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Review Article

Bacterial Exopolysaccharides as Reducing and/or Stabilizing Agents during Synthesis of Metal Nanoparticles with Biomedical Applications

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Bacterial exopolysaccharides (EPSs) are biomolecules secreted in the extracellular space and have diverse biological functionalities, such as environmental protection, surface adherence, and cellular interactions. EPSs have been found to be biocompatible and eco-friendly, therefore making them suitable for applications in many areas of study and various industrial products. Recently, synthesis and stabilization of metal nanoparticles have been of interest because their usefulness for many biomedical applications, such as antimicrobials, anticancer drugs, antioxidants, drug delivery systems, chemical sensors, contrast agents, and as catalysts. In this context, bacterial EPSs have been explored as agents to aid in a greener production of a myriad of metal nanoparticles, since they have the ability to reduce metal ions to form nanoparticles and stabilize them acting as capping agents. In addition, by incorporating EPS to the metal nanoparticles, the EPS confers them biocompatibility. Thus, the present review describes the main bacterial EPS utilized in the synthesis and stabilization of metal nanoparticles, the mechanisms involved in this process, and the different applications of these nanoparticles, emphasizing in their biomedical applications.

1. Generalities of Exopolisaccharides (EPSs)

Microbial exopolysaccharides (EPSs) are biopolymers produced and secreted by microbial cells to the extracellular medium, forming a capsule or slime loosely attached to the cell surface [1]. These compounds can be soluble or insoluble polymers released into the surrounding environment to accumulate outside the cells [2, 3]. Thus, they can be encountered attached to the microbial cell surface or within the fermentation medium [2]. Synthesis of EPSs is important to microbial cells since EPSs play crucial biological roles in their survival. Among these functions include cell protection, attachment to solid surfaces, cell aggregation, and cell-cell interactions [4, 5]. There are various groups of microorganisms that can produce EPS; bacteria (including extreme and marine bacteria) [4–6], cyanobacteria [6], fungi and yeasts [7], and microalgae [8]. Some of the most studied EPSs produced by microorganisms are xanthan, dextran, alginate, gellan, levan, cellulose, curdlan, pullulan, succinoglycan, and hyaluronic acid [9–11]. In this context, based on their functionality, EPSs have been classified in the following categories: constructive or structural, sorptive, surface active, informative, redox active, and nutritive [12]. Moreover, EPSs from extreme bacteria possess unique and specific properties

of interest since metabolic products from these types of bacteria have evolved to adapt to extreme environmental conditions [6].

The structure of EPSs is mainly conformed of carbohydrates such as monomers of D-glucose, D-galactose, D-mannose, L-fucose, L-rhamnose, D-glucuronic acid, D-galacturonic acid, L-guluronic acid, D-mannuronic acid, N-acetyl-D-glucosamine, and N-acetyl-D-galactosamine, as well as noncarbohydrate components that confers an anionic nature to the EPSs such as carboxyl, phosphate, sulfate, and pyruvate substituents [10, 13–16]. In addition of the negative charge, these organic groups increase the lipophilicity of the EPSs and have influence in the interaction with other polysaccharides and cations [10]. The structure of some microbial EPSs is shown in Figure 1.

2. Main Bacterial EPSs

Xanthan gum is a heteropolysaccharide EPS produced by the genus Xanthomonas and is the first natural biopolymer produced at an industrial scale [10, 17]. Dextran is a homopolysaccharide composed of α-glucans and produced by the *Leuconostoc*, *Streptococcus*, and *Lactobacillus* genera [10, 18]. Curdlan is a nonbranching linear polysaccharide composed of β-glucan and produced by *Alcaligenes faecalis* [19]. Gellan gum is a sphingan heteropolysaccharide synthesized by the genera *Sphingomonas* and is composed of acetyl and glyceryl substituents [20]. Cellulose is another β-glucan that can be produced by the genera *Gluconacetobacter*, *Agrobacterium*, *Aerobacter*, *Achromobacter*, *Azotobacter*, *Rhizobium*, *Sarcina*, and *Salmonella* [21]. Levan is a homopolyfructose-branched EPS produced by microorganisms from the genera *Zymomonas*, *Pseudomonas*, *Mycobacterium*, *Corynebacterium*, *Erwinia*, *Bacillus*, and *Azotobacter* [22, 23]. Succinoglycan is a biopolymer composed of one galactose and seven glucose residues with succinyl, acetyl, and pyruvyl as nonsaccharide substituents; this EPS has been found to be produced by some genera such as *Rhizobium*, *Alcaligenes*, *Pseudomonas*, and *Agrobacterium* [10, 24]. Other more recent bacterial EPSs that have been reported are FucoPol, a heteropolysaccharide produced by *Enterobacter* A47, which is composed of fucose, galactose, glucose, and glucoronic acid with the nonsaccharide substituents pyruvate, succinate, and acetate [25] and GalactoPol, a polysaccharide produced by *Pseudomonas oleovorans* aNRRL B-14682 mainly formed by galactose and other saccharides as glucose, mannose, and rhamnose in lower amounts [26]. Both of these EPSs are obtained by their respective bacteria using glycerol as sole carbon source. The information of this section is summarized in Table 1.

3. Application of EPSs

Many areas such as chemistry, food, cosmetics, hydrocolloids, pharmaceuticals, medicine, packaging industries, textiles, detergents, adhesives, agriculture, wastewater treatment, and nanotechnology have benefited from the use of EPS [2, 10, 27]. These industrial areas have taken advantage of the properties of EPS to elaborate many different products; such as adhesives, absorbents, lubricants, rheology modifiers, viscosifiers, emulsifiers, chelating agents, biomaterials intended to serve as drug delivery vehicles encapsulating bioactive biomolecules, anticancer agents, imaging, tissue engineering, antimicrobial agents, and as a reducting and stabilizer agent in the synthesis of metal nanoparticles [2, 6, 28–32]. Moreover, EPS have been reported to be generally recognized as safe (GRAS) compounds, meaning that they do not represent a health risk in their use [33]. Due to these properties, other applications of EPS are currently being explored, among them are sorption, their use in the removal of toxic metals and carbon dioxide [34, 35], improving activated sludge settleability [36], and designing aqueous foams with clay nanoparticles to avoid the emission of volatile organic compounds during oil or gasoline loading and storage [37]. In regard to this, EPS from marine microorganism have also been found to have interesting properties such as good antioxidant activity [38, 39], blocking effect to avoid the adherence of gastrointestinal pathogens, anticancer and antiviral effect in human cell lines [40–42], restoration of bone integrity, and anticoagulant properties [43]. Thus, as described in this section, EPSs offer a wide range of applications. In this review, we focus on the ability of bacterial EPSs to act as reducing and stabilizing agents during the synthesis of metallic nanoparticles for applications in biology and the medical field.

3.1. EPS Used in the Synthesis of Metal Nanoparticles. Metal nanoparticles have been the target of research within the last two decades, since they have been found to have different and enhanced properties when compared to those exhibited by the bulk metals [44]. These nanoparticles also present high reactivity due to their crystallographic surface structure and large surface area [45]. All of these properties allow for metallic nanoparticles to be applied in areas such as medicine, electronics, environment, agriculture, health care, and pharmaceutical products.

There are physical, chemical, and biological methods to produce and synthesize metal nanoparticles. Biological methods or green synthesis mainly use plant extracts. Fungal and bacterial strains and their cultures have been explored recently since they provide an environmentally friendly and cost-effective synthesis platform that employs nontoxic reagents and procedures [46]. Green synthesis has been used to elaborate many different metal nanomaterials such as Ag, Au, Zn, Ti, TiO_2 Ni FeO, Fe_3O_4, Cu, Co, Pd, Ba, CdS, and Pt nanoparticles [47–51]. Thus, much emphasis has been placed in the discovery of effective reducing and stabilizing agents to synthesize metallic nanoparticles. In this context, EPSs contain various functional groups in their structure that can serve as reductive and stabilizing agents in the synthesis of metal nanoparticles by a chelating and capping process [52]. These processes allow control on size, shape, and particle dispersion [33]. Further, during synthesis of metal nanoparticles in the presence of EPSs, their mucoadhesion properties lead to a neutral, low surface energy and low level of nonspecific protein receptor recognition capping, making these nanoparticles more adequate to utilize in broader applications [33]. A general representation of possible interactions

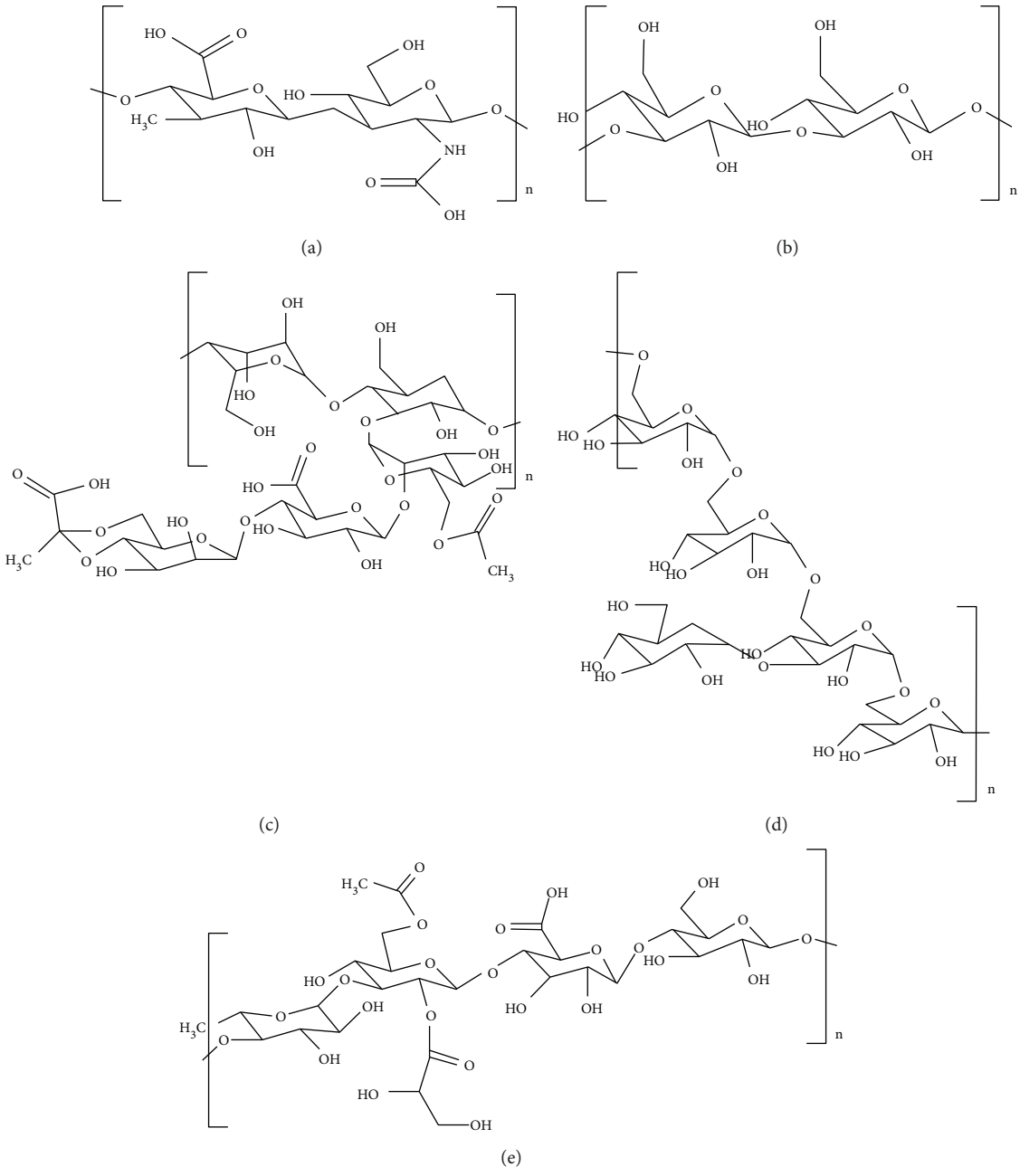

Figure 1: Structure of some microbial exopolysaccharides. The chemical structure of diverse microbial EPSs can differ in functional groups or sugars branched in the main chain structure. (a) Hyaluronic acid, (b) curdlan, (c) xanthan, (d) dextran, and (e) gellan. The "n" indicates the polymerization degree of the polysaccharides, and it can vary significantly from bacteria strain and culture conditions.

between EPS and metal ions to form metal nanoparticles is shown in Figure 2.

In this context, it is important to mention that in most cases in which EPSs are utilized to synthesized metal nanoparticles, the EPSs act both as a reducing and stabilizing agents at the same time due to their properties and structures with many functional groups; which consequently make EPSs suitable and advantageous to produce metal nanoparticles destined to be applied in the biomedical sciences [53–57]. However, there are also studies in which metal nanoparticles are produced with other reducing agents or other reducing methods, where the EPSs act only as a stabilizing or capping agent [58–60].

3.2. Differences between Polysaccharides and Exopolysaccharides in the Preparation of Metal Nanoparticles. There are differences between commercial polysaccharides and extracted microbial exopolysaccharides, mainly regarding their composition. As mentioned previously, polysaccharides are mainly composed by carbohydrates. Cellulose, as well as starch, is composed by D-glucose; alginate is composed by β-D-mannuronate and α-L-

Table 1: Main bacterial EPS and the bacteria that produce them.

Exopolysaccharide	Bacteria	Reference
Xanthan gum	*Xanthomonas*	[10, 17]
Dextran	*Leuconostoc*, *Streptococcus*, and *Lactobacillus*	[10, 18]
Curdlan	*Alcaligenes faecalis*	[19]
Gellan gum	*Sphingomonas*	[20]
Cellulose	*Gluconacetobacter*, *Agrobacterium*, *Aerobacter*, *Achromobacter*, *Azotobacter*, *Rhizobium*, *Sarcina*, and *Salmonella*	[21]
Levan	*Zymomonas*, *Pseudomonas*, *Mycobacterium*, *Corynebacterium*, *Erwinia*, *Bacillus*, and *Azotobacter*	[22, 23]
Succinoglycan	*Rhizobium*, *Alcaligenes*, *Pseudomonas*, and *Agrobacterium*	[10, 24]
FucoPol	*Enterobacter* A47	[25]
GalactoPol	*Pseudomonas oleovorans* aNRRL B-14682	[26]

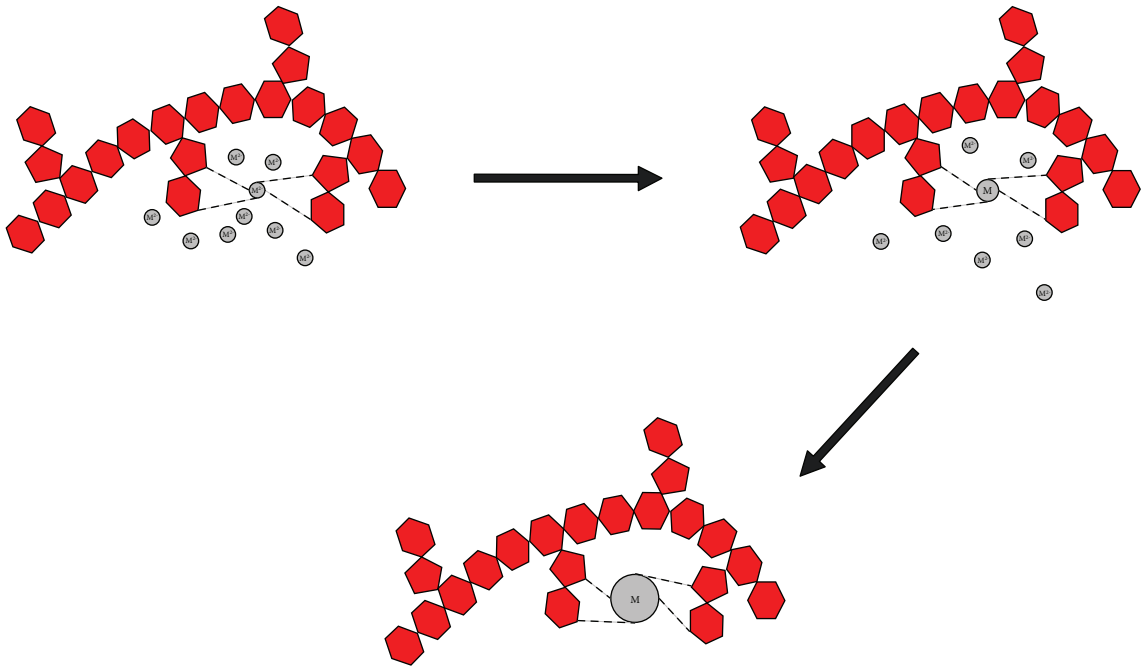

Figure 2: General representation of EPSs as a reducing and stabilizer agent to produce metal nanoparticles. Metal ions can be coordinated by the functional groups of the exopolysaccharide. Then, the metal can be reduced either by the exopolysaccharide or a different reducing agent. Once the nuclei was formed, it can grow stabilized by the microbial exopolysaccharide.

guluronate; carboxymethyl cellulose is a polymer of D-glucose with carboxymethyl groups bonded to the hydroxyl groups; pectin is mainly composed by galacturonic acid, linked to other components as acetic acid, D-apiose, glucorinic acid, etc. Polysaccharides have many functionalities, which include the capability of their hydroxyl groups and hemiacetal ends to reduce metal precursor salts [61]. Metallic nanoparticles synthesized with polysaccharides are often reduced in alkaline conditions to achieve better pH conditions for the synthesis or to hydrolyze the polysaccharide to increase the amount of available reducing sugars [62, 63].

On the other hand, exopolysaccharides, besides being composed primarily of carbohydrates, may have organic and inorganic substituents, as shown in Table 2 [64]. Some EPS of cyanobacteria are mostly heteropolysaccharides, containing S functional groups linked to the sugar backbone [65]. Similarly, there are reports of carbohydrate backbones containing S in their chemical composition in the EPS of some *Bacillus* strains [66, 67]. There are some *N*-acetylamino sugars that have been not found in commercial microbial polysaccharides [64]. The introduction of these amino functionality in the reducing end of EPS make them capable of complexing and stabilizing much better metallic nanoparticles [68].

4. Role of Bacterial EPSs in the Synthesis of Metallic Au and Ag Nanoparticles with Biomedical and Other Applications

Among the most studied and broadly produced nanoparticles, through green synthesis methods, are silver (Ag-NPs)

Table 2: Different noncarbohydrate substituents found in microbial exopolysaccharides.

Substituent	Appearance in microbial EPS
Organic acids	
Acetate	Very common
Glycerate	*Pseudomonas elodea*
Hydroxybutanoate	*Rhizobium irifolii*
Propionate	*Escherichia coli*
Pyruvate	Very common
Succinate	*Rhizobium* spp., *Agrobacterium* spp,
Amino acids	
L-glutamate	*Klebsiella*
Serine	*E. coli*
Inorganic acids	
Phosphate	Common
Sulfate	Cyanobacteria, *Bacillus* spp.

and gold (Au-NPs) nanoparticles. Many of these studies report the use of EPS as reducing and stabilizing agents during their synthesis. For instance, xanthan gum has been used in the synthesis of Au-NPs and these EPSs proved to be an effective drug delivery carrier for doxorubicin hydrochloride to human lung cancer cells [69]. Furthermore, xanthan gum EPSs have been shown to aid in the synthesis of Ag-NPs with enhanced catalytic properties and antibacterial activity against *Escherichia coli* and *Staphylococus aureus* [70].

Dextran is a well-known EPS used to produce Ag-NPs with applications as chemical sensors for cysteine [71]. Moreover, Ag-NPs with antibacterial and antifungal properties have also been synthesized using dextran sulfate [72]. For the case of Au-NPs, these particles have been obtained using dextran as a capping and reducing agent [55]. In this study, the Au-NPs showed antitumor effects against Ehrlich ascites carcinoma and solid carcinoma transplanted in mice through tests performed to evaluate liver and kidney biochemical function, as well as oxidation stress ratio and histopathological studies.

Curdlan and other modified compounds of EPSs have been useful to produce Ag-NPs using 4-acetamido-2,2,6,6-tetramethypiperidine-1-oxyl radical- (TEMPO-) oxidized curdlan [73], and also, nontoxic and biocompatible Au-NPs were produced using carboxylic curdlan. For the last study, the interaction of Au-NPs with bovine serum albumin were tested, indicating that these nanoparticles do not produce significant changes in protein structure [74].

Sphingans, such as gellan, have been used as reducing and stabilizing agents to elaborate Au-NPs for drug delivery formulations with cytotoxic effects against human glioma cell lines LN-18 and LN-229 [75]. Using gellan gum, a highly stable water dispersion of antibacterial Ag-NPs was synthesized and tested their cytotoxicity in mouse embryonic fibroblast cells (NIH3T3), as well as their diffusion across rat skin [76]. Finally, Au-NPs were produced with the same EPS revealing that these nanoparticles are uptaken by the human glioma cell line LN-229 and do not possess toxicity after oral administration in rats [77].

For the case of cellulose, previous works have stated that microbial cellulose in comparison to plant cellulose can be extracted with greater purity and a higher level of polymerization and crystallinity [78]. Bacterial cellulose has been employed as a stabilizing agent of metallic nanoparticles, such is the case of Ag-NPs that coat the surface of bacterial cellulose nanofibers [79]. Ag-NPs stabilized by microbial cellulose have also been synthesized to be used as optical sensors of cyanide ions and 2-mercaptobenzothiazole in water samples [80]. Bacterial cellulose nanofibers have been shown to act as templates for synthesis of Au-NPs to produce nanocomposites formed by Au-NPs nanofibers in aqueous suspension. These nanocomposites have been used to immobilize the horseradish peroxidase enzyme to make a biosensor to detect H_2O_2 [81].

Levan is another microbial EPS, obtained from *Acetobacter xylinum* NCIM 2526, that has been used for the synthesis of Ag-NPs and Au-NPs with catalytic activity, tested by reduction of 4-nitrophenol and methylene blue [82]. In this study, levan acted as an additional reducing and stabilizer agent during thermal reduction method and as stabilizer or capping during chemical reduction method.

Succinoglycan (sinorhizobial octasaccharide) isolated form *Sinorhizobium meliloti* is an EPS used to stabilize Ag-NPs [83]. The presence of this EPS has been shown to confer biocompatible characteristics to the nanoparticles [84]. In addition, it is important to note other novel EPSs extracted from bacteria that have been useful in the synthesis of Ag-NPs and Au-NPs. EPS from *Lactobacillus rhamnosus* has been reported to be used in the synthesis of Ag-NPs with antimicrobial activity against bacterial (*Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Listeria monocytogenes*) and fungal pathogens (*Aspergillus* and *Penicillium* spp.) [33]. Ag-NPs with antibacterial and antibiofilm activity against gram (+) and gram (−) bacteria were produced using an EPS extracted from *Lactobacillus brevis* NM101-1 [85]. These Ag-NPs were effective as antibiotic adjuvants to enhance their antimicrobial activity. EPS from *Lactobacillus plantarum* was utilized in the production of Au-NPs to design a drug delivery agent against multidrug-resistant bacteria. The design involved the use of antibiotics to functionalize the Au-NPs to improve their antimicrobial properties [86]. An additional strain of *Lactobacillus plantarum*-605 was used to produce nonglucan EPS-605 useful for the synthesis of Ag-NPs and Au-NPs [87]. Antibacterial Ag-NPs have been synthesized in the presence of EPSs from *Lactobacillus casei* (LPW2E) and *Lactobacillus fermentum* (LPF6) [88]. Moreover, Ag-NPs with applications in the degradation of azo dyes have been synthesized using EPS produced by *Leuconostoc lactis* KC117496 EPS [89].

The genera *Bacillus* has also been found to produce EPSs with applications in the synthesis of metal nanoparticles. A bioflocculant EPS from marine *Bacillus subtilis* MSBN17 was used to elaborate Ag-NPs tested as an antibacterial agent in sewage water and also as an antibiotic enhancer against pathogenic microorganisms when combined [90]. Au-NPs with antibacterial activity against clinical pathogenic bacteria

were produced using EPS from marine *Bacillus megaterium* MSBN04 [91]. Additionally, Ag-NPs were produced on the basis of low and high molar mass of EPS obtained from diazotrophic *Bradyrhizobium japonicum* 36 strain. In this study, the nanoparticles were synthetized using low molecular mass EPS and had antibacterial and antifungal activities against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* [92].

To summarize this section, the silver and gold nanoparticles as well as their uses in which EPSs have been used as a reducing and/or stabilizing agent to synthesize them are showed in Table 3.

5. Role of Bacterial EPSs in the Synthesis of Other Metal Nanoparticles with Biomedical and Other Applications

EPSs have also been used in the synthesis of other metal nanoparticles, such is the case of xanthan gum, that has been used as a reducing and stabilizing agent to produce palladium nanoparticles (Pd-NPs) with very good catalytic activity during the reduction of 4-nitrophenol to 4-aminophenol by sodium borohydride [93]. Xanthan gum has also been used to stabilize Pd/Fe-NPs employed to remediate polychlorinated biphenyl- (PCB-) contaminated soil in combination with surfactant BriJ35 by means of electrokinetic nanoparticle method, showing an enhancing of the degradation of PCB28 [94].

Dextran has been used to produce iron oxide nanoparticles. Indeed, this EPS was used to coat magnetic nanoparticles to produce biocompatible ferrofluids using the coprecipitation method. In this study, the dextran-coated iron oxide nanoparticles presented significant less cytotoxicity to L929 cells in comparison to the same bare nanoparticles making them more suitable for diagnostic and therapeutic purposes [95]. Likewise, dextran was used as a stabilizing agent of iron oxide magnetic nanoparticles which were evaluated on *in vitro* and *in vivo* toxicological assays, showing them as nontoxic and safe nanoparticles to be used for biomedical applications [96].

Furthermore, carboxylic curdlan (Cur-4, Cur-8, and Cur-24) offers reducing and stabilizing agent properties in the production of selenium nanoparticles (Se-NPs) [57]. These nanoparticles presented a strong antioxidant capacity and low cytotoxic activity against SPCA-1 and HeLa cell lines *in vitro*. Similarly, zinc oxide nanoparticles (ZnO-NPs) were obtained by carboxylic curdlan, evaluating the interaction of these nanoparticles with bovine serum albumin showing mild modification of its conformation [60].

Interestingly, with a combination of alginate and gellan (50 : 50 solution), Pd-NPs were stabilized and used as a catalyst system [58]. In this study, the EPSs combination were carried out looking for improvement of the catalytic function of alginate/gellan-stabilized Pd-NPs taking advantage of synergistic interactions among EPSs [58, 97, 98], showing that combining the appropriately different EPSs may be useful in the synthesis, stabilization, and improving properties of metal nanoparticles. In this context, magnetic nanoparticles tested as drug carrier system of the anticancer drug 2,4-dihydroxy-5-fluoruracil (5FU) against the cancer cells MCF7, G1, and L929 were stabilized and coated using gellan gum and mauran [59].

Cellulose has also been employed to make other metal nanoparticles such as cadmium sulfide (CdS-NPs). These particles were produced by means of bacterial cellulose nanofibers and were proposed to be used as photocatalyst, luminescence, and photoelectron transfer devices [99]. Evenly, antibacterial nanocomposites formed of bacterial cellulose-cooper oxide nanoparticles were obtained by hydrothermal deposition [53].

Levan has been used to produce and coat cerium oxide nanoparticles as both reducing and stabilizing agents. These nanoparticles were suggested to have applications to treat diseases related to oxidative stress, due to their antioxidant activity tested in H_2O_2-stimulated NIH3T3 cells [54]. The above nanoparticles resulted nontoxic and biocompatible in cytotoxic studies with mouse fibroblast NIH3T3 cells and HEK293T cells. Likewise, levan was applied to coat and stabilize biocompatible Se, Fe, and Co nanoparticles as a strategy to obtain better food supplements with micronutrients safer and more efficient for humans [100].

In addition, recent EPSs such as FucoPol have been used to coat functionalized iron oxide magnetic nanoparticles. For instance, these nanoparticles functionalized with synthetic ligand applied for purification and recovery of antibodies were coated with FucoPol [101]. In another study, nanoprobes of the same nanoparticles, in this case, functionalized with meso-2,3-dimercaptosuccinic acid (DMSA), were also coated with the same EPS and tested for cell labeling in magnetic resonance imaging (MRI) [56].

It is important to that note other bacterial EPSs have been used as reducing and stabilizing agents such is the case of EPSs obtained from *Bacillus licheniformis* Dahb1 used to synthetize ZnO nanoparticles by the coprecipitation method [102]. These nanoparticles presented effective antibacterial and antibiofilm activity against both gram negative and gram positive bacteria, as well as antifungal and larvicidal activity with low cytotoxicity in hemolytic assays. In addition, magnetic iron oxide nanoparticles were produced and stabilized by a spore-forming strain of *Bacillus subtilis* EPS [103]. The nanoparticles mentioned presented antibacterial activity, high bioavailability, and cytotoxicity against human epidermoid carcinoma cell line (A431).

To summarize this section, other metal nanoparticles as well as their uses in which EPSs have been used as a reducing and/or stabilizing agent to synthesize them are shown in Table 3.

6. Potential Mechanisms That Explain the Synthesis of Metal Nanoparticles by Bacterial EPSs

In general, it has been noted that once metal ions are in contact with EPSs that contain reducing sugars, they are chelated and then reduced and stabilized by various functional groups. Polyanionic groups are the best known

Table 3: Characteristics of metallic nanoparticles synthesized by means of bacterial exopolysaccharides.

Bacterial EPS	Metallic nanoparticle	Mean size (nm)	Morphology	Applications	Reference
Xanthan gum	Au-NPs	15–20	Spherical	Drug delivery carrier, anticancer therapy	[69]
	Ag-NPs	5–40	Spherical	Antibacterial and catalytic	[70]
	Pd-NPs	10	Spherical	Catalytic	[93]
	Pd/Fe-NPs	10–20	Spherical	Soil remediation	[94]
Dextran	Ag-NPs	12 ± 1.9	Nearly spherical	Sensor for cysteine detection	[71]
	Ag-NPs	10–60	Spherical	Antibacterial and antifungal	[72]
	Au-NPs	13 ± 1.2	Spherical	Anticancer	[55]
	Fe_3O_4-NPs	14, 10.7	Spherical	Biocompatibility	[95]
	Fe3O4-NPs	15.4 ± 4.5	Spherical	Toxicological assays	[96]
Curdlan	Ag-NPs	15	Spherical	Not tested	[73]
	Au-NPs	17, 24	Spherical	Interaction with proteins	[74]
	Se-NPs	82, 56, 65	Spherical	Antioxidant, cytotoxicity assays	[57]
	Zn-NPs	58 ± 6 nm	Spherical	Protein interaction	[60]
Gellan gum	Au-NPs	13 ± 1	Spherical	Drug delivery carrier, anticancer therapy	[75]
	Au-NPs	14	Spherical	Drug delivery carrier, anticancer therapy	[77]
	Ag-NPs	5	Spherical	Antibacterial and topical treatment	[76]
Cellulose	*Pd-NPs	3.4 ± 1.4	Spheroidal	Catalytic	[58]
	Fe_3O_4-NPs	15 ± 3	Spherical	Drug delivery carrier, anticancer	[59]
	Ag-NPs	13.1	Not available	Nanofibers	[79]
	Ag-NPs	10–50	Not available	Chemical sensor	[80]
	Au-NPs	9	Nearly spherical	Enzyme immobilization and biosensing	[81]
	CdS-NPs	30	Spherical	Nanofibers, thermal stability	[99]
	Cu-NPs	25, 35	Not available	Antibacterial, nanofibers	[53]
Levan	Ag-NPs and Au-NPs	5–29 and 10–30	Spherical	Catalytic	[82]
	Ce oxide-NPs	36.4 ± 9.2	Spherical	Antioxidant, biocompatibility	[54]
	Co_3O_4-NPs	9.9 ± 2.3	Spherical	Prebiotic and micronutrients supplements	[100]
	Fe_3O_4-NPs	10.6 ± 3.4			
	Se-NPs	60 ± 26			
Succinoglycan	Ag-NPs	13.3 ± 13.4	Spherical	Not tested	[83]
	Ag-NPs	8.9 ± 3.3	Spherical	Not tested	[84]
FucoPol	Fe_3O_4-NPs	10–20	Not available	Purification and recovery of antibodies	[101]
	Iron oxide magnetic-NPs	15 ± 2	Not available	Contrast agents for MRI	[56]
Lactobacillus rhamnosus EPS	Ag-NPs	10	Spherical, triangular, rod, and hexagonal	Antibacterial and antifungal	[33]
Lactobacillus brevis NM101-1 EPS	Ag-NPs	18	Spherical	Antibacterial, antibiotic adjuvant	[85]
Lactobacillus plantarum EPS	Au-NPs	20–30	Spherical, little ellipsoidal	Drug delivery carrier, antibacterial, and antibiotic functionalization	[86]
Lactobacillus plantarum-605 EPS-605	Au-NPs and Ag-NPs	12 and 20	Spherical	Not tested	[87]
Lactobacillus casei EPS	Ag-NPs	0.2–10	Rectangular, spherical	Antibacterial	[88]

Table 3: Continued.

Bacterial EPS	Metallic nanoparticle	Mean size (nm)	Morphology	Applications	Reference
Lactobacillus fermentum EPS	Ag-NPs	0.0–10	Rectangular, spherical	Antibacterial	[88]
Leuconostoc lactis KC117496	Ag-NPs	35	Spherical	Biodegradation agent	[89]
Bacillus subtilis MSBN17 EPS	Ag-NPs	60	Spherical	Antibacterial, antibiotic adjuvant	[90]
Bacillus megaterium MSBN04 EPS	Au-NPs	10	Spherical	Seawater treatment antibacterial	[91]
Bradyrhizobium japonicum 36 EPS	Ag-NPs	5–50	Rod, oval	Antibacterial, antifungal	[92]
Bacillus licheniformis Dahb1 EPS	ZnO-NPs	100	Hexagonal	Antibacterial, antifungal, antioxidant, and larvicidal	[102]
Bacillus subtilis, VT03 EPS	FeO-NPs	106 ± 12	Spherical	Antibacterial, anticancer	[103]

*Nanoparticles produced by 50 : 50 solution of alginate/gellan mixture.

chemical moieties to be involved in the reduction and stabilization of metal nanoparticles [27]. Moreover, electrostatic interactions between metal cationic ions and anionic groups such as carboxylic and phosphoric functional groups of EPS have been mentioned to be an advantage for the synthesis of metal nanoparticles [29]. Among these functional groups, hydroxyl, carboxyl, phosphoric, hemiacetal, and amino end groups have been proposed to reduce metal ions from the precursor salts to obtain the respective nanoparticles [52, 68, 104]. In relation with the above, hydroxyl groups have been attributed the ability to coordinate with metal ions [105]. In fact, during the reducing process, oxidation of hydroxyl groups to form carbonyl groups as well as oxidation of alcoholic and aldehydic groups to form carboxylic groups has been reported to be an important factor during synthesis of metal nanoparticles [106]. In regard with this, reaction conditions such as temperature, time of reaction, concentration of reactants, and pH have an influence in the morphological characteristics and mechanisms of producing nanoparticles [92, 103]. Once the nanoparticles are made, the EPS matrix forms a film or layer that acts as a capping and stabilizer, thereby obtaining metal nanoparticles with a small and tight size distribution, preventing agglomeration [52, 107]. These processes can be explained by the adsorption of the EPSs in the nanoparticle surface, promoting steric repulsion between them and augmenting the viscosity of the complex nanoparticles-EPS impeding their aggregation [69]. In this context, it is noteworthy to mention that capping agents affect characteristics of metal nanoparticles such as surface charge and colloidal stability [108].

Thus, in relation to the EPSs described in this study, the structure of xanthan gum has been described to be helical with many hydroxyl groups that can carry out reduction of ions. In addition, this structure creates a network by hydrogen bonding in which nanoparticles stabilize [70]. Further, xanthan gum has negative charge due to acetyl groups and pyruvic acid linked with mannose and provides this charge to nanoparticle surface creating a steric repulsion among them [69]. Dextran, is useful in the synthesis of metal nanoparticles since their hydroxyl, ketone, aldehydes, and carboxyl groups interact and allow the reduction of Ag^{+} ions to form Ag-NPs, preventing their agglomeration as well [71, 72]. At this point, it was mentioned that oxygen from dextran functional groups can donate their pair of electrons to gold ions thereby producing Au-NPs [55]. As it is well known, dextran is rich in hydroxyl groups that can interact with magnetic nanoparticles by hydrogen bonds stabilizing them [95, 109].

For curdlan, the carboxylic groups of curdlan derivatives such as carboxylic curdlan and carboxymethyl curdlan have the ability to adsorb metal ions by electrostatic attractive forces. These functional groups reduce the metal ions, and the necessary nucleation is created to form stabilized clusters during synthesis of Au-NPs, Ag-NPs, and ZnO-NP, as well as stabilization of Se-NPs [57, 60, 73, 74]. In this context, it is noteworthy to mention that curdlan is not soluble in water; therefore, it is carboxymethylated, oxidized, and its sodium salt is formed, in order to improve their properties [110].

Moreover, for the case of gellan gum, this anionic EPS envelope itself, which has been attributed to the stabilization of nanoparticles, and also it has abundant carbohydrate units that form the capping of Au-NPs [75, 77]. Similar to others bacterial EPSs, gellam gum has acyl groups and abundant carboxyl groups that may interact with metal ions to reduce and stabilize the respective nanoparticles [59].

Oxidizing bacterial cellulose by TEMPO allows the introduction of carboxylate groups that carry out ion-exchange reactions with metal ions to reduce them and synthesize metal nanoparticles [79, 111]. These EPSs have been utilized in nanofibers which are responsible of reduction and adsorption of metal as Ag^{+} and Cd^{+2} to form nanoparticles by hydroxyl groups, as well as attracting other metal nanoparticles like Au-NPs due to electrostatic

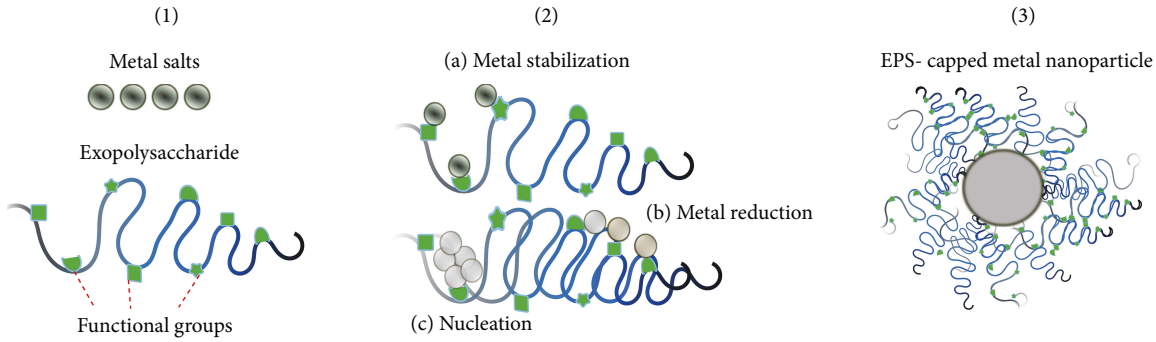

Figure 3: Proposed mechanism during synthesis of metal nanoparticles by EPSs. Electrostatic attractive forces between functional groups of EPS and metal salts lead to stabilization and reduction of metal ions to form their respective metal nanoparticles capped by the EPSs.

repulsion [80, 81, 99, 112]. The hydroxyl groups have been described to be abundant in cellulose nanofibers and very important factor to explain physical properties of cellulose [113, 114].

In the case of levan, it has a lot of keto sugar units, and similar to other bacterial EPSs, it has numerous hydroxyl functional groups that may interact electrostatically with ions such as Ag^+ leading to the formation of the respective nanoparticles [82]. In this context, succinoglycan has been proposed to act as a reducing and stabilizing agent also due to hydroxyl groups that may give an electron to Ag^+ to form Ag and is also capable to be involved in the formation of a complex matrix that carries out the stabilization acting as a capping agent [84]. FucoPol has been used as a capping agent for magnetic nanoparticles being described to have a negative character because of its substituents that exhibit suitable stabilizing properties due to its good flocculation and emulsification process [115]. During stabilizing function of FucoPol, it has been mention that this effect is dependent of steric and electrostatic interactions [56].

Additionally, related to similar mechanisms involved during synthesis and stabilization of metal nanoparticles reported with other EPSs, it has been described abundant functional groups as hydroxyl and hemiacetal ends in EPSs that carried out the reduction and stabilization of nanoparticles making them more suitable for application in different fields of study [86, 89]. Actually, sugar monomers like glucose, galactose, mannose, and fructose have been mentioned to reduce Ag^+ ions to produce Ag-NPs when used EPSs of lactic acid bacteria [89, 116]. In general, many functional groups have been mentioned to carry out the reduction and stabilization of metal nanoparticles (Ag-NPs, Au-NPs, and FeO-NPs) by bacterial EPS such as hydroxyl, carboxyl, ester, aldehydes, methoxyl, sulfated, phosphate, amino, amide, and N-acetylated sugar molecules that possess negative charge and interact with metal ions by electrostatic attractive forces, thereby producing metal nanoparticles as described above [33, 87, 88, 90, 91, 103]. Thus, the above information may explain the reduction process of metal ions to form the respective nanoparticles, as well as their mechanisms to the effective stabilization that bacterial EPSs can carry out during the obtaining of metal nanoparticles. A representation of the information in this section is shown in Figure 3.

7. Main Techniques Used to Characterize Metal Nanoparticles and Biomedical Measurements

7.1. Instrumental Techniques to Characterize Metal Nanoparticles. After the production of metal nanoparticles (in this study, by means of bacterial exopolysaccharides), there are some characteristics that required their proper characterization, such as shape, size, surface, and dispersity [117]. These characterization can be achieved by various instrumental techniques. In this context, ultraviolet-visible spectroscopy (UV-visible spectroscopy) has been very useful to rapidly detect the formation of different metal nanoparticles (silver, copper, gold, and platinum nanoparticles) since the surface plasmon resonance (SPR) phenomenon can be measured [118]. For the case of shape, size, morphology, and particle size distribution of metal nanoparticles, transmission electron microscopy (TEM), high-resolution electron microscopy (HRTEM), scanning electron microscopy, atomic force microscopy (AFM), and dynamic light scattering are suitable techniques that have been used to measure these physical properties of metal nanoparticles [117, 119–124]. Crystallinity and the structure of metal nanoparticles are other physical characteristics which can be measured by X-ray diffraction and selected area electron diffraction (SAED) technique [125, 126]. To identify and confirm the elemental composition of metal nanoparticles and their capping, energy-dispersive spectrometry (EDS) is a proper technique for this purpose [127]. When metal nanoparticles possess a capping or stabilizing agent, Fourier-transform infrared spectroscopy (FTIR) is applied to identify the functional groups present in the nanoparticle surface, and Zeta potential is used to determine the surface charge [128, 129]. In addition, when magnetic nanoparticles are produced, vibrating sample magnetometry (VSM) and superconducting quantum interference device (SQUID) magnetometry are adequate techniques to measure magnetic properties [130].

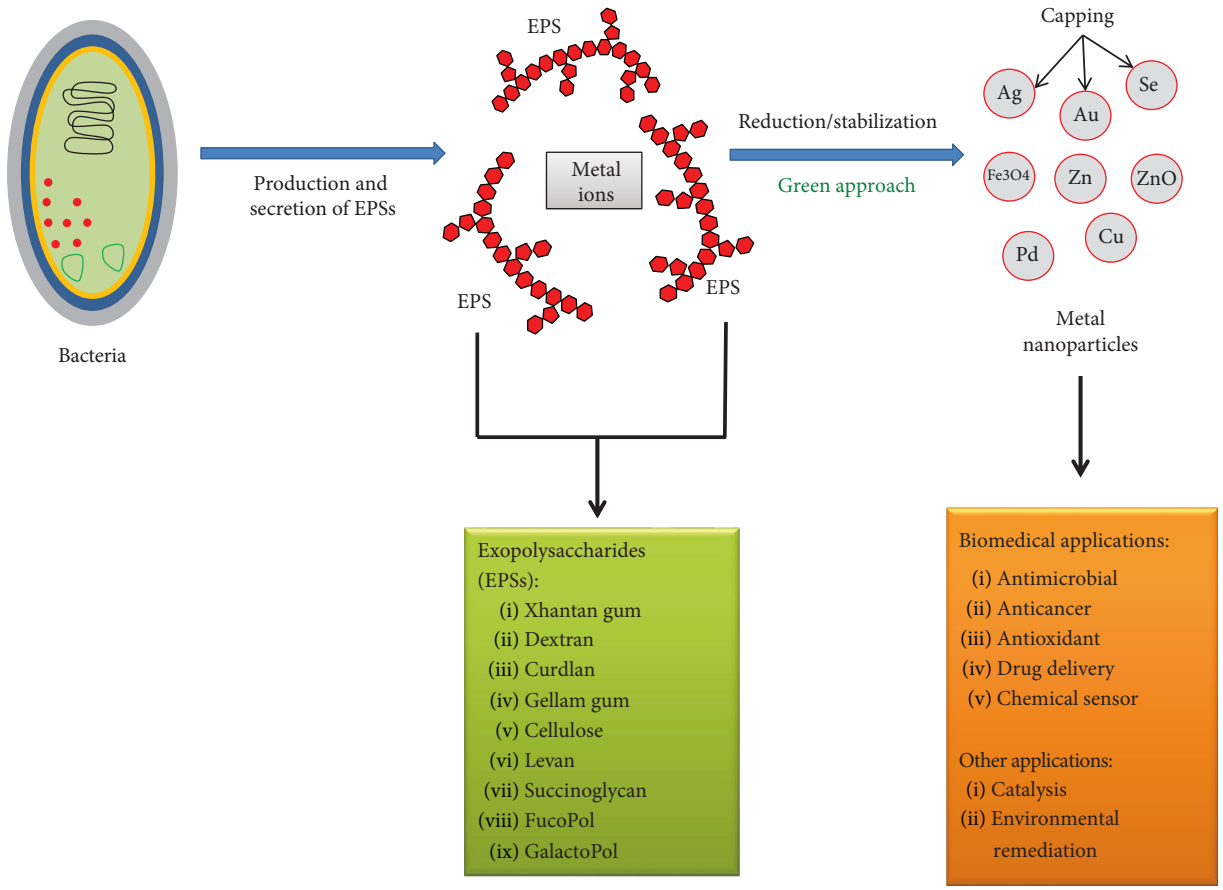

Figure 4: Summary of the content of this review.

7.2. Biomedical Measurements Applied to Metal Nanoparticles Synthesized by EPSs as a Reducing and/or Stabilizing Agents. In relation to biomedical measurements carried out during biomedical applications of metal nanoparticles synthesized by bacterial EPSs, the antimicrobial activity of metal nanoparticles synthesized by bacterial EPSs has been measured by determination of minimum inhibitory concentration (MIC) [85, 86, 102, 120], minimum bactericidal concentration (MBC) [86, 120], fluorescence microscopy imaging (FMI) [120], skin infection model *in vivo* by colony counting method using the pour plate technique [120], agar disc diffusion method [53, 70, 72, 90, 91], agar well diffusion method [33, 85, 86, 88, 90–92, 102], colony counting method [76], antibiofilm activity [85, 102], bacterial growth kinetics tests, and kill time assays [85, 86, 92, 102]. Moreover, antifungal activity was measured by agar well and disk diffusion method [72, 102] as well as larvicidal activity using the World Health Organization method [102, 131].

On the other hand, metal nanoparticles produced by EPS as an anticancer agent and drug delivery carrier has been tested by some of biomedical measurements such as *in vitro* drug-released studies by dialysis method [69], *in vivo* studies of biochemical parameters and histopathological assays of liver and kidney functions and oxidation stress ratio [55], *in vitro* cytotoxicity and anticancer assays against tumor cell lines by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimetric method [75, 103, 132], tumor cellular uptake by confocal laser scanning microscopy [75, 77], internalization of metal nanoparticles in tumor cells by cellular imaging and flow cytometry studies [59], cell viability by *in vitro* cytotoxicity and biocompatibility tests by alamar blue assay [59], antiproliferation of cancer cells using magnetic hyperthermia method (MHM) and qualitatively determination of live and dead cells after MHM [59], and measuring of tumor cell death by acridine orange/ethidium bromide staining assay [103].

In this context, other biomedical measurements related with other applications are cysteine detection by absorption spectroscopy and visual inspection during color change [71], biocompatibility assays by cytotoxicity studies using MTT method [54, 95, 96], toxicological tests by measuring *in vivo* studies of oral, dermal, and immunotoxicity, as well as genotoxicity, carcinogenicity, biochemical and hematological parameters, and histopathological analysis [96], interaction with protein assay employing fluorescence, circular dichroism spectroscopies and UV-visible spectroscopy [60, 74], *in vitro* ROS scavenging assay and antioxidant activities by DPPH (2,2-diphenyl-1-picrylhydrazyl), Trolox and ferric-reducing ability of plasma (FRAP) tests [54, 57], and *in vitro* MRI of cell phantoms to assess nanoprobes for cell labeling by MRI [56]. Thus, there are many ways to measure the potential of metal nanoparticles synthesized by EPSs as a reducing and/or stabilizing agent in different important biomedical applications today.

8. Conclusions

Metal nanoparticles have been an important research target within the last decades, mainly because they have different properties than when in the bulk. Metal nanoparticles have been found to have beneficial properties for biomedical applications such as antimicrobial, anticancer, antioxidant, drug delivery, chemical sensors, contrast agents, and also in other applications such as catalysts and environmental remediation agents. Therefore, there is an interest in finding different compounds capable of effectively reducing and stabilizing metal nanoparticles. Green synthesis methods have gotten a lot of attention in the production of metallic nanoparticles, since these synthesis follow a process that involves almost exclusively the metallic salt precursor and a biological compound that performs either the chelation of the reduced metal, its stabilization, or both functions at the same time. Moreover, green synthesis methods have a wide array of advantages when comparing them with physical and chemical production methods; green synthesis provides and environmental friendly and cost-effective synthesis platform, employing nontoxic reagents and procedures. Bacterial EPSs are biomolecules that possess attractive properties to be exploited, in green synthesis production of metallic nanoparticles, due to their chemical composition. Bacterial EPS are heteropolysaccharides containing different functional groups in their backbone including amino, sulfate, phosphate, and hydroxyl substituents as well as N-acetylamino sugars and hemiacetal ends; all of these functional groups are great candidates in the reduction, complexation, and stabilization of metal nanoparticles during their synthesis. However, there are still several challenges in the use of bacterial EPS to aid in the synthesis of metallic nanoparticles, mainly the wide variability of the EPS chemical composition. Depending on the composition of the chosen EPS, the reaction conditions change, such as the temperature, reaction time, concentration, and rate of precursor salts to EPS. Furthermore, all of these synthesis parameters have shown to have a direct influence on the morphological characteristics of the produced nanoparticles.

Thus, bacterial EPSs are a suitable option to synthesize different functionalized metal nanoparticles to be used in biomedical and other types of applications. Using some bacterial EPS allows the production of metal nanoparticles, with a wide variety of applications, in an eco-friendly and nontoxic manner, conferring interesting characteristics through the functionalization of these nanomaterials. However, more research is needed related to the understanding of mechanisms involved in the process of reduction and stabilization during synthesis of metal nanoparticles, as well as more thorough toxicological and environmental studies to measure their impact on our society and the environment. Figure 4 illustrates a summary of the main content of this review.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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