reported that some bacteria were able to reduce or precipitate soluble toxic inorganic ions into nontoxic insoluble metal nanoparticles (Fang et al., 2019). Bacteria can form nanoparticles with metals and metalloids either intracellularly or extracellularly under different physico-chemical conditions like as exposure period, pH, temperature, concentration of bacteria and metal salts. The biomolecules present in the medium or cell wall components can reduce metal ions in an extracellular process. However, in intracellular process, by electrostatic interactions functional groups present on the cell wall attract metal and metalloids and metal ions interact with proteins present inside the cells for production of nanoparticles. Due to easy extraction procedure and high efficiency extracellular reduction appears to be more favorable as compared to intracellular reduction. Fang et al. (2019) stated that dead bacteria can be used for synthesis of nanoparticles same as live bacteria. Bacteria can be utilized as biocatalyst as they act as biological platform for mineralization (Iqtedar et al., 2019). The bacteria can mobilize or immobilize metals and can reduce or precipitate metal ions. Bacteria can catalyze different reactions due to their enzymes and can produce inorganic nanoparticles (Iravani, 2014). The large quantities of nanoparticles (100–200 nm size) can be produced in a pure form via extracellular secretion of bacterial enzymes. The metal binding capacity of the bacterial cells and S-layer make them useful for their applications in bioremediation. The cell wall of bacteria plays a very crucial function as metals may percolate into the cytoplasm via cell wall and transferred back to the wall for extracellular secretion. The cell wall with metal binding sites can be changed by chemical reactions for specific groups, such as amines and carboxyl groups, which converts positive charge into negative charge. Application of bacteria for nanoparticles production is lucrative process as it does not require any expensive and toxic chemicals for synthesis and stabilization procedures.

Actinomycetes Mediated Synthesis of Metallic Nanoparticles

The actinomycetes show features of fungi and bacteria and they play a pivotal role in the production of metal nanoparticles. *Thermomonospora* species produced gold ions under harsh environmental conditions such as high temperature and alkaline conditions. *Rhodococcus* species alkali-tolerant actinomycetes induced for development of gold nanoparticles between 5 and 15 nm size (Ahmad et al., 2003). The high concentration of nanoparticles was reported on the cell wall in comparison to cell membrane. The metal ions were not toxic to the cells as there was no effect on cell growth after the fabrication of nanoparticles. Actinomycetes are good source for nanoparticles production due to their large surface area and with secretion of secondary metabolites. Actinomycetes can produce metallic nanoparticles either inside or outside the cells (Manivasagan et al., 2016; Hassan et al., 2018). Gold nanoparticles were synthesized by *Nocardia farcinica*, *Rhodococcus* sp., *Streptomyces viridogens, Streptomyces hygroscopicus, Thermoactinomyces* sp. and *Thermomonospora* species (Składanowski et al., 2016). The copper, zinc, manganese, and silver nanoparticles were also synthesized by using *Streptomyces* species (El-Gamal et al., 2018). **Table 1** highlights the actinomycetes mediated synthesis of metallic nanoparticles.

Marine Microbes Mediated Synthesis of Metallic Nanoparticles

The marine microbes have ability to synthesize nanoparticles as they exist in the bottom of sea and they are known to reduce huge amount of inorganic elements. Many marine microorganisms can produce metallic nanoparticles or mineral crystals with same properties of chemically synthesized nanomaterials. Marine microbes like bacteria (*Escherichia coli, Pseudomonas* species), cyanobacteria (*Spirulina platensis, Oscillatoria willei, Phormidium tenue*), yeast (*Pichia capsulata, Rhodospiridium diobovatum*), fungi (*Penicillium fellutanum, Aspergillus niger, Thraustochytrium* sp.) and algae (*Diadesmis gallica, Navicula atomus, Sargassum wightii, Fucus vesiculosus*) have been reported to produce inorganic nanoparticles (Kalabegishvili et al., 2012; Asmathunisha and Kathiresan, 2013). *Penicillium fellutanum*, marine fungus isolated from coastal mangrove sediment generates silver nanoparticles extracellularly after its exposure to silver nitrate (Kathiresan et al., 2009). Gomathi (2009) reported that marine fungi *Thraustochytrids* have poly-unsaturated fatty acids and show extracellular biosynthesis of composites of lipid and silver nanoparticles.

Escherichia coli AUCAS 112 and *Aspergillus niger* AUCAS 237 isolated from mangrove sediments reduced silver ions successfully and formed silver nanoparticles were monodispersed and globular in nature (Kathiresan et al., 2009). *Pseudomonas* sp. 591786 has also produced silver nanoparticles inside the cells which were polydispersed with various sizes from 20 to 100 nm (Muthukannan and Karuppiah, 2011). The culture filtrate of *Pichia capsulate,* a mangrove-derived yeast exhibited rapid production of silver nanoparticles (Manivannan et al., 2010). They revealed that protein was responsible for the silver nanoparticles production and it was present in the culture filtrate of yeast. *Rhodosporidium diobovatum* contained sulfur rich peptide which acted as a capping agent for the synthesis of lead sulfide nanoparticles (Seshadri et al., 2011). Govindaraju et al. (2008) reported the synthesis of silver, gold and bimetallic nanoparticles by *Spirulina platensis.* The protein secreted from *Oscillatoria willei*, marine cyanobacterium reduced silver ions and produced stable silver nanoparticles (Mubarak Ali et al., 2011a). Cadmium sulfide nanoparticles fabrication by applying C-phycoerythrin isolated from *Phormidium tenue* NTDM05 has been observed by Mubarak Ali et al. (2012). *Sargassum wightii*, brown seaweed was reported to synthesize gold nanoparticles (8–12 nm size) (Singaravelu et al., 2007). Mata et al. (2009) observed the use of *Fucus vesiculosus* for recovering gold from electronic scraps leachates and hydrometallurgical solutions for gold nanoparticles production as it has an ability of gold absorption and reduction. The extracellular production of silver nanoparticles in *Sargassum wightii* was reported by Govindaraju et al. (2009). Fucoidan, an algal polysaccharide application can stabilize gold nanoparticles and better method as compared to its synthetic production (Suwicha et al., 2010). Vivek et al. (2011) stated the production of silver nanoparticles by a red seaweed *Gelidiella acerosa*. Rajesh et al. (2012) reported that extracts of *Ulva fasciata* can be used as reducing agent for production of silver nanoparticles. *Navicula atomus* and *Diadesmis gallica* diatoms have the capacity to synthesize gold nanoparticles and silica-gold bio-nanocomposites (Kroger et al., 1999; Schrofel et al., 2011). Silicon-germanium nanocomposite was produced by *Stauroneis* species (Mubarak Ali et al., 2011b). *Pterocladia capillacae*, *Jania rubens, Ulva fasciata* and *Colpomenia sinuosa* were used for silver nanoparticles synthesis (Azizi et al., 2013). *Sargassum crassifolium*, seaweed, was used in gold nanoparticles production. *Cystoseira trinodis* synthesized CuO nanoparticles and reflected antioxidant potential and degraded methylene blue dye (Gu et al., 2018). Roni et al. (2015) used *Hypnea musciformis* seaweed as a stabilizing agent in synthesis of silver nanoparticles. Satapathy and Shukla (2017) observed the generation of highly monodispersed silver nanoparticles by marine cyanobacterium *Phormidium fragile*. The intracellular generation of gold nanoparticles was also reported by *Lyngbya majuscule* (Bakir et al., 2018). Marine microbes mediated synthesis data of metallic nanoparticles are summarized in **Table 1**.

Virus Mediated Synthesis of Metallic Nanoparticles

The application of viruses in synthesis of nanoparticles is a good approach that has been capable to produce inorganic nanomaterials such as cadmium sulfide, silicon dioxide, iron oxide and zinc sulfide. Virus mediated synthesis data of metallic nanoparticles are summarized in **Table 1**. The problem in synthesis of inorganic nano-crystals has been observed in bacteria and fungi due to the use of protein framework, DNA recognizing linkers and surfactant assembled pathways. However, these restrictions can be solved by use of modified viruses with production of self-assemble surfaces with quantum dot structures

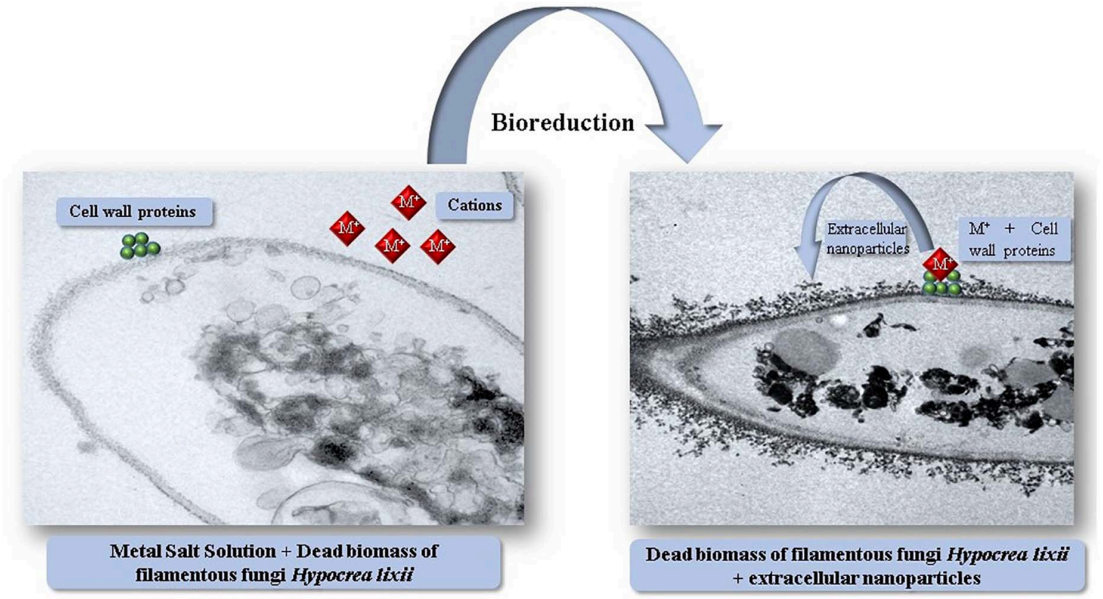

FIGURE 2 | Illustration of the mechanism of extracellular synthesis of metal nanoparticles by dead biomass of *Hypocrea lixii.*

with mono-disperse shape and size along with the length of nanoparticles. Zeng et al. (2013) reported the use of viruses for the production of quantum dots. The genetically modified tobacco mosaic virus generates nanoparticles which can change inorganic nano-crystals in three dimensional materials (Shenton et al., 1999). The synthesized viral films can be kept for long duration and can be stored for high-density engineered DNA with their application in pharmaceutical industry (Mao et al., 2003). Douglas et al. (2002) observed the use of cowpea chlorotic mottle virus and cowpea mosaic virus for the mineralization of inorganic materials. Tobacco mosaic virus helps in sulfide and crystalline nanowires mineralization (Shenton et al., 1999).

MECHANISM OF MICROBIAL SYNTHESIS OF NANOPARTICLES

Microorganisms can produce nanoparticles by the extracellular or intracellular enzymes as described below:

Extracellular Enzymes

The extracellular microbial enzymes act as a reducing agent and play an important role in metallic nanoparticles production (Subbaiya et al., 2017). The extracellular enzymes such as acetyl xylan esterase, cellobiohydrolase D and glucosidase present in fungi takes part in synthesis of metallic nanoparticles (Ovais et al., 2018). *Rhodopseudomonas capsulata* produced gold nanoparticles extracellularly by electron transfer from NADH by NADH-reliant reductase enzymes. After accepting the electrons, gold ions reduced to form gold nanoparticles (He et al., 2007). *Fusarium oxysporum* was utilized as a reducing agent for gold and silver nanoparticles generation. The shuttle quinone and nitrate-reliant reductase obtained from *Fusarium* species were used in production of nanoparticles extracellularly (Senapati et al., 2005). *Fusarium semitectum* and *Fusarium solani* enzymes were used for extracellular production of silver nanoparticles (Ingle et al., 2009). *Cladosporium cladosporioides* and *Coriolus versicolor* were utilized for the extracellular synthesis of silver nanoparticles (Balaji et al., 2009). *Aspergillus fumigatus* extracellularly produced silver nanoparticles only in 10 min as compared to physical and chemical techniques (Bhainsa and D'Souza, 2006). *Sargassum wightii* reduced Au^{3+} ions to form gold nanoparticles (Singaravelu et al., 2007). *Chlorella vulgaris* synthesized gold nanoparticles (Lengke et al., 2006). The mechanism through which filamentous fungi synthesize nanoparticles extracellularly is not explained in the literature. Salvadori et al. (2013) reported interaction between metal ions and enzymes present in filamentous fungi cell wall and its successive reduction and nanoparticles production. **Figure 2** shows a probable mechanism of extracellular nanoparticles synthesis by filamentous fungi.

Intracellular Enzymes

Actinomycetes such as *Rhodococcus* species and *Thermomonospora* species which were alkalo-tolerant and alkalo-thermophilic, respectively, were utilized for fabrication of gold nanoparticles intracellularly (Ahmad et al., 2003). Exposure of *Verticillium* species to an Ag^{+} ion solution showed intracellular reduction and fabrication of silver nanoparticles. Similar procedure was applied for production of gold nanoparticles by using *Verticillium* as a rich source of reducing enzymes (Ovais et al., 2018). Salvadori et al. (2017) suggested a probable natural procedure for the intracellular metal nanoparticles synthesis with yeasts. A possible mechanism behind the intracellular

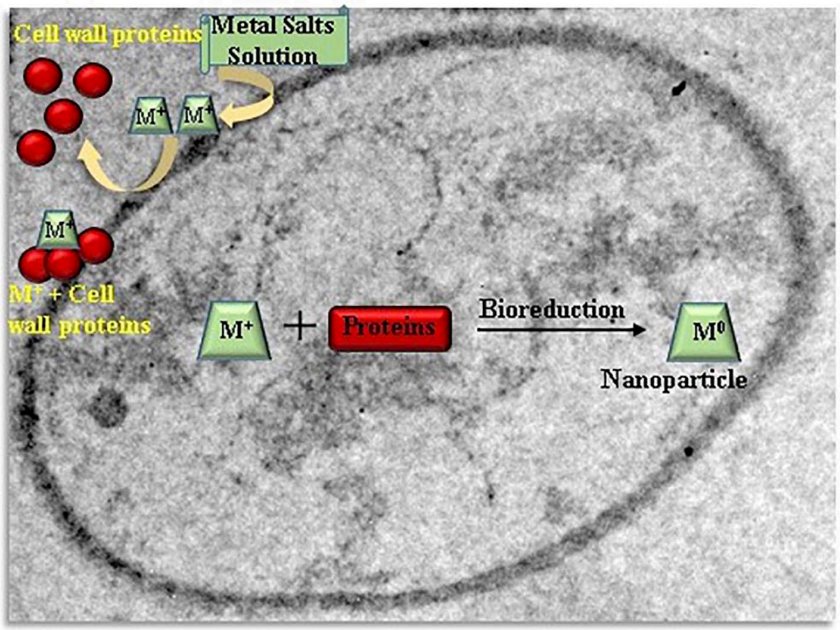

FIGURE 3 | Schematic illustration of the mechanism of intracellularly nanoparticles formation by yeasts.

nanoparticles production is the electrostatic interaction between metal cations and amide groups present in yeast cell wall enzymes, reduction of the ions by enzymes which result in accumulation of metal ions and formation of nanoparticles. The **Figure 3** schematizes a possible mechanism of intracellularly nanoparticles synthesis by yeasts.

APPLICATION OF BIOGENIC NANOPARTICLES FOR BIOREMEDIATION

Nano-bioremediation is an important branch of nanotechnology which deals with the removal of environmental contaminants such as organic and inorganic pollutants, dye, heavy metals from contaminated sites using nanoparticles synthesized from microbes. The nano-bioremediation is promising technology which provides eco-friendly, sustainable and feasible option for treatment of contaminants (Singh and Walker, 2006). As compared to the traditional methods, biosynthesized nanoparticles have some specific properties and can be utilized without any adverse effect in catalysis and degradation of organic pollutants (Naim et al., 2016). High efficiency of biogenic nanoparticles is due to vast surface area when particle size is decreased to nanoscale (Vanalakar et al., 2018).

Degradation of Dyes

The biosynthesized nanoparticles show eminent catalytic activity because of the large surface area with significant number of active sites. Srivastava and Mukhopadhyay (2014) evaluated photocatalytic efficiency of biosynthesized SnO_2-nanoparticles by *Erwinia herbicola* for dye degradation. The SnO_2-nanoparticles reflected significant catalytic activity as 93, 94 and 98% deterioration of methylene blue, methyl orange and, erichrome black T, respectively, was observed. Bhargava et al. (2016) reported that surface proteins present on gold nanoparticles formed by *Cladosporium oxysporum* AJP03 enhanced adsorption of rhodamine B dye. *Pseudoalteromonas* species degraded Napthol Green B dye under anaerobic conditions (Cheng et al., 2019). *Pseudoalteromonas* species synthesized black colored iron-sulfur nanoparticles endogenously during degradation process which inhibited H_2S release and metal sludge accumulation.

Copper nanoparticles were synthesized from *Escherichia* sp. SINT7 and they showed degradation of various azo dyes such as reactive black-5, congo red, direct blue-1 and malachite green (Mandeep and Shukla, 2020).

Catalytic Dehalogenation

The chlorinated aromatic compounds are mostly utilized in various industrial applications due to their resistance against flame, oxidation and less water solubility. The excessive use of chlorinated aromatic compounds is responsible for water, soil and air pollution. Fang et al. (2019) reported the dehalogenation of aromatic compounds by biosynthesized Pd-based nanoparticles. The cell surfaces of *Desulfovibrio desulfuricans, Desulfovibrio vulgaris* and *Desulfovibrio* sp. "Oz-7" were used to produce palladium nanoparticles. The rate of dechlorination of biogenic palladium nanoparticles was thirty times higher as compared to chemical-Pd-nanoparticles. The modification in the catalytic activity was due to chemical composition and presence of functional groups on biogenic

palladium-nanoparticles (Baxter-Plant et al., 2003). *Shewanella oneidensis* MR-1 produced palladium nanoparticles both intracellularly and extracellularly. The 4-nitrophenol, a nitro-aromatic contaminant present in dyes and synthetic pesticides adversely affects our central nervous system. It adversely affects our central nervous system. Zhang and Hu (2018) used *Bacillus* sp. GP to synthesize palladium and gold nanoparticles which showed the catalytic activity of Pd/Au nanoparticles for reduction of 4-nitrophenol. Cumbal et al. (2003) reported better affect of bio-Au-NPs/rGO on the reduction of 4-nitrophenol, but also high catalytic activity for the degradation of nitrobenzene. It was found that 72% catalytic activity was maintained after ten reduction cycles. Liou et al. (2007) stated iron nanoparticles can remediate carbon tetrachloride compound present in ground water. Studies revealed para-nitrophenol degradation to amino phenol in half an hour via gold nanoparticles synthesized by *Trichoderma viride* (Mishra et al., 2014).

Removal of Heavy Metals Ions

Heavy metal pollution is a major environmental problem (Fujita et al., 2014). Wang et al. (2017) observed the reduction in the toxic impact of vanadium and chromium with *Shewanella loihica* PV-4 as removal efficiencies of V and Cr were 71 and 91%, respectively, after 27 days. Ha et al. (2016) used palladium nanoparticles for the elimination of hexavalent chromium from contaminated water. The biosynthesized palladium nanoparticles had small size with more surface-to-volume ratio in comparison to chemically reduced palladium nanoparticles so they showed better catalytic performance. Kimber et al. (2018) stated the intracellular synthesis of copper nanoparticles with *Shewanella oneidensis* MR-1. The silver nanoparticles synthesized from *Aspergillus niger* effectively decolorized 86% of dye within 24 h and dye was completely decolorized within 2 days. However, some limitations in biosynthesis of nanoparticles exist such as less production, contamination of biological cells and tough process of separation of nanoparticles from biological materials. There is an utmost need to search microbial diversity for new and sustainable microorganisms for biosynthesis of nanoparticles (Jiang et al., 2018). The iron oxide nanoparticles were synthesized from *Aspergillus tubingensis* and they were able to remove of heavy metals like lead 98%, nickel 96.45%, copper 92.19%, and zinc 93.99% from wastewater and reusability study revealed iron-nanoparticles had high regeneration ability up to five adsorption/desorption cycle (Mahanty et al., 2020).

Further researches should focus on the identification of the mechanism involved in synthesis of nanoparticles from biogenic sources and control of the morphology, size and dispersity.

CONCLUSION AND FUTURE PERSPECTIVES

The bio resources such as microbes and microbial enzymes, if utilized successfully, can help in the biosynthesis of nanoparticles which can be proving as a potential game changer strategy. There is significant potential for microbial assisted metal nanoparticles synthesis as they are less toxic with high degradation capacity. It has also been discovered that the mechanism behind biologically synthesized nanoparticles is not well understood, despite the fact that stable nanoparticles can be generated by selecting suitable microorganisms and optimizing conditions. Thus, there is a need to choose suitable microbes or microbial consortia for large-scale sustainable production of nanoparticles. Microbial synthesis of nanoparticles can be achieved without the application of high temperature, pressure, energy, stabilizers and toxic chemicals. There is a need to synthesize nanoparticles with a wide range of organic functional groups by manipulating microbial enzymes for selective as well as multi-pollutants removal from wastewater. The nanoparticles synthesis via microbes such as bacteria, actinomycetes, fungi, yeast and algae has many advantages such as easy production, non-expensive, high efficiency, safe and eco-friendly approach. The microbial nanoparticles can be used at the contaminated sites for the treatment of pollutants. The residues left after the degradation of contaminants by microbial nanoparticles are biocompatible and can be separated easily by filtration or precipitation technique. The value-added products such as construction materials can be prepared with left residues by incorporating biochar, hence there will be zero waste at the end. Therefore, a greener route for nanoparticles synthesis opens new channels for many biotechnological applications. The biological synthesis of metallic nanoparticles has been achieved at laboratory scale but industrial scale escalation is needed for their mass production. The application of efficient microbes-assisted nanotechnology can boost the industrial economy but unfortunately only 1% nanotechnology materials have been commercialized till date. The cost effective production of microbial nanoparticles is required to make this process economically feasible and sustainable as per the requirements of industries. The cost-benefit analysis should also be conducted for its commercial exploitation as no cost related data is available till date. Application of chemicals, salts, reducing and stabilizing agents in chemical synthesis process are expensive whereas in microbial synthesis use of metal salts and media for microbial growth is also expensive. The waste biomass which is recyclable can be an alternative for the production of nanoparticles to lessen the expenditure. Further investigations about the biosynthetic pathways of microbes and researches in genetic engineering may open new avenues for breakthrough development of these promising nanofactories for scaling-up and industrial exploitation as efficient sustainable strategies for the bioremediation. Advanced computational tools are required to exploit the omics derived data for better understanding of microbial processes. Hence, green chemistry can be used successfully for production of nanoparticles by microbes and efforts in this direction will be a giant jump toward the adoption of green nanotechnology.

AUTHOR CONTRIBUTIONS

All the authors contributed equally to the study design, collection of data, development of the sampling, analyses, interpretation of results, and preparation of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Encapsulation of *B. bassiana* in Biopolymers: Improving Microbiology of Insect Pest Control

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The fungus *Beauveria bassiana* is widely used for pest control; however, biostability and dispersion for broth pulverization are limiting factors for its application in the field. In this context, formulation techniques such as microencapsulation are viable alternatives. The aim of this work is to optimize *B. bassiana* formulations by spray dryer and evaluate its stability and biological activity against *Spodoptera cosmioides* compared to ionic gelatinization formulations. The fungus was biocompatible with all evaluated biopolymers (lignin, cellulose, starch, humic substances, and alginate). The encapsulation by spray drying was optimized by factorial design in an inlet and outlet air temperature of 120°C and 68°C, respectively; aspirator rate of 35 $m^3 \cdot h^{-1}$, feed flow rate of 12 $mL \cdot min^{-1}$; and drying gas flow at 35 $L \cdot h^{-1}$. The ionic gelation capsules were obtained using a 0.5% quantity of conidia in a 1% sodium alginate solution dropped into a 0.5 $mol \cdot L^{-1}$ $CaCl_2$ solution using a peristaltic pump. Spray drying provided smaller microcapsules than those by ionic gelation. Both techniques produced more stable conidia when exposed to temperature and UV-radiation than non-formulated *B. bassiana*. The formulations prepared by spray drying showed gains at aqueous dispersion. Biological assays against *Spodoptera cosmioides* showed a mortality rate of up to 90%. These results demonstrate the suitability of encapsulating *B. bassiana* conidia stably in aqueous dispersion without loss of viability and virulence.

Keywords: ***Beauveria bassiana*, Spray-drying, microencapsulation, *Spodoptera cosmioides*, biopolymers**

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INTRODUCTION

The control of agricultural pests has been conducted mainly by synthetic chemical insecticides. This control system has been efficient in promoting productivity gains every year. However, it is responsible for several harmful damages to the environment (Sharma et al., 2019). Prolonged exposure to conventional synthetic pesticides raises occupational risks, disturbances to human health, and harmful impacts on ecosystems and the environment. More specifically, these substances may also attack non-target species and/or lead to the emergence of new pests (Keshani et al., 2015). Lastly, several studies highlight the negative effects of synthetic pesticide use on human health (Heckel, 2012; Asghar and Malik, 2016; Bourguet and Guillemaud, 2016; Op de Beeck et al., 2017; Sharma et al., 2019).

In the search for sustainable agriculture, there is a plethora of alternative products that have been continuously evaluated to replace conventional agrochemicals, such as agricultural biodefensives for biological control (Mossa, 2016). The entomopathogenic fungus *Beauveria bassiana* (Bals.) Vuill. has a prominent position among these so-called green insecticides. It is a broad-spectrum biological control agent against insects considered agricultural pests. Alali et al. (2019) and Mascarin and Jaronski (2016) demonstrated the virulence from several *B. bassiana* strains on arthropods, with a mortality rate of up to 90%. It has shown promising results in controlling pests such as *Ephestia kuehniella, Bemisia tabaci, Metamasius hemipterus, Hyphotenemus hampei, Anastrepha fraterculus, Tetranychus urticae, Nezara viridula, Diaphorina citri,* and *Thaumastocoris peregrinus*, which are commonly found in coffee, eucalyptus, soy, citrus, etc.

Several entomopathogenic microorganisms are already produced on a commercial scale; however, their agricultural use still faces limitations due to lack of stability to temperature and UV-light. These abiotic factors not only compromise their biological efficiency but also present problems with storage, transport, and field application (Parra, 2014; Sinha et al., 2016). The optimum temperature for the development of these microorganisms in the field in order to keep its virulence is ∼25°C (Bugeme et al., 2008). Under Brazilian climatic conditions, this temperature is easily exceeded in agricultural fields and storage places, compromising their viability and efficiency. García-Estrada et al. (2016) highlighted that the low shelf life and field stability of microbial formulations compromise their commerce and acceptance.

The demand for sustainable techniques for integrated pest management requires methods to stabilize biopesticides, emphasizing the conservation of microbial propagation features and the upkeep of their genotypic and phenotypic characteristics. Microbial microencapsulation may provide the conservation of these characteristics. Muñoz-Celaya et al. (2012) demonstrated that the process of encapsulation of *Trichoderma harzianum* in polymeric carbohydrates showed a 330-fold increase in shelf life. Maruyama et al. (2020) also demonstrated that *T. harzianum* encapsulation increased the potential for biological control of *S. sclerotiorum*. Lastly, Qiu et al. (2019) developed methods for encapsulating *Metarhizium anisopliae* in gelatin, showing gains in UV-light protection and shelf life, keeping bioactive microorganisms against *Solenopsis invicta*.

The encapsulation processes include the trapping of an active compound in a matrix (in this case, microbial conidia), ideally with gains in biotic and abiotic protection within the microenvironment generated by the encapsulating material (Vemmer and Patel, 2013). Another advantage is the possibility of controlling the release of encapsulated conidia by environmental activators. Maruyama et al. (2020) demonstrated that encapsulation influenced the release kinetics of *T. harzianum*, increasing its bioavailability in comparison to non-encapsulated fungus.

The use of biodegradable materials in formulations is ecologically advantageous and biologically safe. Biodegradable materials often do not present harmful residues to the environment, nor toxicity, facilitating registration and approval for use (Sawalha et al., 2011; Rajeswari, 2017). Examples of available biodegradable compounds are starch, chitosan, alginate, gum arabic, cellulose, lignin, gelatin, etc. Each material has different properties regarding stability, solubility, swelling/erosion, release kinetics, biocompatibility, etc. These characteristics may affect microbial development. Therefore, the association/choice of microorganism and its encapsulation material should be investigated, evaluating its benefits and compatibility with the encapsulation process (Wandrey et al., 2010; Silva et al., 2014).

Among the encapsulation techniques, dripping methods have a stand out position. They form droplets through a nozzle, either by spray drying or ionic gelation (Vemmer and Patel, 2013). The spray drying process works by nebulizing the dispersion medium that contains the polymer and active compounds into a hot air stream, evaporating the solvent during its way to the storage vial, obtaining dried particles (Santos et al., 2018). Ionic gelation promotes the formation of a highly ordered hydrogel encapsulation structure when a solution containing the biopolymer and the active agent is dropped into a crosslinking solution containing divalent cations (Ching et al., 2017). Both techniques can be used for thermally sensitive compounds, such as essential oils, pharmaceuticals, and biological supplies (Vemmer and Patel, 2013; Rigon and Zapata Noreña, 2016; Arpagaus et al., 2018; Veiga et al., 2019). Liu and Liu (2009) demonstrated that the spray drying encapsulation of *B. bassiana* conidia maintained 80% of viability for up to 6 months when stored at low temperature (4°C). However, Rosas-García et al. (2001) demonstrated losses in *B. bassiana* viability regardless of the type of evaluated polymer in spray dryer processes. As a result, there is a lack of studies that help understand the encapsulation process for entomopathogenic conidia.

Therefore, the objective of this work was to establish encapsulation parameters for the entomopathogenic microorganism *B. bassiana* via spray drying using biodegradable materials. We also investigated the maintenance of microbial viability and virulence using *Spodoptera cosmioides* caterpillars as a model. The spray dryer encapsulation was evaluated comparatively to the ionic gelation process.

MATERIALS AND METHODS

B. bassiana Conidia

Pure *B. bassiana* conidia was provided by Biocontrol—Controle Biológico (Sertãozinho, SP-Brazil), and were kept at −12°C until use. The *B. bassiana* conidia (strain IBCB 66) were isolated initially from *Hypothenemus hampei* (coffee borer beetle) and preserved in mineral oil at the "Oldemar Cardim Abreu" Entomopathogenic Microorganisms Collection in the Campinas Experimental Center at the Biological Institute, São Paulo, Brazil. This strain is a commercial product widely applied in Brazilian crops (Ribeiro et al., 2012). The commercial powder of *B. bassiana* was initially evaluated in terms of germination before any experiment was carried out. For this we incubated the microbiological powder for 7 days at 25.5°C ± 0.5°C in B.O.D (Biochemical Oxygen Demand, Eletrolab, EL101, Brazil),

under a 14-h light photoperiod, using PDA (Potato-Dextrose-Agar, KASVI, Brazil) in 9-cm-diameter Petri dishes. In order to assure a standard stock, the quantification of spores per milligram of commercial powder was carried out with the aid of a hemocytometer (Neubauer chamber, KASVI, Brazil) in sextuplicates, as described in section Quantification of *B. bassiana* Conidia.

Materials to Encapsulation

We evaluated six substances as encapsulation agents, soy oil, corn starch, cellulose, lignin, alginate, and humic acid. The soy oil and starch were purchased in a local supermarket in the city of São Carlos, state of São Paulo, Brazil. Cellulose and alginate were bought from Vetec Química (Rio de Janeiro, RJ–Brazil). The humic acid and lignin were provided by Agrolatina Biotecnologia AS (Rincão, SP–Brazil), and Suzano Papel e Celulose (Suzano, SP–Brazil), respectively. The $CaCl_2$ used on ionic gelation was purchased from Sigma-Aldrich, and all the growth media are from Kasvi do Brasil (São José dos Pinhais, PR–Brazil).

Quantification of *B. bassiana* Conidia

Initially, we quantified the total *B. bassiana* conidia in the commercial product before using it in the formulations and stability studies. The quantification was performed with a hemocytometer (Neubauer chamber, Kasvi, Brazil) under an optical microscope on a microscope slide using sticky tape. In this case, a sticky tape was placed under the dish containing *B. bassiana* and put on a microscopy slide containing Amman's lactophenol dye (Newprov, Brazil) (Rice and Cogburn, 1999). Samples were evaluated with a LX500Phase Contrast optical microscope (Labomed, Los Angeles, CA, USA) equipped with a IVU5000 digital video camera and magnified up to 400× for counting conidia (Rice and Cogburn, 1999). Microscopy images can be seen in **Supplementary Figure 1**.

Biocompatibility Assay Between *B. bassiana* and Biopolymers

Previously, we evaluated the biocompatibility of alginate and cellulose to *B. bassiana* (Wenzel Rodrigues et al., 2017). In short, conidia were inoculated in a culture medium containing the compound of interest, and the evaluation of its growth was performed using the protocol described by Rice and Cogburn (1999). In this work, we expanded the biocompatibility study for soy oil, humic acids, corn starch, and pine lignin. These results contributed to the initial selection of working biopolymers.

This part of the study was carried out by inoculating a 10-μl drop of the unformulated microorganism suspension at 10^9 CFU (colony forming unit)·ml^{-1}. These were placed at the center of 9-cm-diameter Petri dishes containing PDA previously sterilized in an autoclave at a pressure of 1 atm at 121°C, for 20 min. The encapsulating agent was incorporated into the growth medium at a temperature of 45 ± 2°C before microbial inoculation at 1.0% and 2.0% (w/v) concentration. We also included a pentabiotic (Zoetis, Campinas, SP–Brazil) at 0.5 g·L^{-1}. Petri dishes were kept in a germination chamber (B.O.D.) at temperature of 25.0 ± 0.5°C, in a 12 h photophase for 3 days. We observed the microbial development daily, evaluating the fungal radial growth. At the end of the incubation period, we quantified the conidia and performed a germination analysis using an optical microscope.

We used the Biological Index according to Gonçalves Diniz et al. (2020) to calculate the compatibility factor between conidia and encapsulating agents, using the following equation:

$$BI = \frac{[(47 \times VG) + (43 \times CS) + (10 \times GER)]}{100}$$

Where: *BI*: Biological Index, *VG*: percentage of vegetative growth of the colony compared to control after 3 days, *CS*: percentage of colony sporulation compared to control after 3 days, and *GER*: percentage of conidia germination after 24 h. The *BI* values for product classification are arranged as follows: (a) $BI \leq 41$: Toxic (*T*), (b) $BI \geq 42$ and ≤ 66: Moderately toxic (*MD*), and (c) $BI > 66$: Compatible (*C*).

TABLE 1 | Variables of fractional factorial design (2^{6-2}) for used encapsulating agent mixtures in the formulation processes.

	Variables	Levels	
		−1	+1
A	Lignin	Absent	2.5 g·L^{-1}
B	Cellulose	Absent	2.5 g·L^{-1}
C	Soy oil	Absent	2.5 g·L^{-1}
D	Humic acid	Absent	2.5 g·L^{-1}
E	Starch	Absent	2.5 g·L^{-1}
F	Sodium alginate	Absent	0.1 g·L^{-1}

Experiment	Coded levels					
	A	B	C	D	E	F
1	−1	−1	−1	−1	−1	−1
2	+1	−1	−1	−1	+1	−1
3	−1	+1	−1	−1	+1	+1
4	+1	+1	−1	−1	−1	+1
5	−1	−1	+1	−1	+1	+1
6	+1	−1	+1	−1	−1	+1
7	−1	+1	+1	−1	−1	−1
8	+1	+1	+1	−1	+1	−1
9	−1	−1	−1	+1	−1	+1
10	+1	−1	−1	+1	+1	+1
11	−1	+1	−1	+1	+1	−1
12	+1	+1	−1	+1	−1	−1
13	−1	−1	+1	+1	+1	−1
14	+1	−1	+1	+1	−1	−1
15	−1	+1	+1	+1	−1	+1
16	+1	+1	+1	+1	+1	+1

Preparation of Pre-encapsulation Formulations

After biocompatibility assays, we selected cellulose, lignin, starch, soy oil, and humic acids to develop in the formulations. The search for an ideal formulation was carried out by a fractional factorial design 2^{6-2}, totaling 16 formulations, as described in **Table 1**.

Compounds were initially solubilized in water under magnetic stirring and later incorporated into the microbial dispersion. The fungal dispersion was prepared in a saline solution containing

TABLE 2 | Optimization by full factorial design 2^4 for *B. bassiana* formulation using spray drying.

	Variables	Levels	
		−1	+1
A	Inlet temperature (°C)	70	120
B	Feed flow rate (L·h^{-1})	0.005	0.01
C	Aspirator rate (L·h^{-1})	301	414
D	Air injection flow (m^3 h^{-1})	20	35

Experiment	Coded levels			
	A	B	C	D
1	−1	−1	−1	−1
2	+1	−1	−1	−1
3	−1	+1	−1	−1
4	+1	+1	−1	−1
5	−1	−1	+1	−1
6	+1	−1	+1	−1
7	−1	+1	+1	−1
8	+1	+1	+1	−1
9	−1	−1	−1	+1
10	+1	−1	−1	+1
11	−1	+1	−1	+1
12	+1	+1	−1	+1
13	−1	−1	+1	+1
14	+1	−1	+1	+1
15	−1	+1	+1	+1
16	+1	+1	+1	+1

NaCl 0.15 mol·L^{-1}, and Tween 80 (0.001%, w/v), keeping a ratio of 1:7 between conidia and encapsulating agents. This dispersion solution protocol was developed according to Liu and Liu (2009) and Aziz Qureshi et al. (2015). These mixtures were then used in the spray dryer and ionic gelation microencapsulation processes.

B. bassiana Encapsulation Processes

Spray Drying Process Optimization

For this process, we used a Büchi B-290 (Büchi Labortechnik AG, Flawil, Switzerland) spray dryer, equipped with a drying chamber of 500 × 100 mm and an atomizing spray nozzle of 0.7 mm. The drying parameters were optimized by a full factorial design 2^4 according to Antony (2014) with three different independent variables, in two levels: low and high, transformed in (−1) and (+1), respectively. These levels were previously defined in preliminary tests. In total, we randomly performed 16 experiments avoiding systematic error trends (**Table 2**).

The random error was evaluated by duplicates calculated as described by Pereira and Pereira-Filho (2018). As responses (dependent variables), we calculated the dry powder mass recovery (% w/w) and conidia viability, calculated as follows:

$$Recovery\left(\%, \frac{w}{w}\right) = \frac{Md}{Mn} \times 100$$

Where M_d = mass of material after drying, and M_n = nominal mass value of the material added to the formulation. The calculation of the effects, the probability graphics, and responses were performed using the Octave® 4.2.1 software, using the script described by Pereira and Pereira-Filho (2018).

Encapsulation by Ionic Gelation

The ionic gelation process was prepared according to Wenzel Rodrigues et al. (2017). The composition of the formulations is also described, as highlighted in **Table 1**, allowing a comparison between ionic gelation and spray drying. In summary, the previously dispersion of fungi and polymers were added to a concentration of 0.5% (w/v) in a 1% (w/v) sodium alginate solution. After homogenization, the dispersion was dripped into a 0.5 mol·L^{-1} $CaCl_2$ solution using a peristaltic pump (TPM 600 55RPM, Watson-Marlow Inc., Wilmington, MA, USA) at 35 drops·min^{-1} flow. The resulting capsules were carefully washed in distilled water, removing $CaCl_2$ and alginate excess. The washed spheres were placed on glass dishes at 25°C for 24 h for dehydration.

Microencapsulated Conidia Thermal Stability, UV-Light Protection, and Dispersion Assays in Aqueous Media

The formulations that showed the best recovery and viability results were selected for dispersion capacity in an aqueous medium, UV-light protection, and thermal stability analysis. This assay was carried out using ultrapure water (Direct-Q 8 UV Milli-Q, Millipore, Molsheim, France) without additives, as we were looking for low-cost and straightforward spraying field methods. The powder formulations were weighed and dispersed in water at a concentration of 1.0 mg·ml^{-1}. As a control, we used the commercial non-formulated powder product of *B. bassiana* with the same concentration. The stability of the aqueous dispersion was monitored visually for 2 h observing (or not) the formation of precipitates.

We tested photostability by evaluating the microbial viability of the formulated powdered materials after exposure to UV-light. The compounds were aliquoted in Eppendorf tubes and placed in a glass base inside a wooden chamber, complementarily lined with mirrors (l = 60.0 cm, h = 40.0 cm, and w = 60.0 cm). The wooden chamber was built containing four 15 W G15T8E USHIO lamps (l = 45.0 cm, w = 2.6 cm; USHIO, Tokyo, Japan), with an intense emission spectrum around 306 nm (UV-B region). The energy of the lamps was similar to an irradiance of 6,153 m W·m^{-2}. The total radiance inside the wooden chamber was 22.15 kJ·m^{-2} · h^{-1}. The wooden chamber was equipped with one thermostat and two mini-fan coolers keeping the internal temperature at 25 ± 2°C. As positive and negative controls, samples of non-encapsulated conidia were exposed to UV-light, while others were protected from it, respectively. The UV-light protection was evaluated in exposure periods of up to 48 h.

The thermostability assay was performed with formulation treatment samples arranged in the support tray for Eppendorf tubes in a dry heating bath (KASVI, K80-0, Brazil) protected from light. This test was performed at 60°C for 4 h. As control, we used samples kept under light protection at 4°C.

Aliquots were inoculated in a PDA medium afterwards to check for conidia viability. The dishes were kept for 72 h in a B.O.D. chamber at 25°C. The formulations that showed better stability in the powder were solubilized in an aqueous medium and again subjected to the stability analyses. After

the experimental period, the suspensions were inoculated as described above, evaluating conidia viability maintenance.

Virulence Assay Against *Spodoptera cosmioides*

Rearing of *S. cosmioides*

S. cosmioides eggs were purchased at PROMIP– Manejo Integrado de Pragas (Limeira—SP, Brazil), and kept in B.O.D. (Biochemical Oxygen Demand, TECNAL, TE-3911, Piracicaba, SP-Brazil) under a photoperiod of 14 h of light and 10 h in the dark at 25°C, until hatching. After the start of the newborn caterpillars' feeding period, their containers were cleaned daily to remove feces. Additionally, insect development was also monitored daily. For feed, we used Greene's artificial diet (Greene et al., 1976). For each 1 L of diet, we initially dissolved agar into 500 ml of water previously sterilized in an autoclave for 15 min. In another container, we solubilized ascorbic acid, formaldehyde, and methylparaben using a homogenizer (RI1364, 400W, Philips Walita, Varginha, MG, Brazil) in a volume of 500 ml of water. After cooling to ∼45°C, we mixed both solutions with tetracycline. The final solution was poured into a sterile container for gelation and kept at 4°C until use. Their feed was cut in 2 × 2 cm blocks, ∼10 g each, and were supplied as needed.

The L2 stage of caterpillar development (second instar) is the phase with great significant damage to crops due to greater intensity of feeding (Silva et al., 2017). We transferred the caterpillars to larger containers, changing Greene's diet to a new composition, which was prepared using soy protein 50.0 g, wheat germ 50.0 g, beer yeast 31.2 g, casein 25.0 g, beans 62.5 g, ascorbic acid 3.0 g, vitamin complex 5.0 ml, and agar 18.7 g (*q.s.* 1 L water). The rearing of *S. cosmioides* was adapted from Elvira et al. (2010). We did not use microbiological growth-inhibiting agents (tetracycline, formaldehyde, and methylparaben) to avoid compromising fungal development in this modified diet.

Inoculation of Formulated *B. bassiana*

S. cosmioides caterpillars between stages L3 and L4 were exposed to previously selected *B. bassiana* formulations. These stages are responsible to most crop damage, and hence, the reason why they were selected (Barros et al., 2010; Ayala et al., 2013). The prepared formulations via spray dryer were dispersed in an aqueous medium in an amount of 100 mg·ml^{-1}, with 10 μl being dropped onto each caterpillar (1.0 mg of formulated *B. bassiana* in powder). Granular formulations prepared by ionic gelation were weighed and inoculated (1.0 mg) over each diet block.

It is important to highlight that we used the same initial spore concentration for each formulation and technique. Both encapsulation processes changed the final concentration of viable conidia, however, as shown in the results. Therefore, we assayed the same formulated product mass in this step to evaluate the effectiveness of each processed formulation. Since we used the same quantity of viable conidia in each formulation, applying the same mass from formulated products in the assays could show losses during the processes. As such, we were able to compare the formulated and non-formulated conidia in colloidal dispersion by the same number of viable conidia and the same quantities in mass to the different formulations.

For each formulation, two containers with 10 caterpillars were used, totaling 20 caterpillars. We used three controls: (1) positive control (C+), where 1.0 mg of the unformulated *B. bassiana* commercial product was added for analyzing the results of the biological agent, (2) negative control for alginate (CA–) using 1.0 mg of the polymer, free of *B. bassiana*, and (3) negative control (C–) using only the diet in the presence of caterpillars.

We point out that other species, *S. frugiderda* and *S. eridania* were tested in this study. After inoculation, however, a cannibalistic behavior was observed, hindering the maintenance of an adequate number for continuation of the experiments. For this reason, only the results with *S. cosmioides* are reported.

We observed possible daily changes in the morphology of caterpillars after inoculation when removing dead insects. Visual analysis was maintained until the pupal phase of all surviving caterpillars. We determined the mortality of caterpillars, the percentage of formed and defective pupa, average pupal weight, and total mortality, counting non-viable caterpillars and pupae. The insects resulting from viable pupae were segregated into three groups: (1) a group previously treated with formulated conidia by spray drying, (2) a group previously treated with formulated conidia by ionic gelation process, and (3) a control group formed by insects not treated with *B. bassiana*. The pupae were added to glass dishes containing moistened filter paper in order to evaluate the hatching of adults. After the moths hatched,

TABLE 3 | Results of the biocompatibility evaluation between *B. bassiana* conidia and encapsulating agents in PDA growth medium.

Biopolymer (% w/v)	Microbial growth (cm)	Sporulation (×10^7)	Germination	BI[a]	Classification
Control	1.50 ± 0.18	4.12 ± 1.10	100 ± 0.00	-o-	-o-
Corn starch 1%	0.90 ± 0.22	3.77 ± 0.67	105 ± 2.50	78.0	Compatible
Corn starch 2%	1.10 ± 0.13	3.00 ± 1.20	73.0 ± 1.20	73.1	Compatible
Soy oil 1%	1.00 ± 0.11	3.63 ± 0.92	99.0 ± 2.30	79.1	Compatible
Soy oil 2%	0.90 ± 0.08	4.03 ± 1.40	91.0 ± 1.80	79.4	Compatible
Lignin 1%	0.10 ± 0.03	2.72 ± 0.66	77.0 ± 1.90	39.2	Toxic
Lignin 2%	0.00 ± 0.03	0.77 ± 0.45	3.00 ± 0.30	8.33	Toxic
Humic acid 1%	1.00 ± 0.23	3.37 ± 0.56	8.00 ± 0.50	67.3	Compatible
Humic acid 2%	1.20 ± 0.19	0.15 ± 0.06	0.00 ± 0.00	38.7	Toxic

[a]*Biological Index; The BI values for product classification were arranged as follows: (a) BI ≤ 41: Toxic (T); (b) BI ≥ 42 and ≤66: Moderately toxic (MD); and (c) BI > 66: Compatible (C).*

we fed them with a 5% (w/v) honey diet soaked in cotton (Elvira et al., 2010). The adult insects were kept in cages for 20 days, with daily feed replacement. After this period, they were removed from the cages, as well as the filter paper, for analyzing the presence of eggs.

RESULTS

B. bassiana Conidia

Biocompatibility Assays Between the Biopolymers and *B. bassiana*

The assay allowed the calculation of the Biological Index (Gonçalves Diniz et al., 2020), assigning different levels to fungal development stages, quantified by the impacts of encapsulating agents to the microbial growth medium. **Table 3** illustrates the results in the biocompatibility evaluation among the encapsulating agents and *B. bassiana*.

Microbial development after 72 h is illustrated in **Supplementary Figure 2**. The results indicated that *B. bassiana* was resistant to the encapsulating agents in almost all evaluated concentrations, suffering little or no influence during its life cycle. Exceptions in its biocompatibility were observed for lignin (in both dosages, 1% and 2% w/v) and humic acids at a concentration of 2% (w/v).

Microencapsulation of *B. bassiana*

Spray Drying: Optimization Process

In this experiment, we observed that, independent of the temperatures we assessed, the germination and sporulation of *B. bassiana* were maintained. We also noted that we obtained the best conidia recovery (w/w) at the highest evaluated temperature (120°C). The data suggested an accumulation of conidia per gram of powder due to moisture removal from the conidia in the non-formulated commercial product. The conidium quantification data is also displayed in **Supplementary Figure 3**. This experiment showed that aqueous fungal dispersions withstood temperature exposure in the spray dryer.

Subsequently, we performed the Spray dryer parameter optimization through a full factorial design 2^4 (**Table 2**). This optimization was performed with an aqueous fungal solution without encapsulating agents to find the best operational parameters for the recovery of conidia per gram.

Conditions 4, 8, and 12 were more efficient for drying *B. bassiana* in terms of powder recovery (**Figure 1A**).

We calculated the effects of each variable from the powder recovery data, considering primary and interaction effects. The experimental variance, experimental error, and effect errors were calculated by effect in a percentages analysis using a confidence level of 95%, with 16 degrees of freedom and a T-value = 2.1. These statistical parameters were calculated according to Pereira and Pereira-Filho (2018) and summarized in **Supplementary Table 1**. The effects percentage and probability can be analyzed in **Figure 2**.

Effects in percentage analysis indicated that the variables of greatest importance were inlet temperature (24%), feed flow rate (22%), as well as their secondary interaction (inlet temperature/feed flow rate, 17%). The representativeness of both variables was 63% in the total of observed effects. The effect of aspirator rate and air injection flow variables corresponded to only 14% of the total effects. Inlet temperature and feed flow rate variables, plus their interaction demonstrate a positive effect on recovery by spray drying. On the other hand, the aspirator rate and air injection flow variables showed a negative effect. The response surface graphs indicate that the best probability of obtaining good yields in experimental conditions would be an inlet temperature and feed flow rate at maximum levels (+1). In contrast, the aspirator rate and air injection flow should be the opposite, at low levels (−1) (**Supplementary Figures 5–7**).

Experiment 12 (**Table 2**) was carried out at the high level of inlet temperature and feed flow rate and low level of

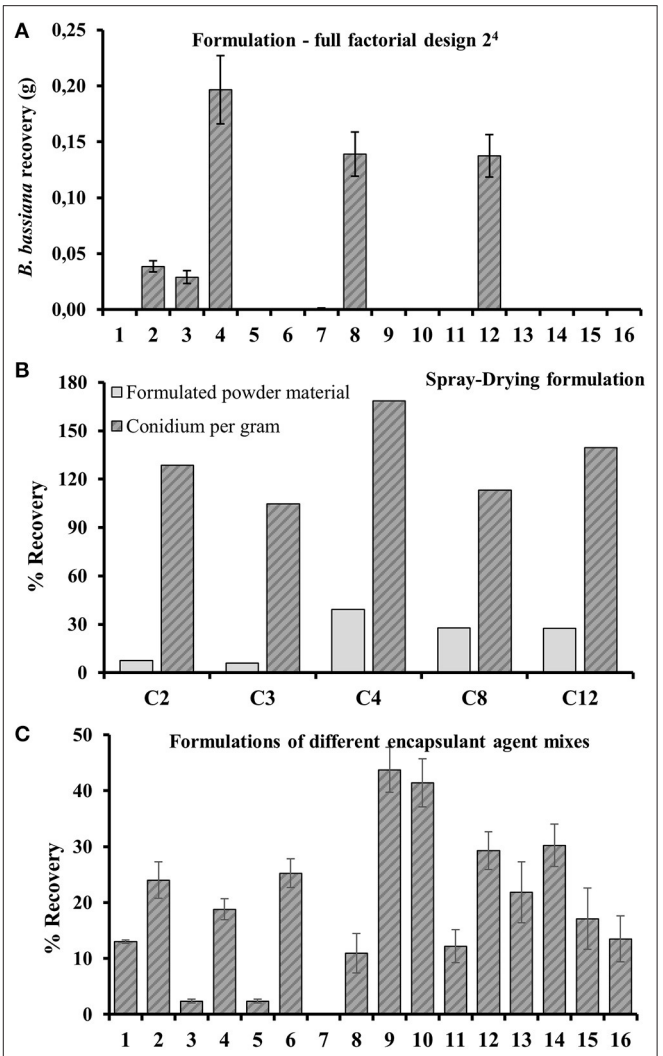

FIGURE 1 | (A) *B. bassiana* powder recovery (grams) to the 16 spray drying experiments within the full factorial design 2^4 in **Table 2**. **(B)** Recovery of total conidia in powder and conidia per gram of powder after spray drying conditions (Conditions 2, 3, 4, 8, and 12 from **Table 2**). **(C)** Powder recoveries for spray drying formulations in **Table 1** after their optimized configuration. Spray drying parameters concerning experiment 4 of full factorial design 2^4.

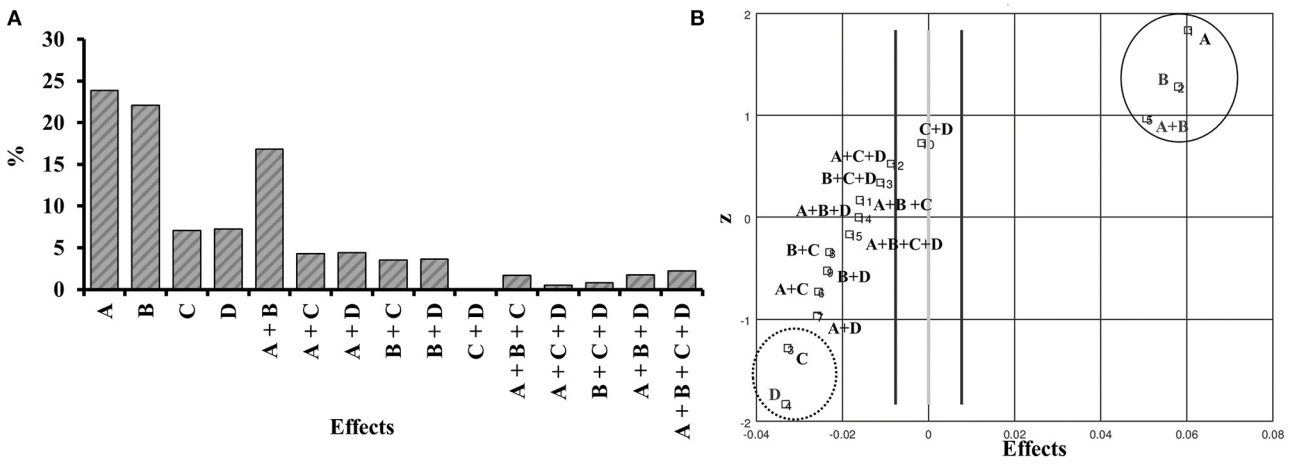

FIGURE 2 | Percentage of primary effects and interactions **(A)**, and distribution of effects **(B)**. A: Inlet temperature; B: Feed flow rate; C: Aspirator rate; D: Air injection flow.

the aspirator rate, presenting satisfactory yield and quantity of conidia per gram of powder product. The obtained product in this experiment, however, showed difficulties in handling, with high container wall adhesion and a high humidity rate, probably because it was prepared using a high level of air injection flow. Therefore, we defined the parameters for experiment 4 (**Table 2**) as optimal for *B. bassiana* conidia spray-drying microencapsulation when using encapsulant agents. The inlet temperature application at the established high level (120°C, +1) has a relationship between reducing inject air moisture and increasing evaporation power.

The inoculation of spray-dried samples in the PDA growth medium showed a greater conidia concentration per gram of dried powder than the starting commercial product. This increase may be associated with the withdrawal of the wet volume from the medium and conidial dehydration. In fact, dehydration of the conidia prolongs their survival by inhibiting their germination and reducing metabolism to a minimum, thus decreasing loss during the drying process and improving the stability of the fungus during storage (Horaczek and Viernstein, 2004). Therefore, experiment 4 (**Table 2**) was the best condition regarding recovery and the number of conidia per gram of dried product (**Figure 1B**).

The operational parameters of experiment 4 assigned to the spray dryer were applied in the encapsulation agent evaluation (**Table 1**). The average recovery of formulations loaded with *B. bassiana* and encapsulating agents after spray drying was 19.7 ± 13.48% (17.04–22.36%) in the 16 formulations described in **Table 2** (**Figure 1C**). The best spray drying recoveries were observed for formulations using a mix of encapsulating agents. Under these conditions, we obtained recoveries of 44, 41, 30, 29, 24, and 21% (w/w) to formulations 9, 10, 14, 12, 2, and 13, respectively (**Figure 1C**). Individually, among the best recoveries, 70% of them contained lignin, 40% cellulose, 50% soy oil, 70% humic acids, 40% corn starch, and 60% sodium alginate.

Preparation and Analysis of Capsules Loaded With *B. bassiana* by Ionic Gelation

After preparing the particles loaded with *B. bassiana* by ionic gelation, we obtained powder material recoveries close to 100% for all formulations (**Table 1**). All formulations and controls were inoculated in PDA growth medium in order to quantify the number of conidia per gram of formulated powder product. Formulations 3, 8, 12, and 16 of the factorial design (**Table 1**) for ionic gelation showed reduced viability regarding the non-formulated control; however, superior to most of the ones obtained through spray drying.

Considerations About Spray Drying and Ionic Gelation

The products obtained by both processes were analyzed for growth and fungal release for up to 96 h. We observe some similarities and a few differences between the capsules obtained by spray dryer and those obtained by ionic gelation. In the first 48 h, we observed that the formulations 1, 5, and 13 showed the release of hyphae for both preparation processes. However, spray-dried capsules 3 and 11 showed a growth onset, which was not observed for the same capsules obtained by ionic gelation. On the other hand, gelation formulations 6, 9, and 10 had hyphae growth, which did not occur for the same spray-dried formulations. Formulations 2, 4, 7, 8, 12, 14, 15, and 16 did not present fungal release in the observed period of 48 h.

After 72 h, some formulations showed intense sporulation. We highlight that the importance of spore release in the final stage of the insect's infectious process when analyzing virulence. The formulations with intense sporulation for both techniques were 1, 5, and 13. Among the formulations that had not shown a release start within 48 h, 2, 4, 7, 8, 12, 14, 15, and 16 had no posterior hyphae growth. The only exception was formulation 7, which showed the beginning of development, but only those from the ionic gelation process. Formulations 3 and 11 showed intense sporulation when obtained by spray dryer, but hyphae only developed in those prepared by ionic gelation. A reverse

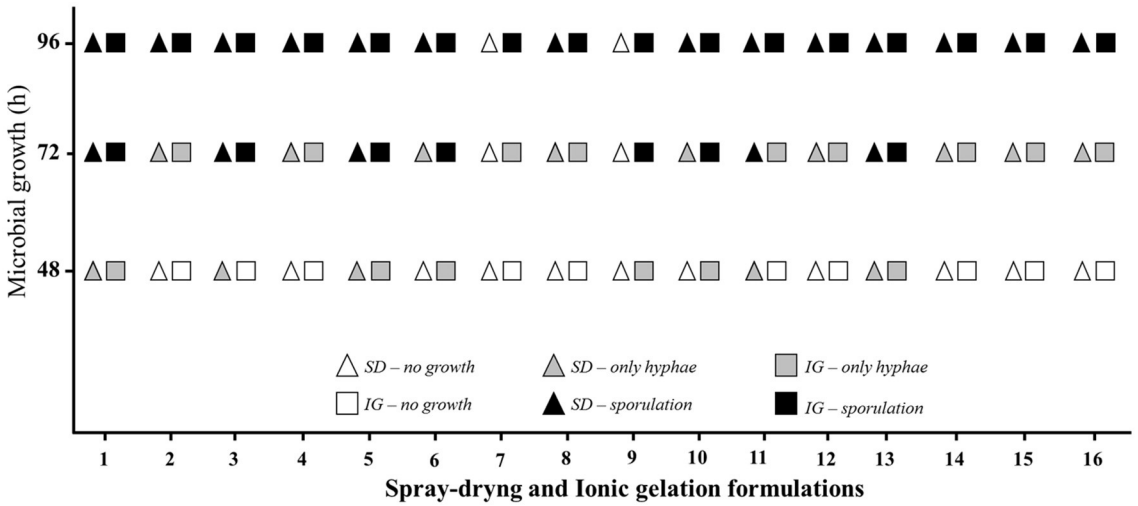

FIGURE 3 | Cultivation of microencapsulated *B. bassiana* by spray dryer and ionic gelation in Potato-Dextrose-Agar growth medium for 96 h. SD, spray-drying; IG, ionic gelation.

result was observed for formulation 6 and 10, which showed sporulation when obtained by ionic gelation and the beginning of hyphae growth by spray-drying. Formulation 9 also showed sporulation only when obtained by ionic gelation without any fungal development by spray drying.

After 96 h, all formulations showed intense sporulation, except for formulations 7 and 9 obtained by spray drying, which did not start the fungal release. These formulations were kept for an additional period. After 10 days, there was still no observed fungal development. **Figure 3** summarizes what was observed during the cultivation period of 96 h.

We observed that 37.5% of the formulations prepared by ionic gelation and 31.25% of those by spray drying started rapid release, progressing to intense sporulation within 72 h. In comparison, 62.5% of ionic gelation formulations and 56.25% of spray dryer formulations only started the release process after 72 h. At the end of the observed period, we observed that 100% of the formulations obtained by ionic gelation showed intense sporulation, against 87.5% of those by spray drying. A total of 12.5% of the formulations prepared by spray drying did not show any form of growth or fungal release.

Aqueous Dispersion, Thermal Stability, and UV-Light Protection of Formulated *B. bassiana*

The spray drying and ionic gelation formulations that showed the best results during the viability assays were subjected to thermal and UV-light analyses. From spray drying, we select formulations 1, 3, 5, 6, 8, 9, 11, 13, and 15; from ionic gelation, we chose all 16 formulations. As a variable answer, we once again monitored microbial viability. The results are described in **Table 4**. Images of microbial development after the thermal stress and UV-light assays are illustrated in **Supplementary Figure 8**. The thermal stability assays were carried out at 60°C, and UV-light protection was evaluated using an exposition period of 48 h for both spray drying and ionic gelation. Unprocessed conidia (commercial) presented limited development in the growth medium after thermal and UV-light exposition. Conidia processed by spray drying without the use of encapsulating agents (Formulation 1, **Table 1**) showed reasonable rates of vegetative and germinative growth, with an intense presence of spores (**Table 4**). Similarly, Formulation 1 obtained by ionic gelation (**Table 1**), also without encapsulating agents, presented thermal resistance, but not to UV-light.

In general, all previously selected formulations prepared by spray drying and ionic gelation had gains in thermal stability and UV-light protection compared to unprocessed material (**Table 4**). Therefore, we chose formulated products with good results on yield and stability for solubility and biological assays such as formulations 1, 3, 5, and 11, obtained by spray dryer and 4, 6, 8, 10, 15, and 16, by ionic gelation. Formulation 8 prepared by spray dryer using lignin was also selected for the biological assays.

During the stability evaluation, the encapsulating agents that stood out were lignin for ionic gelation assays, and cornstarch in both processes. Starch was present in three (1, 3, and 5) of the four selected formulations prepared by spray drying, while lignin was present in five (4, 6, 8, 10, and 16) of the six chosen formulations obtained by ionic gelation. Formulation 15, obtained by ionic gelation without lignin, showed lower germination growth than the others prepared by the same process.

We noted that the formulations obtained by ionic gelation showed a higher level of UV-light resistance, as 56% presented high sporulation against 33% of those obtained by spray drying. However, both showed similar growth rates concerning temperature, with 33% of spray drying formulations growing after thermal exposure against 37.5% of ionic gelation formulations. Among the nine ionic gelation formulations with the highest sporulation index (1, 3, 4, 6, 7, 8, 10, 14, and 16) obtained after UV-light exposure, only three (1, 3, and 7) had no presence of lignin. On the other hand, the only formulation

TABLE 4 | Microbial growth analysis of microencapsulated *B. bassiana* exposed to UV-light and controlled temperature (Formulation codes are listed in **Table 1**).

Spray drying formulations

	Formulation code	**1**		**3**		**5**		**6**		**8**		**9**		**11**		**13**		**15**		**CF**	
	Fungal development	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**
Conditions	Control UV I	++	++	++	++	++	++	++	++	++	++	++	+	++	++	+	+	++	++	+	+
	Control UV II	++	++	++	++	++	++	++	++	++	++	++	+	++	++	+	+	+	+	+	–
	UV (48 h)	++	++	++	++	++	+	++	+	–	–	++	+	++	++	+	+	++	–	+	–
	60°C (4 h)	++	++	+	+	++	+	++	++	++	++	+	–	+	–	–	–	++	+	+	-

Ionic gelation formulations

	Formulation code	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**CF**	
	Fungal development	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**
Conditions	Control UV I	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	+	+
	Control UV II	++	++	++	++	++	++	++	++	++	+	++	++	++	++	++	++	+	+
	UV (48 h)	++	++	–	–	++	++	++	++	++	–	++	++	++	++	++	++	+	-
	60°C (4 h)	–	–	++	++	–	–	++	++	–	–	++	++	–	–	++	++	+	-

	Formulation code	**9**		**10**		**11**		**12**		**13**		**14**		**15**		**16**	
	Fungal development	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**	**YH**	**HG**
Conditions	Control UV I	++	++	++	++	+	+	++	+	++	++	++	++	++	++	++	++
	Control UV II	++	+	++	++	+	+	++	+	++	++	++	++	++	++	++	++
	UV (48 h)	++	–	++	+	–	–	++	+	–	–	++	++	++	++	++	++
	60°C (4 h)	++	++	++	++	–	–	+	–	–	–	++	–	++	+	++	+

YH, young microbial hyphae; HG, hyphae showing germinative structure; CF, Commercial formulation, unprocessed commercial conidia under no UV or temperature treatment; Control UV I = conidia without exposure to UV radiation kept at 20°C for 48 h; Control UV II = conidia without exposure to UV radiation, however, they were kept inside the chamber during all 48 h of the assay; "++": vegetative and germinative growth in BDA culture medium after abiotic stress, covering an area larger than 50% of the Petri dish; "+": vegetative and germinative growth in BDA culture medium after abiotic stress, covering an area <50% of the Petri dish; "–": no observed vegetative and germinative growth in BDA culture medium after abiotic stress.

with lignin obtained by spray drying (8) did not show resistance to UV-light. Such a finding may indicate that the ionic gelation encapsulation process maintains the lignin's UV-light protection ability. Other intrinsic factors to powder formulation are related to the resistance presented by spray drying formulations, not necessarily due to the presence of lignin.

Formulations 1, 3, and 8 obtained by spray drying showed a fast dispersion rate, compatible for use in the field when added in an aqueous phase at a concentration of 1.0 $mg{\cdot}ml^{-1}$. Formulations 5 and 11 formed small clusters in an aqueous medium which persisted even after hard stirring. The commercial conidia in powder not processed by spray drying presented problems in dispersion stability, producing precipitates soon after the stirring in an aqueous medium.

In general, we observed a loss of thermal stability and UV-light protection in dry powder formulations when analyzing *B. bassiana* conidia after dispersion in an aqueous medium. The spray drying formulations 1, 8, and 11 in suspension maintained the germinative and vegetative growth after the 48 h UV-light protection assay; however, they lost viability after 4 h of exposure at 60°C. Formulations 3 and 5 did not present germination after UV-light protection and temperature assays in aqueous suspension. The unformulated commercial product did not show germination even after simple dispersion in an aqueous medium and maintenance at room temperature for 4 h. These results highlight the stability gain of *B. bassiana* when formulated by spray drying.

No product obtained by ionic gelation showed dispersion capacity in aqueous media. The ionic gelation process generated larger particles than spray drying, presenting limitations for dispersion in an aqueous medium. The spray-dried particles showed an average size on a scale of micrometers while those by ionic gelation were on a scale of millimeters (**Supplementary Figure 9**).

Biological Activity of Formulated *B. bassiana* Against *S. cosmioides*

After 23 days of exposing *S. cosmioides* to a diet containing the *B. bassiana* formulated products, we observed an average mortality of 66% (±0.05%) and 76% (±0.07%) for the products prepared by spray drying and ionic gelation, respectively. The average values were similar to the positive control. In this work, the *S. cosmioides* surviving pupae were kept in an incubator chamber for analysis at the adult stage and grouped into three different sets: (1) insects exposed to formulations prepared by spray drying, (2) insects exposed to formulations prepared by ionic gelation, and (3) a control group unexposed to microorganisms. At this stage, we observed that after 13 days, the control group showed an adult outbreak rate of 94.1% for the formed pupae. Although the average total mortality rate of caterpillars to formulations prepared by ionic gelation (76%) was higher than that observed for spray drying (66%), the former presented a smaller number of viable adults at the end of the experiment. These results confirm the maintenance of *B. bassiana* virulence after spray drying formulation (even when using high temperatures as high as 120°C) and ionic gelation.

We also observed that adults formed in the treatments with spray-dried products did not show oviposition during their reproductive cycle. Several caterpillars treated with spray-dried products did not finish their development process. On the other hand, the treatments by ionic gelation products showed a smaller number of adults than spray drying, but they presented oviposition. However, these eggs did not hatch. This result indicates that the low number of viable adults remaining was sufficient for oviposition but not for eggs fertilization and life cycle maintenance. This observation reinforces the hypothesis that due to the small particle size of conidia obtained by spray drying, the insects could ingest them, affecting its development. At the end of the life cycle, the spray drying and ionic gelation products performed similar results to control on *S. cosmioides*, as indicated in **Table 5**. The **Supplementary Figures 10–12** illustrate some *S. cosmioides* during their life cycle after exposition to our formulations.

DISCUSSION

The use of biocontrol agents in the field shows several advantages, such as reducing toxic compounds in the environment and a better balance to the plant-insect microsystem. The popularization of biological control agents, however, depends on the optimization of processes and/or formulations that reduce their costs and increase their stability, ensuring easy application and maintenance in the field. Thereby, the stability of the biocontrol agents should be one of the pillars in their development, since it has impacts on logistic costs, storage protocols, and field application methods.

Microencapsulation is a process that can increase the stability of biological agents, providing a protection and releasing them from the matrix in a controlled manner in the environment. Several polymers are described as viable matrices for encapsulating different chemical classes of compounds (Vijeth et al., 2019). It is crucial for microorganisms that the encapsulating polymer be biocompatible, not reducing its viability and/or virulence, and acting as a protective and inert carrier, for its eventual controlled release. Therefore, we highlighted three points that should be considered in developing microbial formulations for insect control: (1) stability, (2) biocompatibility to the microorganism, and (3) sustainability of the encapsulating polymer.

As possible encapsulating material, we selected sodium alginate, humic acids, cellulose, corn starch, lignin, and soy oil, all of which were subjected to biocompatibility assays. These materials were chosen due to their low costs, their abundance in the Brazilian territory with some of them actually being waste from other agricultural activities, and all of them being biodegradable and non-toxic products. Cellulose and lignin show high rigidity, tensile strength, and thermal stability (Wandrey et al., 2010). According to Leland and Behle (2005) and Sipponen et al. (2019), lignin can protect against UV-light. Corn starch is easily found with high availability, low cost, and water retention ability (Forssell et al., 2004). Soy oil shows tolerance to thermal stress, has a low cost, and can stick fast to the surface of materials

TABLE 5 | Impacts of spray drying microencapsulated *B. bassiana* by (SD) and ionic gelation (IG) in *S. cosmioides* life cycle stages.

Formulation	Caterpillar mortality (%)	Formed pupae (%)	Average pupal weight ± σ (g)	Total mortality (%)
SD 1	30	30	0.320 ± 0.015	70
SD 3	40	40	0.370 ± 0.023	60
SD 5	30	30	0.290 ± 0.024	70
SD 8	20	40	0.300 ± 0.002	60
SD 11	50	30	0.360 ± 0.034	70
IG 1	70	30	0.390 ± 0.025	70
IG 4	70	20	0.310 ± 0.000	80
IG 6	50	20	0.290 ± 0.007	80
IG 8	40	30	0.340 ± 0.014	70
IG 10	0	10	0.370 ± 0.000	90
IG 15	50	30	0.280 ± 0.042	70
IG 16	40	30	0.320 ± 0.000	70
Control C–	0	100	0.360 ± 0.037	0
Control CA–	0	100	0.340 ± 0.039	0
Control C+	50	0	-o-	100

SD, caterpillars subjected to assay with products formulated by spray drying; IG, caterpillars subjected to assays with products formulated by ionic gelation; C+: positive control, containing unformulated B. bassiana; C–, negative control, treatment free of entomopathogenic microorganisms; CA–, negative control, entomopathogenic treatment free of microorganisms, however, containing alginate. Numbers are the formulation as described in ***Table 1****; σ, standard deviation.*

(Leland and Behle, 2005; Wandrey et al., 2010). In turn, humic acids promote resistance and thermal and UV-light stability and are beneficial to soil and plants (Tomaszewski et al., 2011; De Melo et al., 2016).

The exceptions in its biocompatibility that were observed for lignin (in both dosages, 1 and 2% w/v) and humic acids at a concentration of 2% (w/v) could be related to their toxicity. The toxicity of lignin and humic acid is probably related to variation in the pH value due to the change in the composition of the growth medium. The initial pH value of the PDA growth medium was 5.8. However, after adding lignin into the culture medium, the pH rose to 8.2 and 9.3 with 1 and 2% (w/v) of lignin, respectively. Meanwhile, humic acids reduced the pH values to 5.3 and 4.5 with 1% and 2% (w/v) in mass, respectively. Previous studies demonstrate that *B. bassiana* was able to withstand a wide variation in the pH values between 5 and 10 (Padmavathi et al., 2003; Luo et al., 2015). Therefore, the toxicity observed to lignin and humic acid may be related to chemical changes and nutrient availability due to pH variation, resulting in a poor environment and compromising fungal development. With this in mind, we decided to keep lignin among the compounds for the next stages due to its potential properties as an encapsulating agent (biodegradability, photoprotective properties, low cost, etc.) and also its cost efficiency, as it is a waste product from the pulp and paper industry. Moreover, previous studies in our research group showed that lignin, when applied in formulations, was not harmful to *Spodoptera frugiperda* (Costa et al., 2017).

A possible disadvantage to using spray drying to living organisms is the possibility of dehydration with a reduction in biological viability. Therefore, we evaluated the fungal resistance to spray dryer temperatures in the absence of encapsulating agents.

The resistance to thermal degradation during spray drying can be explained by the equipment operating principles. The solvent surface tension protects the compounds present in the formulation during the warm air flow. Heat promotes solvent evaporation after nebulization. An internal cooling occurs during the evaporation process in the micro-drops, since it consumes sensitive heat, turning it into latent heat, keeping the thermo-unstable compounds protected (Santos et al., 2018). Therefore, during the whole process, there is little thermal change inside the droplets, resulting in a low impact on microbial viability (Keshani et al., 2015).

The final product by spray-drying tends to have less moisture, directly impacting the recovery of the powder products (Woo et al., 2007; Santos et al., 2018). The feed flow rate also showed better recovery results when optimized at the highest level. Using a higher feed flow rate, the particle size is influenced due to the presence of a larger volume of dispersion liquid, producing more diluted drops and better-separated particles. The partial system pressure is also affected due to a larger volume of liquid for evaporation in a given period. Moreover, higher feed flow rates reduce the outlet temperature consuming thermal energy during evaporation, which is important for protecting biological samples from temperature exposure (Santos et al., 2018). Therefore, we observed that a higher feed flow rate associated with a higher inlet temperature provided a better recovery index of conidia powder, with a refined appearance and low adherence to the containers.

The formulations that showed the best recoveries were not necessarily those that performed best in the biological assays. We observed that the encapsulating agents that better-influenced powder material recoveries such as lignin and humic acids were also the compounds that showed the worst biocompatibility rates.

The products obtained by spray drying in formulations 1, 3, 5, 11, 13, and 15 presented the best *B. bassiana* growth in the PDA medium. Similarly, the formulations that showed the most significant quantity of conidium per gram of dried products were not prepared using lignin. Only two of them had humic acids in their composition. On the other hand, all formulations with corn starch present as an encapsulating agent showed good results on microbial viability, even when associated with cellulose and alginate, alginate and soy oil, humic acids and cellulose, and humic acids and soy oil. It is relevant to highlight the importance of biological viability analysis together with product development, since formulations with better powder yield results (% w/w) may not necessarily present the best biological activity.

The *B. bassiana* encapsulation by the extrusion of a hydrocolloid alginate solution in a calcium chloride solution is a simple operational process. It consists of mixing the compound/conidia of interest to the alginate solution and dripping it into a gelling solution containing a divalent cation (usually calcium chloride) (Ching et al., 2017). The particle size can be controlled by the extruder nozzle and by the transfer rate. Alginate is a porous trapping matrix allowing the controlled release of the active compound. Moreover, the process does not need high temperatures, collaborating to preserve the microbial viability (Skjåk-Bræk and Draget, 2012; Perullini et al., 2015).

This viability reduction of the formulated products by ionic gelation may be due to a slow-release mechanism of the conidia or loss of viability during the trapping process. Maruyama et al. (2020) encapsulated *Trichoderma harzianum* using alginate. In this work, they observed not only the maintenance of the microorganism virulence but also an efficiency increases in the bioassays. Several studies demonstrate that microbial encapsulation by ionic gelation presents little stress to the entomopathogenic microorganisms (Loomis et al., 1997; Batista et al., 2017; Wenzel Rodrigues et al., 2017).

Thermal stability and UV-light protection are important parameters to be analyzed during the development of biological control products. Thermal and UV-light experiments confirmed an increase in the stability of *B. bassiana,* especially by the spray drying process, which produces dehydrated conidia. The moisture loss as described before, where we observed an increase in the number of conidia compared to the commercial starting product, occurred after the drying process. Mascarin et al. (2016) also demonstrated an increase in the stability and shelf life of *B. bassiana* blastospores after the convection drying process, corroborating our results. Lignin is a polymer with a recognized ability to protect against UV-light (Sadeghifar et al., 2017).

This ability to disperse the conidia formulated by spray drying decreases the need for additives when preparing broth for field application. This gain in aqueous medium dispersion capacity is probably due to the smaller size of the microparticles obtained via spray drying. Peil et al. (2020) demonstrate that the use of lignin in the production of particles loaded with *Trichoderma reesei* spores resulted in a solvent-free system, which could be applied in the field using only water as a vehicle.

The stability of formulated conidia after aqueous dispersion suggests that the spray broth need to be prepared moments before field application. Greenhouse studies are still needed to confirm this. No product obtained by ionic gelation showed dispersion capacity in aqueous media limiting its use as granulated powder.

An *in vitro* biological assay was carried out to analyze the virulence of *B. bassiana* conidia against *S. cosmioides* after formulation. Microbial virulence is associated with genetic factors, such as expression at the level of specific genes, which can change during the microorganisms' exposure to stress (Al Khoury et al., 2019). Therefore, the preparation of formulations in powder using encapsulating agents could change *B. bassiana* virulence due to exposition to stress factors intrinsic to each process.

When exposing *S. cosmioides* to a diet containing the *B. bassiana* formulated products, we observed an average mortality similar to the positive control and other described works in the literature using entomopathogenic fungi in the caterpillar control for the *Spodoptera* genus. Thomazoni et al. (2014) observed a mortality of 44.5% after immersion of *S. frugiperda* into a fungal solution containing different *B. bassiana* isolates. The Ahmed and El-Katatny (2007) work describes the application of *B. bassiana*, *Trichoderma harzianum*, and *Aspergillus flavus* unencapsulated suspensions at *Spodoptera littoralis* with mortality rates of 90, 80, and 100, respectively at the pupal stage. Bugeme et al. (2008) highlighted that the room temperature variation to non-formulated *B. bassiana* caused a loss in viability and virulence. Moreover, the authors showed that the formulated *B. bassiana* products kept the microbial virulence and were able to control *S. cosmioides*, presenting low viability of caterpillars, pupae, and eggs.

The results observed during the bioassays confirm the maintenance of *B. bassiana* virulence after spray drying formulation (even when using high temperatures as high as 120°C) and ionic gelation. A hypothesis to the differences we observed may be the role of smaller particle diameter obtained in the powder products by spray drying in comparison to ionic gelation. Small particle sizes present favorable features to ingestion and adherence to insects (Stadler et al., 2018; Arthur et al., 2019).

CONCLUSIONS

In this work, we were able to prepare different powder formulations loaded with *B. bassiana* conidia. These materials presented a high mortality rate against *S. cosmioides* in biological assays. Moreover, we also concluded that the formulated materials showed gains in thermal stability and UV-light protection. These results were possible using low-cost materials such as corn starch, soy oil, cellulose, lignin, alginate, and humic acids.

Both spray drying and ionic gelation processes were able to perform the encapsulation of *B. bassiana* conidia. Ultimately, the products obtained by both methods showed similar biological control against *S. cosmioides*; however, the spray-dried powder material showed better aqueous dispersion capacity and smaller storage volume

for the same conidium concentration. Nevertheless, the gains in thermal stability and UV-light resistance were similar for both encapsulation techniques. Although alginate microcapsules have better compatibility with encapsulating agents, the final product obtained by spray drying appears to be more advantageous in the context of field application.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MF conceived the study, analyzed and interpreted the data, and critically read and revised the manuscript. AF and RM designed the experiments, acquired, analyzed, interpreted the data, and drafted the manuscript. IR participated in the data discussion. MS and JF participated in the data discussion and with financial support. All of the authors contributed to data analysis, reviewed, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmicb.2021.704812/full#supplementary-material

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A Review of Green Synthesis of Metal Nanoparticles Using Algae

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The ability of algae to accumulate metals and reduce metal ions make them a superior contender for the biosynthesis of nanoparticles and hence they are called bio-nano factories as both the live and dead dried biomass are used for the synthesis of metallic nanoparticles. Microalgae, forming a substantial part of the planet's biodiversity, are usually single-celled colony-forming or filamentous photosynthetic microorganisms, including several legal divisions like Chlorophyta, Charophyta, and Bacillariophyta. Whole cells of *Plectonema boryanum* (filamentous cyanobacteria) proved efficient in promoting the production of Au, Ag, and Pt nanoparticles. The cyanobacterial strains of Anabaena flos-aquae and *Calothrix pulvinate* were used to implement the biosynthesis of Au, Ag, and Pt nanoparticles. Once synthesized within the cells, the nanoparticles were released into the culture media where they formed stable colloids easing their recovery. *Lyngbya majuscule* and *Chlorella vulgaris* have been reported to be used as a cost-effective method for Ag nanoparticle synthesis. Dried edible algae (*Spirulina platensis*) was reported to be used for the extracellular synthesis of Au, Ag, and Au/Ag bimetallic nanoparticles. Synthesis of extracellular metal bio-nanoparticles using *Sargassum wightii* and *Kappaphycus alvarezi* has also been reported. Bioreduction of Au (III)-Au (0) using the biomass of brown alga, *Fucus vesiculosus*, and biosynthesis of Au nanoparticles using red algal (*Chondrus crispus*) and green algal (*Spyrogira insignis*) biomass have also been reported. Algae are relatively convenient to handle, less toxic, and less harmful to the environment; synthesis can be carried out at ambient temperature and pressure and in simple aqueous media at a normal pH value. Therefore, the study of algae-mediated biosynthesis of metallic nanoparticles can be taken toward a new branch, termed phyco-nanotechnology.

Keywords: nanoparticles, biosynthesis, algae, bio-nano factories, environment-friendly, psycho nanotechnology

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INTRODUCTION

Green synthesis has become a reliable, sustainable, and ecological protocol for the synthesis of numerous nanomaterials such as metal oxides, hybrids, and bio-inspired materials in the field of materials science (Singh et al., 2018). Metallic nanoparticles are already intriguing scientists for more than a century and are now utilized widely in biomedical sciences and engineering

(Lespes et al., 2020). Due to their anomalous size (length spanning within 1–200 nm) and shape-dependent properties and attractive applications in medicine, biofuel production, catalysis, electronics, and biotechnology, the synthesis of metal nanoparticles is a major area of research in nanotechnology (Ganesan et al., 2020). Green synthesis is thus considered to be an important tool to reduce the ill side effects of nanoparticles commonly used in laboratories and industry by conventional synthesis methods. The present review discussed all the established green synthesis methods used worldwide but focused on algae-based green synthesis only.

Among various microorganisms, microalgae are primitive microscopic plants, and they have significant advantages as cell factories for the production of nanoparticles compared to larger plants. Algae are aquatic filamentous photosynthetic organisms that fall under the kingdom of *plantae*. All these algae are broadly classified into two types: microalgae and macroalgae (Leaf et al., 2020). Macroalgaes can be counted under the naked eye whereas microscopes are required to observe microalgae. Unlike most biomass, both the algaes can be harvested several times in a single year. Algae also have the ability to grow without the help of any addition of outside chemicals or fertilizers. Microalgae grow extremely quickly and, on average, double their mass 10-fold faster than higher plants. It is known that various species of microalgae reduce metal ions. Algae are recognized as primitive microscopic plants and have few advantages, such as growth rate and nutrient requirements, for producing nanoparticles compared to higher plants (Jacob et al., 2021). The present review makes an attempt to improve researchers' knowledge of green synthesis methodology of nanoparticle synthesis using different algal species and their various pros and cons.

CLASSIFICATION OF NANOMATERIALS AND METHODS OF SYNTHESIS

The worldwide biocompatibility of green nanoparticles and their enormous potential for use like catalysts, antimicrobials, biofuel generation, cancer/gene therapy, and sensorization have been attracting extensive interest. It is fascinated by the inherent proprietors of nano-materials like particular form, shape, composition, larger volume/superficial area, and the purity of the single constituents. Nanoparticles are characterized by their synthesis process. For the synthesis of nanoparticles, there are several methods available. Synthesis by using physical and chemical methods are quite costly and produce toxic by-products. For nanoparticle synthesis, two approaches exists: bottom-up and top-down (Shukla et al., 2021). The first step is the attrition of large macroscopic particles. The most common technique employing the role of the top-down approach for nanomaterial synthesis is the lithographic interferometric (Agarwal et al., 2017). This technique involves the synthesis by self-assembly of nanoparticles of miniaturized atomic components. It is a relatively inexpensive approach. It is based on the approach to the kinetic and thermodynamic balance. Among the various synthesis methods, the green synthesis methods are more promising as they will not produce any hazardous chemicals or leave almost negligible amount of waste products and utilizes environment-friendly chemicals for the synthesis of nanoparticles.

Bio-Based Mechanism of Nanoparticle Synthesis

Biosynthetic methods are classified into intracellular and extracellular synthesis based on the location of nanoparticles produced (Öztürk, 2019). Extracellular production of nanoparticles, for example, is also being developed in order to further grasp the processes of synthesis, as well as to enable downstream processing and scale-up processing. Therefore, usage of algae for synthesis of inorganic nanoparticles has gained a lot of interest among researchers (Dahoumane et al., 2017). There are three major techniques used for synthesis of nanoparticles using algae. Apart from direct exploitation of live algae cells for nanoparticle synthesis, there are two other common methods: lysis of algal cells followed by extraction using different downstream process techniques such as centrifugation and filtration, and harvestion of nanoparticles from the supernatants of the algal broth (Dahoumane et al., 2017).

Algae-Assisted Synthesis

The field of processing algal biomass under catalytic conditions has received a lot of interest over the last decade. Algae should have a considerable economic significance in the future provided cost-effective upstream and downstream processing are developed. Algae are renowned for their capacity to hyper-accumulate heavy metal ions and remodel into more malleable shapes (Fawcett et al., 2017). Therefore, algae have been proposed as model organisms for fabricating bio-nanomaterials. The nucleation, development, and stabilization of nanoparticles are regulated by physical factors such as pH, precursor concentration, reaction time, exposure time, and temperature. These variables may be modified to adjust the size and morphology of the cells, as well as to avoid agglomeration. Carbohydrates, vitamins, nutrients, oil, fats, polyunsaturated fatty acids, bioactive compounds like antioxidants (polyphenols and tocopherols), pigments like carotenoids (carotene and xanthophyll), chlorophylls, and phycobilins are all found in algal extracts (phycocyanin and phycoerythrin) in different levels of concentration depending on alga species and its age. These active compounds have been described theoretically as nanoparticle synthesis reducing and stabilizing agents (Fawcett et al., 2017). The synthesis of nanoparticles from a wide diversity of algal resources proved to be one of the recent and most innovative areas of biochemical research as they have the property of reducing metal ions (Ponnuchamy and Jacob, 2016). Nanoparticles can be symthesized either intra- or extracellularly depending on the algal species and mode of operation. The different species of algae and the nanoparticles brought out are tabulated in **Table 1**. The table clearly depicts that algae (irrespective of species) can be used for the production of metallic nanoparticles.

Algae, especially microalgae, are the new and up-and-coming organisms used for synthesis of nanomaterials. The choice of algae as a nanomaterial synthesizing agent is more promising

TABLE 1 | List of nanoparticles synthesized by different algae and their size and shape.

Algae	Nanoparticles	Size	Shape	References
Bifurcaria bifurcate	CuO	5–45 nm	Spherical and elongated	Abboud et al., 2014
Galaxaura elongata	Au	3.85–77.13 nm	Spherical	Abdel-Raouf et al., 2017
Sargassum plagiophyllum	AgCl	18–42 nm	Spherical	González-Ballesteros and Rodríguez-Argüelles, 2020
Cyanobacterium Oscillatoria limnetica	Ag	3.30–17.97 nm	Quasi spherical	Hamouda et al., 2019
Caulerpa racemose	Ag	5–25 nm	Spherical and triangle	Aboelfetoh et al., 2017
Ulva fasciata	ZnO	77.81	Spherical	Alsaggaf et al., 2021
Turbinaria conoides	Au	6–10 nm	Tri-spherical, triangle, and pseudo-spherical	Rajeshkumar et al., 2013
Jania rubens	Fe_3O_4	22.22–33.33 nm,	Spherical	Salem et al., 2020
Portieria hornemannii	Ag	70–75 nm	Spherical	Fatima et al., 2020

than other living organisms or biomaterials. The researchers used different methods such as open cultivation systems (e.g., open ponds, tanks, and raceway ponds) and closed cultivation systems (e.g., photo bioreactors) to cultivate various algae species (Narala et al., 2016).

The following main steps are observed for the biosynthesis of metal nanoparticles using algae in the majority of the experiments:

(i) Heating or boiling an algal extract in water or an organic solution for a specified period of time.
(ii) Preparation of ionic metallic compound molar solutions.
(iii) Both algae and solutions of ionic metallic compounds are incubated for a definite period of time under controlled conditions, either with regular stirring or without stirring.

Based on characteristics of algae, nanoparticle synthesis can be accomplished by either an extracellular or an intracellular method in a precise and quantitative manner. The possible extracellular metallic nanoparticle production has been proposed to be attributed to polysaccharides, reducing carbohydrates, proteins, peptides, or other reducing factors present in the algal culture, and precipitating reducing metal ions to nanoparticles (Gahlawat and Choudhury, 2019). Both photosynthesis and respiration activity in algae are responsible for reduction of metallic ions, which further lead to formation of intracellular production of metallic nanoparticles. The enzyme nitrogenase has been proposed to have a function in the reduction of nanometals that occurs in cyanobacteria. The synthesis process was reported by participating in a photosynthetic electron transport system (PETS) and respiratory electron transport system (ETS) present on the cell membrane and in the cytoplasm of algae (Dahoumane et al., 2014). Reducing agents such as NADPH or NADPH-dependent reductase have also been proposed to be a key component for the reduction of metallic ions to nanoparticles in cyanobacteria through energy-generating reactions within the electron transport system and redox reactions occurring at the thylakoids, cell membranes, and in the cytoplasm (Oza et al., 2012). The pH of a material impacts on change of metallic nanoparticles concentration in solution. At a lower pH, the reduced power of the functional groups of the metallic nanoparticles is less relative to the pH greater than 6.5; however, the reduced power of the functional groups rises with higher pH values. After further increases in pH, the reduced power of the functional groups is not enough and hence cytotoxicity suffers. The hydrophobic and hydrophilic interactions between the nanoshells can inhibit the aggregation of the nanoparticles.

Cyanobacteria *Nostoc ellipsosporum* were first utilized in the laboratory for the intracellular biosynthesis of gold nanorods. After discovering healthy growers of 15 mg L^{-1} gold (III) solution (pH 4.5), the nanorods were formed inside cells at 20°C for 48 h (Parial and Pal, 2015). Gold nanoparticles (AuNPs) may be easily synthesized using a variety of processes for a variety of industrial and medical uses. However, due to their vast size distribution and strong aggregation property, their effectiveness as a catalyst has not been adequately researched and optimized.

The nutrient demands and maintenance cost of growth conditions such as light and temperature for the growth of algal cells are less than any prokaryotic and eukaryotic species. Many algae growing in a polluted environment with both metals and non-metals demonstrate that they are able to resist large quantities of metal or non-metal materials. In order to minimize and enhance their survival in higher concentrations of metals and the toxic effects of metal ions, algae have effectively developed defense-related mechanisms. Algae make excellent bio-sorbents due to their abundance in both seawater and fresh water, their cost-effectiveness, reusability, and their high metal sorption capabilities. The theoretical equilibrium model for bio-sorption (Langmuir model and Freundilich isotherm model) performs well in describing and forecasting metal uptake processes (He and Chen, 2014). The mechanisms of toxicity on algae (*P. subcapitata*) were also assessed and reported that higher sensitivity of the algal growth inhibition was observed by metalbased nanoparticles (Aruoja et al., 2015). The toxic effects of zinc oxide nanoparticles were studied on two marine algae *Tetraselmis suecica* and *Phaeodactylum tricornutum*. The study reported zero observable effect on growth inhibition by zinc oxide nanoparticles (Li et al., 2017).

Microalgal live cells are used to synthesize metallic nanoparticles in a one-step process that includes an aqueous

solution containing metallic salts that is applied directly to the cells as they are being cultured. After being synthesized, the nanoparticles are released into the culture medium wrapped inside the matrix, which is often responsible for the formation of colloids. Due to its weight, the latter settles in the photo bioreactor. Repetitive cycles for nanoparticle biosynthesis may be conducted if needed by inserting fresh culture medium. Furthermore, microalgae preserved their nanoparticle biosynthetic capability when entrapped within organic vesicles. Several micro-algal organisms have been used in the biosynthesis of nanomaterials by extracting biomolecules from its cell.

Since silver nanoparticles are commonly used as antibacterial agents, a novel idea is needed for the effective application of silver nanoparticles as therapeutic agents to unknown diseases and infections. Silver nanoparticles have important advantages in biomedicine due to their physical and chemical flexibility. Although various chemical and biochemical methods still exist, an improved version of silver nanoparticles for extended applications in an environmentally friendly manner is urgently needed (Shanmuganathan et al., 2019).

Silver has been used for decades. Silver and silver nanoparticles are widely used in hard surface products and textiles, and are used in a broad variety of pharmaceutical, food industry, and domiciliary applications. Silver nanoparticles, which are well recognized for their antimicrobial function, may be synthesized by microalgae. Furthermore, the biomass generated in micro-algal culture for nanoparticle biosynthesis exhibits antimicrobial properties, as it can increase the antibacterial and antifungal ability of silver nanoparticles (Terra et al., 2019). Usage of silver nanoparticles was seen to extend to *C. vulgaris* conditioned media with a bright yellow to dark brown color shift (UV-Vis absorbance at 415 nm) (da Silva Ferreira et al., 2017).

Application of Algae-Mediated Nanomaterials

Algae belonging to *Cyanophyceae, Chlorophyceae, Phaeophyceae*, and *Rhodophyceae* families have been used as nano-machines by intracellular and extracellular synthesis of gold (Au), silver (Ag), and other metallic nanoparticles. Algae are an attractive medium for the processing of diverse nanomaterials, owing to the inclusion of bioactive compounds in their cell extracts such as pigments and antioxidants that serve as biocompatible reductants. Silver nanoparticles synthesized in an environmentally friendly manner effectively inhibit bacterial growth by eliciting bactericidal activity against Gram-negative and Gram-positive biofilm-forming pathogens. As a result, silver nanoparticles produced by *G. amansii* (brown algae) may serve as potential anti-fouling coatings for a variety of biomedical and environmental applications (Pugazhendhi et al., 2018). Nanoparticles produced by algae can compete with standard drugs and have been shown to have antibacterial, anticancer, and antifungal effects. Aside from medical uses, metal nanoparticles have a broad variety of applications in computing, optics, cosmetics, and other areas.

Antioxidant Activity

Defatted algal biomass was reported for synthesis of silver nanomaterial by Chokshi et al. (2016). After lipid extraction, the residual biomass of the microalgae *Acutodesmus dimorphus* was used by the researcher to make a micro-algal water extract, which was then used to make silver nanoparticles (with a scale of 2–20 nm). The antioxidant ability of the biosynthesized silver nanoparticles was assessed using 2,2′-azino-bisphosphate (3-ethylbenzothiazoline-6-sulfonic acid) (Chokshi et al., 2016).

Antibacterial Activity

Antibacterial behavior of nanoparticles synthesized from algae has been studied against a variety of bacterial strains. Silver nanomaterials manufactured from the brown seaweed *Padina tetrastromatica* effectively slowed the growth of *P. aeuroginosa, Klebsiella planticola*, and *Bacillus subtilis* (Sangeetha et al., 2012). Another research found that robust and colloidal-shaped silver nanomaterials made from an aqueous extract of the green marine algae *Caulerpa serrulata* had excellent antimicrobial activity against *Shigella* sp., *S. aureus*, *E. coli*, *P. aeruginosa*, and *Salmonella typhi* at lower concentrations. *E. coli* had the largest zone of inhibition of 21 mm, while *S. typhi* had the smallest zone of inhibition of 10 mm at 50 μl solution of silver nanomaterials (Aboelfetoh et al., 2017).

Antifungal Activity

The antifungal function of nanoparticles is defined by their size and form. The broad surface region of small nanoparticles ensures that microbial growth is inhibited. The enhanced contact area of the spherical form with size-reduced ions eliminates growth of fungus.

TABLE 2 | Different imaging techniques used in nanoparticles.

Imaging type	Type of nanoparticle used	Applications	References
Magnetic resonance imaging (MRI)	$Gd_2Hf_2O_7$ nanoparticles	Chemo-/photo-thermal-/radiotherapy of resistant tumors	Kuang et al., 2020
Fluorescence-based imaging (FBI)	Carbon quantum dots with gold nanoparticles	Detection of aldicarb	Sajwan et al., 2021
Confocal microscopy	Zinc oxide nanoparticle	Check sunscreen toxicity	Yamada et al., 2020
Transmission electron microscopy (TEM)	V_2O_5 nanoparticles	Photocatalytic and antibacterial studies	Karthik et al., 2020
Scanning electron microscopy (SEM)	Silver nanoparticles	To check *in vitro* anti-acne activity	Srivastava et al., 2020
Reflection electron microscopy (REM)	Germanium nano islands	Nucleation control	Shibata et al., 2000

GENERAL CHARACTERIZATION TECHNIQUES

A range of analytical techniques such as transmission or scanning electron microscopy (TEM or SEM), atomic force microscopy (AFM), dynamic light scattering (DLS), x-ray photoelectron spectroscopy (XPS), powder x-ray diffractometric (XRD), Fourier infrared transform spectroscopy (FTIR), and UV-Vis spectroscopy are used to characterize metal and non-metal nanoparticles. The aforementioned techniques are used to characterize the morphology of the nanoparticles, including particle size, shape, crystallinity, fractal dimensions, pore size, and surface area. The image of nanoparticles using different image capturing instruments and their versatile applications are tabulated in **Table 2**.

The change in color of a mixture formed at a particularly specific temperature has been utilized as a visual indication for the synthesis of silver and gold non-metals in certain instances. A shift of the color of the reaction mixture to brownish violet or a change to violet suggests the formation of silver nanoparticles, and a change of the reaction mixture to purple or pink indicates the formation of gold nanoparticles (AuNPs). The biosynthesis of nanometals in the aqueous process is monitored using absorption spectroscopy in the UV-Vis spectral range (190–1,100 nm) since nanometals have striking optical properties due to surface plasmon resonance (SPR) (Borah et al., 2020). The combined motions of the free electrons of metal nanoparticles in resonance with the light wave produce a special SPR absorption band (λ_{max}) that is dependent on size, shape, aspect ratio, and the dielectric constant of the metals. As the particle size of the nanomaterial grew in the aqueous solution, the bandwidth dropped with the increased band amplitude; hence, a UV-Vis spectrophotometer may be used to determine the particle size of the metal nanoparticles in the aqueous solution. Blue and green light rays, which have a lower intensity and are more diffuse, are employed in a broad spectrum band (between 320 and 580 nm) (Gopu et al., 2021).

Biomolecules present in algal extracts, such as polysaccharides, peptides, and pigments, can play an important role in the formation of biomolecular complexes for bio-mining the metals. These materials are often observed to be responsible for stabilizing and capping metal nanoparticles that are created by the use of amino-derived or cysteine-conjugated polysaccharides, while polysaccharides are used for metal core stabilization and capping. The reducing agents responsible for the reduction, stabilization, and capping of metal nanoparticles may be identified using Fourier transform infrared (FTIR) spectrometry. Through using the FTIR spectra, it is understood that functional groups such as the -C = O-, -NH_2, and -SH- groups conform to the surface of the biosynthesis non-metals (Huq, 2020).

To illustrate the development of various sizes of nanoparticles, TEM and SEM are majorly used by researchers. SEM imaging needs a prolonged preparation phase, which is often completed by metal coating to minimize charging artifacts and rapid radiation damage to biomaterials during the imaging process. Besides this, electron diffraction (EDX) machine is also paired with SEM and TEM for better identification. Samples are prepared by drop coating the metal nanoparticle solution onto carbon copper grids followed by drying the grids in preparation for measurement. X-ray diffraction (XRD) study will reveal the crystalline structure of nano-metals. Energy-dispersive spectroscopy (EDS) is also a very common instrument to determine the presence of metal (Abbasi et al., 2020). Typically, EDS systems are integrated into either a SEM or an EPMA equipment. A sensitive x-ray detector, a liquid nitrogen dewar for cooling, and software for collecting and analyzing energy spectra are all included in an EDS system. Through these methods, researchers can easily quantify the structural characteristics of nanomaterials.

CONCLUSION

Algae, like other biological species such as mushrooms, yeast, and bacteria, have significant nanoparticle synthesis effects. Algal-based nanosynthesis has developed into a separate branch known as phyco-nanotechnology. Various studies on the biosynthesis of nanoparticles using seaweed extracts have been conducted. However, the use of microalgae for nanoparticle synthesis is very limited. In this regard, several recent experiments have shown that microalgae can be used to synthesize metal nanoparticles. Both micro- and macroalgae are the frontrunners in the development of nanoparticles that can effectively provide a range of applications. Algae are also common in agriculture. When seaweeds (macroalgae) are used as fertilizers, there is less nitrogen and phosphorus runoff than when animal manure is used. Algae are recognized for their capacity to hyperaccumulate heavy metal ions and remodel into more malleable shapes. Because of these appealing characteristics, algae have been proposed as model organisms for the processing of bio-nanomaterials.

Different forms of algae that have not been extensively researched will be used to study the processes of nanoparticle synthesis. To identify the proteins and enzymes involved in algal nanoparticle synthesis, extensive research would be needed to understand the exact mechanisms of the reaction. Designing easy and low-cost techniques will make the synthesis process commercially viable. Nano-biotechnology has the ability to revolutionize human health, as well as the agriculture and food markets, by offering new methods for disease prevention and identification. As a result, useful methods for investigating the biological capacity of algae and blue-green algae for nanoparticle synthesis should be established, as well as their behavior and aggregation in animals and plants.

Future studies should look into the size distribution and chemical structure of nanoparticles made from algae. Overall, nano-biotechnology that uses algae and blue-green algae to synthesize nanomaterials is still in its early stages, and further research and development is required.

AUTHOR CONTRIBUTIONS

All authors wrote, reviewed, and approved this manuscript for publication.

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