UNIVERSIDAD DE INVESTIGACIÓN DE TECNOLOGÍA EXPERIMENTAL YACHAY

Escuela de Ciencias Biológicas e Ingeniería

TÍTULO: Biogenic Sulfur-based Nanocrystals: Methods of Fabrication and Applications

Trabajo de integración curricular presentado como requisito para la obtención del título de Ingeniero Biomédico

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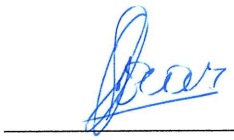

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Con mucho cariño,

A mis padres, porque han sido el pilar fundamental de mis estudios, por su confianza, y por todo el soporte. A mis hermanos, Verónica, Luis y Jefferson, por su apoyo incondicional y motivación

Oscar Patricio Yanchatuña Aguayo

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RESUMEN

El presente trabajo de revisión describe los logros sobre la biosíntesis de nanopartículas semiconductoras a base de azufre (S-NPs). En general, la biosíntesis se realiza utilizando organismos vivos o derivados tales como extractos de plantas, biomoléculas aisladas y virus. Entre los organismos vivos se encuentran bacterias, hongos y algas. La biosíntesis utilizando organismos se produce generalmente de forma intracelular o extracelular, mediado por enzimas, proteínas y péptidos específicos. Comúnmente, las sales metálicas y de sulfuro se suministran a la solución de reacción que contiene la biomasa celular o extractos libres de células. En muchos casos, la biosíntesis de S-NPs ocurre sin agregar una fuente de sulfuro, en este caso, la fuente de azufre es sintetizada por los organismos a través de procesos específicos, la participación de péptidos, enzimas y proteínas. Se han sintetizado diversos tipos de NPs de sulfuro con diversas propiedades altamente dependientes de varias condiciones como la bioentidad, tiempo, pH, mediadores externos, concentración de metales, sulfuros y biomasa, entre otras. El ajuste de estas condiciones podría conducir a la generación de nanocristales de diferentes tamaños y formas, propiedades que aún representan un desafío para controlar en la biosíntesis. Se ha demostrado que la biosíntesis de S-NP es una ruta prometedora para la generación de nuevos materiales. Además, debido a sus propiedades ópticas, eléctricas y biocompatibles únicas, las NPs biogeneradas han obtenido resultados interesantes aplicados en la investigación del cáncer, bioimagen, actividad antimicrobiana y campos eléctricos. En este trabajo se proporciona una extensa revisión bibliográfica sobre la biosíntesis de S-NPs utilizando entidades biológicas, mecanismos de síntesis, factores que controlan las propiedades de las NP, técnicas de caracterización y aplicaciones.

Palabras Clave:

Nanopartículas a base de azufre biosíntesis, bacterias, hongos, levaduras, plantas, virus, caracterización, bioaplicaciones

ABSTRACT

The present review work describes the achievements about the biosynthesis of metal sulfide nanoparticles, or sulfur-based NPs (S-NPs). In general, biosynthesis is performed by utilizing living organisms or derivatives like plant extracts, single biomolecules, and viruses. Among the living organisms are bacteria, fungi, and algae, by which the biosynthesis is generally performed intracellularly or extracellularly, mediated by specific enzymes, proteins, and peptides. Commonly, metal and sulfide salts are supplied to the reaction solution with cell biomass or free-cell extracts. In many cases, the biosynthesis of S-NPs occurs without adding a sulfide source, in this case, the sulfur source is synthesized by the organisms through certain pathways, the participation of peptides, enzymes, and proteins. Diverse types of sulfide NPs have been synthesized with diverse properties highly dependent on several conditions such as the bioentity, time, pH, external mediators, metal, sulfide, and biomass concentration, among others. Adjusting these conditions could lead to the generation of different sized and shaped nanocrystals, properties that still represent a challenge to control in the biosynthesis. Biosynthesis of S-NPs has been demonstrated to be a promising route of novel materials generation. Besides, due to their unique optical, electrical, and biocompatible properties, the bio-generated NPs have performed interesting results applied in cancer research, bioimaging, antimicrobial activity, and electrical fields. In this work, it is provided an extensive bibliographic review about the biosynthesis of S-NPs using biological entities, mechanisms of synthesis, factors controlling the properties of NPs, techniques of characterization, and applications.

Keywords:

Sulfur-based nanoparticles, biosynthesis, bacteria, fungi, yeast, plant, virus, characterization, bioapplications.

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1. INTRODUCTION AND JUSTIFICATION

Nanotechnology is the field of science responsible for the deep study and engineering of nanoparticles (NPs) or nanomaterials (NMs), which are materials with at least one dimension between 1 nm to 100 nm (Dolez, 2015; Singh et al., 2016). This discipline has become one of the most relevant sciences worldwide due to the wide range of NM applications, such as in agriculture, electronics, biomedicine, catalysis, and bioremediation (Saleh, 2020). During the last decades, several NMs have been manufactured; the motivation is their unique properties compared to their bulk counterpart and molecular components (Mageswari, Srinivasan, Subramanian, Ramesh, & Gothandam, 2016). That divergence between bulk and NMs is related with interaction and behavior between surface atoms. When the matter is at the nanoscale, its surface atoms become less established than in bulk (Roduner, 2006). The amount of atoms at the surface increases together with average binding energy (Roduner, 2006). Besides, the surface area-to-volume ratio increases inversely with the size providing characteristics controlled by surface properties, similar to free atoms (Roduner, 2006). In the same way, Van der Waals and electromagnetic forces become predominant compared to gravity and inertia in NMs (Dolez, 2015). All these properties together render NPs special and with unique optical, electrical, mechanical, chemical, physicochemical, thermal, and magnetic properties, for example (Dolez, 2015).

The NMs are classified according to their dimensionality, morphology, state, and chemical composition (Dolez, 2015; Gleiter, 2000). Based on the dimensionality and shape, NMs are commonly divided into four categories (Dolez, 2015; Saleh, 2020). Zero-dimensional NMs (0D), in which all dimensions are in nanoscale or below 100 nm, including cubic NPs, nanorods, polyhedral NPs, nanospheres, core-shell NPs, and quantum dots (QDs) (Saleh, 2020). One-dimensional NMs (1D) are materials with two dimensions at the nanoscale and one over 100 nm (Dolez, 2015). Examples of 1D are nanotubes, nanowires, and nanofibers. Two-dimensional NMs (2D) comprise those with only one dimension at the nanoscale, such as nanofilms, nanoplates, and nanocoating (Saleh, 2020). The last division is the three-dimensional (3D) materials that have their three dimensions beyond 100 nm and result from a combination of multiple NPs (Dolez, 2015). For example, 3D materials are foams, carbon

nanobunds, fullerenes, polycrystals, and honeycombs, to name a few (Ealias & Saravanakumar, 2017; Mageswari et al., 2016; Saleh, 2020).

Several methods are developed for the synthesis of NPs. These are categorized into two general categories: bottom-up and top-down methods (Ealias & Saravanakumar, 2017). Bottom-Up approaches are based on the synthesis of NPs from atoms to build up and integrate into the desired material (Ealias & Saravanakumar, 2017). For example, the Sol-Gel method, spinning, Chemical Vapor Deposition (CVD), pyrolysis, and biosynthesis (Saleh, 2020). On the other side, Top-Down or destructive approaches take bulk material and trim it down to nanometric scale (Saleh, 2020). Among these methods are encountered mechanical milling, nanolithography, laser ablation, sputtering, and thermal decomposition (Ealias & Saravanakumar, 2017; Mageswari et al., 2016; Saleh, 2020).

Bottom-Up Chemical synthesis of NPs has been explored for many decades, being the most preferred by researchers due to high yield production, relatively low energy required (i.e., in comparison with physics approaches), and excellent control of the size and morphology of NPs (Albanese, Tang, & Chan, 2012; Gahlawat & Choudhury, 2019). Although there are numerous advantages and applications of the NPs produced by chemical routes, limitations still exist that restrict the introduction of these products in other areas. Commonly, chemical synthesis of NPs involves the use of toxic reagents during the processes such as hazardous chemicals, that make the products highly toxic, no biocompatible, and release dangerous byproducts to the environment, besides the high production cost due to expensive reagents employed (Abdel-Salam, Omran, Whitehead, & Baek, 2020; Gahlawat & Choudhury, 2019).

Therefore, new methods are necessary to produce biocompatible NMs, providing them with novel properties to overcome current limitations. In this sense, the biosynthesis of NPs has emerged and has been studied during the last decades. This relatively new “green approach,” in comparison with chemical and physical methods, has shown to be environmentally friendly, feasible, cost-effective, and low-toxic (Dahoumane et al., 2017; Mageswari et al., 2016). Besides, NMs processed through this route have shown increased biocompatibility, optical, and stable properties compared to chemically synthesized (Abdel-Salam et al., 2020; Hazra et al., 2013; Shivaji et al., 2018; Singh et al., 2016). Although biosynthesis of NPs has been seen as a promising route for the synthesis of new materials and applications, more

research is still needed to understand the mechanisms, control of morphology, size, and stability of NPs, yielding production and scalability. In this way exploit the advantages and benefits of the biosynthesis of NPs.

The purpose of this work is to review the multiple achievements regarding the synthesis of S-NPs employing different bio-entities such as bacteria, fungi, yeast, algae, plants, single biomolecules and viruses. The most important aspects and particularities of the biosynthesis mechanisms performed will be described here, aiming to comprehend the processes involved in the synthesis of NPs, which provide them interesting properties, making them attractive sources for the application in several disciplines. Besides, principal techniques of characterization are also described, providing important information, features, and properties of the biosynthesized NMs. Furthermore, general aspects and achievements concerning the control over NP biogenesis are considered, followed by the utilization of sulfur-based nanocrystals in the fields of bioimaging, biosensing, anticancer research, biosensing, antimicrobial, bioremediation, and electronics.

2. PROBLEM STATEMENT

As described before, NPs are known to possess very peculiar properties mainly due to its size comprised between an atomistic scale and bulk. These properties are particularly interesting in the context of biological applications. Chemical routes are well-known and well-studied but can present problems related to toxicity when used in biological systems, mainly due to the reactants used during the synthesis.

On the other side, bio-synthesis of NPs using biological systems seems particularly promising regarding bio-compatibility but still suffers from a lack of deep understanding of the synthesis mechanism and is fairly recent. The understanding is a complicated matter both due to the wide range of existing systems present in the nature such as algae, fungus, enzymes or virus between others, and also due to the relatively big sizes of systems compared to their chemical counterparts.

This complexity should be tacked down in order to render bio-synthesis of NPs as one of the main routes which is not presently the case. Considering that, this work focuses on to provide an extensive and updated review work about the synthesis of S-NPs through biological systems, making emphasis on the NPs' properties provided by these green routes, applications and challenges in the matter.

3. OBJECTIVES

3.1 General Objective

Make an exhaustive review over different scientific reports published in the last 30 years presenting the biosynthesis of S-NPs, aspects of synthesis and applications, in order to promote the bio-synthesis of these particles in the scientific community.

3.2 Specific Objectives

- Find the different biological that has been reported to be able to synthesize S-NPs.
- Understand the biosynthesis mechanism of the S-NPs.
- Understand the biological, chemical and physical key factors which are governing the morphology and properties of these NPs.
- Describe the different characterization techniques which are used in this field.
- Outline and briefly summarize the results about the different bioapplications of the biosynthesized S-NPs.

4. BIOGENIC SYNTHESIS OF SULFUR BASED NANOCRYSTALS.

Biosynthesis of NMs is defined as a bottom-up approach that uses natural bio-resources as promotors of different types of NPs (Dahoumane et al., 2017a; S. Dahoumane et al., 2017b). The properties of the as-produced NPs via green processes are of paramount interest because these display high stability, water solubility, and most importantly, the improvement on biocompatibility, which has a direct impact on the applications of these NPs in the biomedical field (Bruna et al., 2019; Fariq, Khan, & Yasmin, 2017). A long list of NMs has been synthetized in the last decade, between these NPs are metallic (Das, Das, & Guha, 2010; Valsalam et al., 2019), oxides (Brayner et al., 2010; Mahdavi, Namvar, Ahmad, & Mohamad, 2013), carbonates (Li et al., 2009; Li & Gadd, 2017), and chalcogenide (Mareeswari, Brijitta, Harikrishna Etti, Meganathan, & Kaliaraj, 2016; Sandoval et al., 2017).

Several studies have reported the biosynthesis of NMs using various biological entities such as bacteria (Cunningham & Lundie, 1993; Gallardo et al., 2019; Plaza et al., 2016), fungi (Alsaggaf et al., 2020; Mirzadeh et al., 2013; Owais et al., 2011; Sandoval et al., 2017), yeast (Prasad & Jha, 2010; Sandana & Rose, 2014), plants (Kaviya, 2018; Shivaji et al., 2018), algae (Dahoumane et al., 2012, 2014, 2016; Jena et al., 2015; Mandal et al., 2016; Rao & Pennathur, 2017), viruses (Ahiwale et al., 2017), and biomolecules (Spangler et al., 2017). This method is taking a considerable importance due to the sustainability, ecofriendly and nontoxic alternative compared to classical chemical and physical synthesis (Ahmed et al., 2016; Gahlawat & Choudhury, 2019). Although the biosynthesis processes performed by organisms and derivatives is not at all understood, and research is still needed, it is essential to study the knowledge generated regarding mechanisms performed for the production of NMs aiming to take advantage of these methods for better control of properties and production.

Figure 1 illustrates the general processes employed in the biosynthesis of S-NPs. Usually, S-NPs synthesis process begins with biomass generation. In the first place, organisms are growth in culture mediums at adequate conditions, according to established procedures (Dahoumane et al., 2017; Uddandarao & Mohan, 2016; Ulloa et al., 2016). Once obtained the necessary biomass, the next step is to perform its treatment according to the research's purpose. The biosynthesis of NPs can be developed with isolated cells, cell-free extracts, or

whole living cultures (Feng et al., 2018; Liu et al., 2015; Rahman et al., 2020). In the same way, there is utilized plant extracts, single isolated biomolecules, and viruses. Subsequently, metal and sulfide salts are employed for metal and sulfide sources for the synthesis of S-NPs. In many cases, synthesis is performed without sulfide source since the bioentity can produce it (Bruna et al., 2019; Gallardo et al., 2019; Hosseini et al., 2013), mechanisms discussed in the following sections. After some time, the biosynthesis of NPs is completed, and in the majority of cases, it is visible to the naked eye, changing the color of the reaction solution. Finally, S-NPs are purified for respective characterization (**Figure 1**). The mechanisms involved in the synthesis are more fully detailed in the following sections.

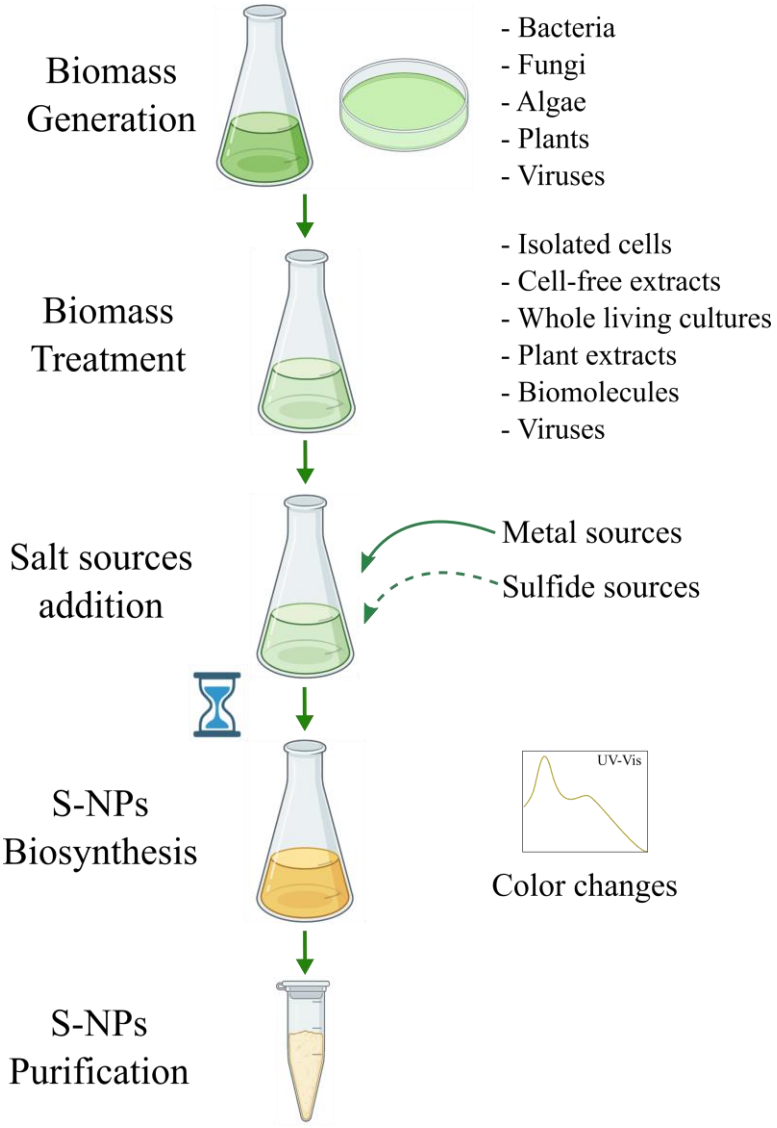

Figure 1. General schematization of the process for the biosynthesis of sulfur-based nanoparticles (S-NPs). Created in BioRender.com

4.1 Mechanisms of sulfur-based NPs biosynthesis

4.1.1 Intracellular synthesis

Rai et al. (2011) describe a general hypothetical intracellular biosynthesis divided into three principal processes: trapping, bioreduction and synthesis (Rai et al., 2011). During trapping electrostatic interactions occur due to the cell surface's negative charge and the ions' positive charges in the medium (Rai et al., 2011). Following bioreduction takes place, where biological molecules, like enzymes and amino acids, act as reductants of the metal ions (Rai et al., 2011). Finally, synthesis is performed by agglomeration of complexes, forming the NPs (Rai et al., 2011). In microbes, before synthesis, ions dissolved enter inside the cell through the magnesium or manganese transfer system, and then NPs formation occurs in the cytoplasm by the activity of intracellular enzymes and other peptides (Bai et al., 2009; Holmes et al., 1997; Malarkodi et al., 2014). Due to the NPs generation taking place inside the cell, the production costs of these materials may result expensive due to the recovery and purification processes employed. In this situation, cell lysis is commonly applied; thus, cells will not continue producing NPs, followed by centrifugations, freeze-thawed, and columns of ion exchange for NP purification (Abdel-Salam et al., 2020).

4.1.2 Extracellular synthesis

Extracellular synthesis consists of NPs biosynthesis outside the cell (Dahoumane et al., 2017b; Gahlawat & Choudhury, 2019). Ion salts from cadmium chloride, copper sulfate, sodium sulfide, silver nitrate, for example, interact with enzymes located at the cell membrane or biomolecules excreted by these to the growth medium (Alsaggaf et al., 2020; Hosseiniet al., 2013; Tripathi et al., 2014; Xie et al., 2007). NPs produced commonly get suspended in the medium or absorbed on the cell membrane (Hosseini & Sarvi, 2015). Extracellular synthesis may happen using a cell-free medium and with cells' presence (Murray et al., 2017; Rajeshkumar et al., 2014; Rao & Pennathur, 2017; Yang et al., 2016). Compared with intracellular approaches, the living cells could be used later and the processes for NPs recovery used are simple, resulting in an exciting mechanism due to low cost and large scale production interests (Hosseini & Sarvi, 2015; Narayanan & Sakthivel, 2010).

It has been showed biosynthesis of metal-sulfide NPs employing only metal precursors without sulfide source and, in the other case, metal and sulfide precursors together (Hosseini & Sarvi, 2015). In the first case, the common organisms are bacteria, yeast and fungi. Although biosynthesis of S-NPs is still unknown, many authors argue that the presence of metal ions in the medium activates the organisms to produce sulfide (S^{2-}) to detoxify the medium, resulting in the formation of metal-sulfide NPs (Cunningham & Lundie, 1993; Holmes et al., 1997; Malarkodi et al., 2014; Smith et al., 1998). Sulfide production is possible in many organisms like bacteria, fungi and plants (Kushkevych et al., 2020; Schiff & Fankhauser, 1981). Two pathways are attributed in terms of sulfide synthesis by these organisms: Assimilatory and dissimilatory sulfate reduction, anaerobic processes that use sulfate (SO_4^{2-}) as starting material to obtain energy (Hosseini & Sarvi, 2015; Kushkevych et al., 2020).

4.1.3 Dissimilatory sulfate reduction

Dissimilatory sulfate reduction (DSR) is an anaerobic pathway of specific specialized organisms called Sulfate Reducing Bacteria (SRB) (Kushkevych et al., 2020; Muyzer & Stams, 2008). In this process, sulfate is used as a terminal electron acceptor and energy source (Kushkevych et al., 2020; Muyzer & Stams, 2008; Peck, 1961; Schiff & Fankhauser, 1981). This pathway can be divided into three main steps (Kushkevych et al., 2020). First, sulfate must be activated before cell absorption (Kushkevych et al., 2020). The enzyme sulfate adenylyltransferase (Sat) reduces sulfate into adenosine-5-phosphosulfate (APS) and pyrophosphate (PPi) as co-product (Kushkevych et al., 2020). The second step occurs inside the cell; the enzyme APS reductase reduces the APS to sulfite (SO_3^{2-}) and adenosine monophosphate (AMP) (Kushkevych et al., 2020). Finally, the enzyme dissimilatory sulfite reductase reduces sulfite to sulfide in form of hydrogen sulfide as a terminal product released by the SRB to the medium (Kushkevych et al., 2020; Muyzer & Stams, 2008; Yue, Wang, Zhang, Qi, & Xin, 2016). **Figure 2 a** represents a schematic description of the DSR process.

4.1.4 Assimilatory sulfate reduction.

ASR pathway is mainly performed by bacteria and plants. This pathway uses sulfate to produce cysteine as the final product, an essential structure for proteins (Kushkevych et al., 2020; Schiff & Fankhauser, 1981). As in DSR, firstly, sulfate is activated by Sat enzyme and

reduced to APS. The previous product is then reduced to 3-phosphoadenosine-5-phosphosulfate (PAPS) by the action of the adenylyl-sulfate kinase (Kushkevych et al., 2020). PAPS is then reduced to sulfite by PAPS reductase, which will be transformed to sulfide and finally cysteine, reactions catalyzed by assimilatory sulfite reductase and cysteine synthase, respectively (Kushkevych et al., 2020). **Figure 2 b** describes the ASR pathway, differently form DSR, Cysteine is the final product of ASR.

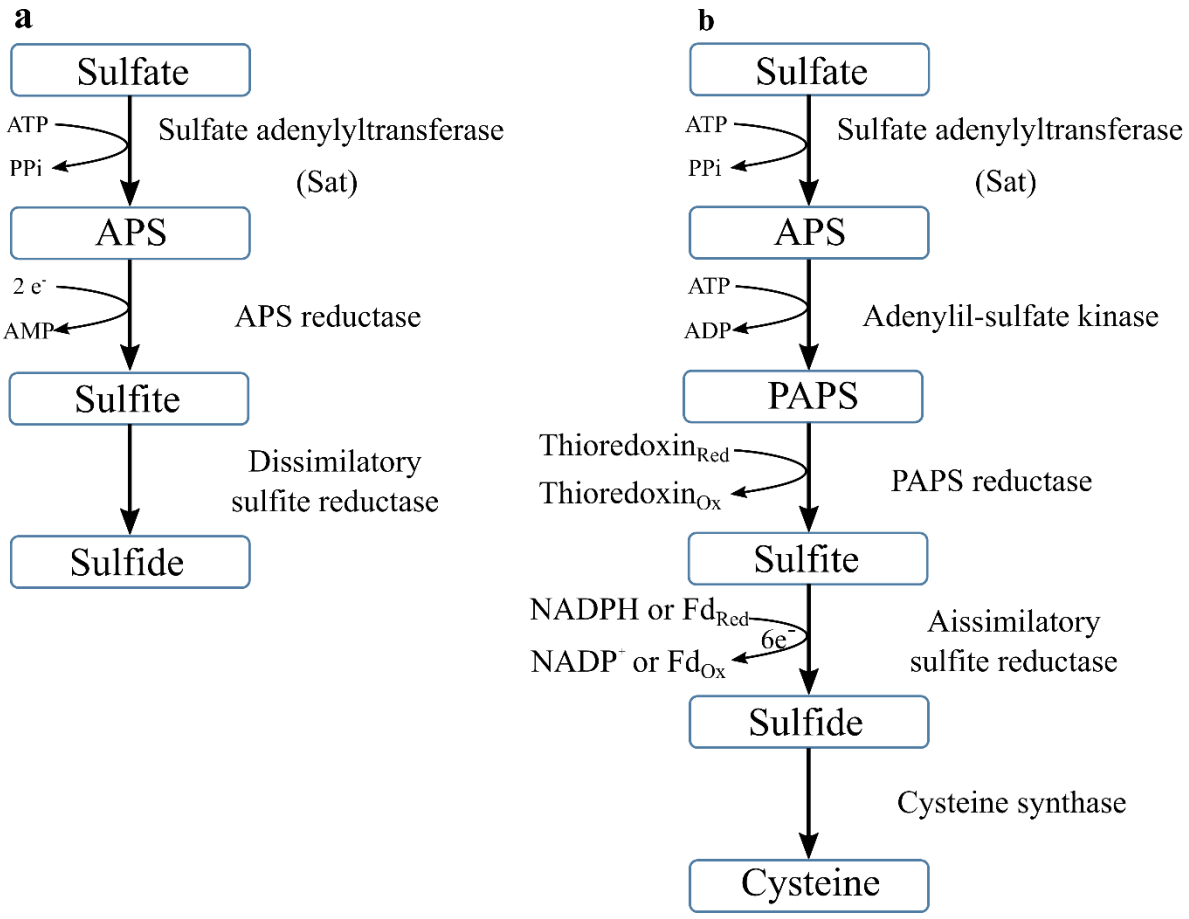

Figure 2. Sulfate reduction pathways. **a**: Dissimilatory sulfate reduction (DSR), and **b**: Assimilatory sulfate reduction (ASR). Adapted from Kushkevych et al. (2020)

4.1.5 Metal-sulfide biosynthesis using metal and sulfide precursors

Thus, DSR and ASR are the pathways attributed to produce sulfide from organisms when only metal salt is supplied for the biosynthesis of metal-sulfide NPs (da Costa et al., 2016; Hosseini & Sarvi, 2015). On the other hand, many authors suggest if metal and sulfide salts are added to the culture medium, toxicity caused by metal ions induces the organisms to

produce or excrete proteins and other peptides. These molecules will bind to metal cations and successively interact with sulfide anions. Consequently, less toxic particles are formed (Cunningham & Lundie, 1993; da Costa et al., 2016). Bimolecular excretion and binding with metal ions is also associated with the stabilization, size, and properties of the biosynthesized produces NPs (Bakhshi & Hosseini, 2016; Órdenes-Aenishanslins et al., 2020; Qi et al., 2019; Tripathi et al., 2014).

4.2 Biosynthesis by Living Organisms

The most common living organisms able to participate in NPs' synthesis have been bacteria, fungi, and yeast (da Costa et al., 2016; Hosseini & Sarvi, 2015; Narayanan & Sakthivel, 2010) due to their high capacity of toleration to environments with high levels of metal ions (Barbas et al., 1992; Malarkodi et al., 2014). Stress conditions activate the mechanism of detoxifications, such as ASR and DSR pathways, and produce other proteins like metallothioneins phytochelatins and glutathione related peptides (Cunningham & Lundie, 1993; Holmes et al., 1997; Malarkodi et al., 2014; Ortiz et al., 1995; Seregin & Ivanov, 2001). These produced peptides chelate metal ions into metal-peptide complexes; specifically, metal ions interact with the sulfide group of peptides, therefore forming coated metal-sulfide crystals (Barbas et al., 1992; Dameron et al., 1989a; Dameron et al., 1989b; Dameron & Winge, 1990). Additionally, its relatively easy cultivation and growth in ambient temperatures, pressure and pH; have made these microbes preferred to study NPs' biosynthesis (Abdel-Salam et al., 2020). Following are described the achievements regarding the biogenesis of S-NPs using living organisms, namely bacteria, fungi and algae, as well as particularities regarding the processes, mechanisms and results.

4.2.1 Biosynthesis using Bacteria

Bacteria are microorganisms widely used in research and industry owing to their relatively easy genetic manipulation and fast growth (Patel et al., 2021). For example, in medicine, they use *E. coli* to produce Tau proteins and the study of its relationship with Alzheimer's and Parkinson's diseases (Ferrari & Rüdiger, 2018; Jia et al., 2020; KrishnaKumar & Gupta, 2017; Sandberg & Nyström, 2018). In agriculture, the synthesis of proteins with specific pesticide activity (Hofte & Whiteley, 1989; Saxena, Stewart, Altosaar, Shu, & Stotzky, 2004). And probiotic microencapsulation in the food industry (Rokka & Rantamäki, 2010).

Although nanotechnology is a young field, bacteria have been widely used, especially for NMs' biosynthesis. **Table 1** and **Table 2** summarize the information about type of synthesized NPs using different bacteria, mechanism (i.e. extracellular or intracellular), shape, size, and applications of the bioproduced S-NPs.

Among the biosynthesized S-based chalcogenides NPs, the most reported in scientific publications are cadmium sulfide (CdS) NPs (da Costa et al., 2016; Hosseini & Sarvi, 2015). In 1993, Cunningham and Lundie (1993) presented the biosynthesis of spherical CdS NPs utilizing *Clostridium thernoaceticum* ATCC 39073 bacteria. This study shows a dependency on energy for CdS NPs biosynthesis. In two sets of bacteria cultures, cadmium chloride and cysteine were added to the culture media, but only in one group was added glucose as energy source (Cunningham & Lundie, 1993). The formation of CdS occurred exclusively in the non-starved cells after 12 hours of $CdCl_2$ addition (Cunningham & Lundie, 1993). A change in coloration to bright yellow in the medium was observed, an initial indication of CdS formation, later confirmed by other characterization techniques (Cunningham & Lundie, 1993). Contrary to starved cells, no CdS formation was registered even for seven days, but NPs formation started 24 h after being supplied with glucose (Cunningham & Lundie, 1993). Additionally, sulfide production was about fourfold more in cultures treated with cadmium compared with controls without cadmium. Similarly, the cysteine desulfhydrase activity started early in the reaction solution containing the metal ions, suggesting that cadmium's presence activates the enzyme expression for sulfide production by desulfhydration of cysteine, in that way reduce the toxicity in the medium (Cunningham & Lundie, 1993).

In 1997, Holmes and colleagues showed an extracellular biosynthesis of CdS NPs using *Klebsiella pneumoniae* NCIMB 418 bacteria, with a yield of 3-4 % of the cell biomass and particle diameter between 5-200 nm. Apart from cadmium; lead, zinc, mercury, copper, and silver ions were supplied to the cell cultures, no metal sulfide NPs occurred, neither sulfide production was high, compared with the sulfide production of 0.18 mM reached in the presence of 2 mM of Cd^{2+} (Holmes et al., 1997). The same bacteria were employed by Smith et al. (1998) to synthesize CdS NPs and evaluate photocatalytic activity compared to chemical synthesized CdS NPs. Photochemical reactions with methyl viologen (MV^{2+}) and methyl orange (MO^{-}) were performed, demonstrating that bio-produced NPs perform similar

reduction rates of these two components as chemically produced CdS NPs (Smith et al., 1998). Continuing with the synthesis of NPs using *Klebsiella pneumoniae*, another study (Malarkodi et al., 2014) presents the bio-production of CdS and zinc sulfide (ZnS) spherical NPs and the microbial activity against pathogens *Streptococcus* sp. *Staphylococcus* sp. *Lactobacillus* sp., and *Candida albicans* (Malarkodi et al., 2014). According to the well diffusion method results, CdS and ZnS NPs inhibited the growth of pathogens considerably, measured by the zone of inhibition (ZOI) around NPs charged wells in bacterial cultures (Malarkodi et al., 2014). In 2018, Abd Elsalam et al. utilized the bacteria *E. coli E-30* and *K. pneumoniae* K-6 for the extracellular biosynthesis of spherical CdS NPs. The biosynthesized NPs were compared with NPs produced by the wet chemical method in terms of antimicrobial activity against different pathogens. In that way, the authors demonstrate that the highest inhibition growth was observed applying the bio-NPs, rather than using the chemically synthesized materials (Abd Elsalam et al., 2018).

Another bacterium widely investigated is *E.coli*. The first published work using this bacterium for the biosynthesis of CdS NPs is described by Sweeney et al. (2004). Four *E. coli* strains were evaluated for the synthesis of NPs, but it happened only with *E. coli* ABLE C cells and *E. coli* TG1 (Sweeney et al., 2004). Bacteria incubated with cadmium chloride and sodium sulfide results in wurtzite nanocrystals' formation with spherical and elliptical-like morphologies with a size distribution of 2-5 nm. Authors demonstrated that, in this case, nanocrystals formation is dependent on the phase of the bacteria phase growth, as CdS NPs were about twentyfold in the stationary phase compared to the mid-logarithmic phase. Also, the authors hypothesized that glutathione content might have an essential function in the growth of NPs inside the cells (Sweeney et al., 2004). In another study, a genetically modified *E. coli* was developed to express the peptide CDS 7, reported to participate in the formation of CdS NPs. In this research, successful biosynthesis of fluorescent CdS quantum dots by the action of the genetically modified bacteria was conducted (Mi et al., 2011). More NPs and fluorescent quantum dots (QDs) biosynthesis using *E. coli* are presented in (El-Shanshoury, Elsilk, & Ebeid, 2012; Venegas et al., 2017; Yan, Du, Qian, Wan, & Wu, 2017).

Sulfate reducing bacteria (SRB) are anaerobic microorganisms able to degrade organic compounds using sulfate as a terminal electron acceptor (Kushkevych et al., 2020; Muyzer

& Stams, 2008). These bacteria have been widely studied due to their high impact on the natural sulfur cycle and waste water treatments (Muyzer & Stams, 2008). Besides, SRB has attracted significant attention for the biosynthesis of S- NPs owing to their high capacity to produce sulfide ions via the DSR pathway (da Costa et al., 2016; Hosseini & Sarvi, 2015). For example, Qi et al. (2016) reported the intracellular and extracellular production of CdS NPs using *Desulforibrio caledoiensis* SRB. In this report, the biosynthesis of CdS NPs is highly related to SRB metabolism sulfide production. The fluorescence intensity of the bio-produced NPs was in a direct linear relationship with the bacteria concentrations, as both parameters increased simultaneously (Qi et al., 2016). This can be explained considering that high SRB concentrations produce elevated sulfide sources through their metabolism (Qi et al., 2016). Furthermore, CdS NPs were employed to detect SRB (Qi et al., 2016). Similarly, Chávez et al. (2015) present the extracellular biosynthesis of CdS NPs using *Desulfovibrio alaskensis* 6SR bacteria. NPs produced were of cubic and hexagonal crystallinity and with average particle sizes of 10-46 nm, depending on the Cd salts concentration (Rangel-Chávez et al., 2015). In a recent study, the effective removal of EDTA-chelated cadmium ions from the medium of *Desulfovibrio desulfuricans* SRB was confirmed by precipitating spherical CdS NPs of about 40-80 nm in diameters. These NPs were produced extracellularly and shown a high photocatalytic activity by efficient degradation of Rhodamine B (RhB) (Liu et al., 2020). Apart from CdS biosynthesis, other S-NPs such as zinc sulfide (ZnS) and lead sulfide (PbS) have been synthesized using SRB (Gong, Zhang, Bai, & Yang, 2007; Labrenz et al., 2000; Yoon, Yáñez, Bruns, Martínez-Villegas, & Martínez, 2012; Yue et al., 2016).

Many reports present the production of ZnS NPs employing SRB. Labrenz et al. (2000), presented a report on the NP formation of sphalerite ZnS within biofilms of *Desulfobacteriaceae* sp. The observed nano-aggregates have a spherical morphology with diameters of about 2-5 nm, confirmed by Transmission Electron Microscope (TEM), Scanning Electron Microscopy (SEM) and X-ray diffraction XRD characterization techniques (Labrenz et al., 2000). Another approach reported the precipitation of sphalerite and wurtzite ZnS nanocrystals with sizes of 12-14 and ~48 nm, respectively (Yoon et al., 2012). This is an *in situ* study made on peatlands, where it was found dissimilatory sulfite reductase (*dsr*AB) genes by PCR tests, suggesting that the primary organisms participating in the biosynthesis are sulfate reducing bacteria (Yoon et al., 2012). Moreover, controlled

experimental methodologies have been implemented for the bio-production of NPs using SRB. *Desulfotomaculum* sp. serve as biofactories for controlled crystal growth of PbS NPs at different pH ranges and temperature conditions (more details in section 5) (Gong et al., 2007). Another controlled bio-production of NPs was developed (Yue et al., 2016). The authors used the *Clostridiaceae* sp. SRB for the extracellular biosynthesis of PbS NPs with cuboidal, nanosheets, and sphere morphologies, mediated principally by changing polyethylene glycol (PEG) concentrations in the cell cultures (Yue et al., 2016). The process developed in this study demonstrates favorable conditions for easy and low-cost NPs purification (Yue et al., 2016).

In another study, Murray et al. (2017) reported a cell-free approach for ZnS NPs production using *Desulfovibrio desulfuricans*, NCIMB 8307 bacteria. In this study, the off-gas H_2S from SRB were injected into solutions containing Zn^{2+}, which immediately turn into whitish-like solutions indicating ZnS formation and later confirmed by XRD analysis. The bio-produced NPs were characterized as spherical QDs with cubic crystalline phase and a particle diameter of ~2.4 nm (Murray et al., 2017). More recently, Qi et al. (2017) described a controlled biosynthesis of ZnS QDs employing *Clostridiaceae* sp. SRB. The nucleation and growth of NPs were highly influenced by the action of hydroxypropyl starch (HPS) (Qi et al., 2017). The crystallinity of the bio-produced NPs varies between wurtzite and sphalerite when low or high concentrations of HPS were added to the culture medium (Qi et al., 2017). Authors argue that HPS serves as a matrix for the formation of NPs, and together with EDTA, contributed to the easy NPs purification (Qi et al., 2017).

Qi and colleagues (2019) achieved a purely extracellular biosynthesis of ZnS QDs with high yields that could reach a production of 35.0−45.0 g/L per month, extrapolated from the results obtained in one week. The organisms used were a mix of SRB conformed by *Desulfovibrio* sp., *Clostridiaceae* sp., *Proteiniphilum* sp., *Geotoga* sp., *Sphaerochaeta* sp., to produce NPs with an APS of 6.5 nm and a high photoluminescence activity (Qi et al., 2019). The particles were in constant production for six days. During this time, their properties were kept almost unchanged. Besides, Fourier-transform infrared (FTIR) results evidenced that QDs formation was greatly influenced by secreted proteins (EPs) from SRB, which, in addition to elevated sulfide synthesis, were the main contributing factors in the control in growth size and

morphology of the QDs (Qi et al., 2019). Qi et al. (2019) mention that similarly to ZnS, CdS, PbS, and copper sulfide (CuS) QDs were produced (Qi et al., 2019). Using other SRB, ZnS NPs were biosynthesized employing the *Desulfovibrio desulfuricans* bacteria, taking advantage of the sulfide generated by this organism (Da Costa et al., 2012). In this study, TiO_2 and SiO_2 powders serve as substrates for forming sphere-like NPs with diameters of about 20-30 nm (Da Costa et al., 2012). Apart from these, ZnS biosynthesis has been reported in many studies using *Serratia nematodiphila* (Malarkodi & Annadurai, 2013), mixed SRB (Xin, Huang, Chen, & Tang, 2008), and with other bacteria of the genus *Thermoanaerobacter*, *Rhodobacter*, *Pseudomonas*, *Bacillus*, *Enterococcus*, and *Lactobacillus* (**Table 1** and **Table 2**)

Bacteria isolated from extreme environments, or halophilic bacteria, have also been investigated for their ability to mediate S-based nanocrystals production (Gallardo et al., 2014; Ulloa et al., 2016; Ulloa et al., 2018). In (Gallardo et al., 2014), peroxide and cadmium chloride resistant bacteria, identified as *Pseudomonas* spp., were isolated from Antarctica and evaluated to produce CdS NPs. These bacteria produced interesting CdS QDs at 15 °C, with 10-40 nm in size and time-dependent fluorescence responses, changing from green to red colors. It is proved that sulfide production is essential for the biosynthesis of CdS QDs under the presence of cysteine and the action of cysteine desulfhydrase enzymes. Following, in a time-lapse of two hours, QDs production was detected using three *Pseudomonas* spp., while it was not the case for *Pseudomonas fragi* ATTC 4973, strain not able to produce H_2S in the settled conditions (Gallardo et al., 2014). Similar results were obtained by (Ulloa et al., 2016) using *Acidithiobacillus* spp, a study complemented with (Ulloa et al., 2018) demonstrating that the addition of inorganic phosphate (Pi) to the growth medium can enhance the biosynthesis of CdS QDs at pH of 3.5. More reports expose the influence of Pi regarding the biogenesis of CdS (Feng et al., 2018; Ulloa et al., 2018; Venegas et al., 2017).

Cadmium sulfide NPs have been synthesized using just metal precursor (Plaza et al., 2016). Plaza et al. (2016) revealed the biosynthesis of CdS QDs with no addition of external sulfur source to the bacteria culture medium in *Pseudomonas*, *Psychrobacter* and *Shewanella*, Antarctic bacteria (Plaza et al., 2016). On the other hand, Gallardo et al. (2019) demonstrated CdS QD's biosynthesis employing the Antarctic bacteria *Pseudomonas fragi* GC0.

Extracellular and intracellular nanocrystal synthesis was evaluated considering sulfate, sulfite, thiosulfate, sulfide, cysteine and methionine as sulfur sources. QDs formed inside the cells in the presence of all sulfur sources, but extracellular biosynthesis only occurred by the influence of cysteine (Cys) and methionine (Met) (Gallardo et al., 2019). The salt-resistant halophilic bacteria *Halobacillus* sp. DS2 isolated from Atacama Salt Flat (Chile), Uyuni Salt Flat (Bolivia) and the Dead Sea (Israel) by the group of Bruna et al. (2019) were able to promote the biosynthesis of CdS QDs. These bacteria could produce stable QDs in the presence of different NaCl concentrations (0% - 8%), contrary to the control bacteria *E. coli* that could not synthesize at NaCl concentrations of 6% and higher (Bruna et al., 2019).

Recently, core/shell NPs have been synthesized for the first time using bacteria; specifically, CdS/CdSe core/shell was bio-produced through *E. coli* BW25113 reported in (Órdenes-Aenishanslins et al., 2019). In the same report, CdS QDs were bio-generated and compared to core/shell NPs. According to the results, core/shell QDs performed better photovoltaic responses than CdS (Órdenes-Aenishanslins et al., 2019). Thus, biosynthesis could be an alternative method for the generation of novel photovoltaic materials. Utilizing the same bacteria, ternary CdSAg QDs were produced for the first time, together with, CdS and Ag2s QDs (Órdenes-Aenishanslins et al., 2020). In this study, CdS QDs were produced in the presence of Cd^{2+} and cysteine at different reaction times, resulting in the formation of fluorescent NPs in colors green, yellow and red. Ternary QDs were synthesized through cation exchange, starting from the production of CdS QDs and followed by the addition of Ag^{+} ($AgNO_3$) at different concentrations. Fluorescence responses indicate the existence of an isosbestic point (IP) at Ag^{+} concentrations between 25 uM - 40 uM, indicating the formation of CdSAg QDs (Órdenes-Aenishanslins et al., 2020). These two reports indicated that living cells are important for the biosynthesis of core/shell and ternary QDs since no NP production occurred in the absence of bacteria *E. coli*.

There are two particular forms among S-based biosynthesized iron sulfide NPs: greigite (Fe_3S_4) and pyrite (FeS_2), mainly produced by magnetotactic bacteria (Bharde et al., 2008; Heywood, Bazylinski, Garratt-Reed, Mann, & Frankel, 1990; Mann, Sparks, Frankel, Bazylinski, & Jannasch, 1990; Watson, Ellwood, Soper, & Charnock, 1999). In 1990, Mann et al. (1990) reported biogenic greigite and pyrite nanocrystals inside of magnetotactic

bacterium collected from brackish sites rich in sulfide. The NPs appeared to have rhombohedral and hexagonal morphologies and sizes of around 75 nm (Mann et al., 1990). Similarly, greigite NPs with a size distribution of 50-90 nm were evidenced inside magnetotactic bacteria (Heywood et al., 1990). Sulfate Reducing Bacteria (RSB) (Watson et al., 1999) and *Actinobacter* sp. (Bharde et al., 2008) have also participated in the biosynthesis of iron sulfide (FeS), greigite (Fe_3S_4) and pyrite (FeS_2), NPs. On the other hand, biogenesis of PbS nanocrystals has also been reported in (Bai & Zhang, 2009) and (Zhang & Huang, 2020). These studies demonstrated the participation of specific enzymes for the control and formation of NPs. The expression of the enzyme cystathionine γ-lyase (smCSE) was highly linked with the crystallization of PbS, CdS, and PbS/CdS Core/Shell NPs. The substrate of this enzyme is L-cysteine, producing H_2S, NH3 and pyruvate as products. Sulfide source for the synthesis of S-based NPs comes principally from H_2S catalyzed by smCSE enzymes, according to the authors (Spangler et al., 2016; Yang et al., 2016)

Bismuth sulfide (Bi_2S_3) NPs have also been produced through bacteria. In a study performed by Yue et al., (2014), two morphologies of Bi_2S_3 in nanoscale dimensions are produced employing *Clostridiaceae* ap. bacteria. The "water-oil two-phase" was reproduced in this study for the biosynthesis of nanorods and nanoneedles detected by SEM analysis (more details in section 5). The morphology depended on the concentration of both lactic acid and SO_4^{2-} (Yue, Wu, Liu, Xin, & Chen, 2014). In another approach, hexagonal Bi_2S_3 NPs were extracellularly synthesized using the bacteria *Clostridium acetobutylicum*. The dimensions of NPs were time-dependent as cultures incubated for five days produced NPs of about 6-10 nm, while crystals of about 440-500 nm were formed with cultures kept for seven days (Kamaraj, Venkatachalam, Arumugam, & Berchmans, 2014). Besides, biogenesis of different S-based NPs is presented in other published works, such as spherical Silver sulfide (Ag_2S) NPs (Debabov et al., 2013; Sureshet al., 2011), arsenic-sulfide nanotubes (Jiang et al., 2009; Lee et al., 2007), and copper sulfide (CuS) nanorods (Xiao et al., 2017) (**Table 1** and **Table 2**).

Table 1. Biosynthesis of Cadmium based S-NPs using Bacterial.

Type	Bacteria	Mechanism	Shape	Size (nm)	Application	Reference
CdS	*Acidithiobacillus* spp.	Int., Ext.	(QDs)	(~) 6, 10	-	(Ulloa et al., 2016)
	Acidithiobacillus thiooxidans ATCC 19703	Int., Ext.	(QDs)	(~) 6.9, 10	-	(Ulloa et al., 2018)
	Bacillus amyloliquifaciens KSU-109	Ext.	Spherical	~ 3.2	-	(Singh et al., 2011)
	Bacillus cereus	-	-	30-100	Antimicrobial	(Harikrishnan, Shine, Ponmurugan, Moorthy, & Kumar, 2014)
	Bacillus licheniformis	Ext.	-	2-10	-	(Bakhshi & Hosseini, 2016)
	Bacillus licheniformis MTCC 9555	Int.	Spherical	~ 5.1	-	(Tripathi et al., 2014)
	Bacillus subtilis ATCC 6633	Ext.	Spherical	2.5-5.5	-	(El-Shanshoury et al., 2012)
	Citrobacter braakii AX5	Int.	Spherical	50-100	-	(Zhu, Kumari, Huang, & Achal, 2016)
	Clostridium thernoaceticu ATCC 39073	Ext	Spherical	50	-	(Cunningham & Lundie, 1993)
	Desulfovibrio caledoiensis	Int., Ext.	Spherical	40 - 50	Bioimaging	(Qi et al., 2016)
	Desulfovibrio alaskensis 6SR	Int., Ext.	-	10-46	-	(Rangel-Chávez et al., 2015)
	Desulfovibrio desulfuricans	Ext.	Spherical	40-80	-	(Liu et al., 2020)
	Enterococcus sp.	Ext.	Spherical	50–180	Antimicrobial	(Rajeshkumar et al., 2014)
	Escherichia coli	Int.	Spherical, elliptical	2–5	-	(Sweeney et al., 2004)
	Escherichia coli	Int.	-	~ 6	-	(Mi et al., 2011)
	Escherichia coli	Int.	Spherical	~ 10	-	(Yan et al., 2017)
	Escherichia coli	Int.	-	7.5, 3.5	-	(Venegas et al., 2017)
	Escherichia coli ATCC 8739	Ext.	Spherical	2.5-5.5	-	(El-Shanshoury et al., 2012)
	Escherichia coli BW25113	Ext.	Spherical	3-9	-	(Órdenes-Aenishanslins et al., 2020)
	Escherichia coli BW25114	Ext.	Spherical	~ 12	Solar cells	(Órdenes-Aenishanslins et al., 2019)
	Escherichia coli E-30	Ext.	Spherical	3.2 -44.9	Antimicrobial	(Abd Elsalam et al., 2018)
	Halobacillus sp. DS2	Ext.	Hexagonal	~ 4	-	(Bruna et al., 2019)
	Klebsiella pneumoniae	Ext.	Spherical	10-25	Antimicrobial	(Malarkodi et al., 2014)

	Klebsiella pneumoniae K-6	Ext.	Spherical	5.7-26.3	Antimicrobial	(Abd Elsalam et al., 2018)
	Klebsiella pneumoniae NCIMB 418	Ext.	Spherical	5-200	-	(Holmes et al., 1997)
	Klebsiella pneumoniae NCIMB 418	Ext.	Spherical	5-200	-	(Smith et al., 1998)
	Lactobacillus acidophilus DSMZ 20079T	Ext.	Spherical	2.5-5.5	-	(El-Shanshoury et al., 2012)
	Lactobacillus sp.	Ext.	Spherical	3.5–5.5	-	(Prasad & Jha, 2010)
	Pedobacter sp. UYP1	Ext.	-	(~) 2.8, 4.9	Solar cells	(Carrasco et al., 2021)
	Phormidium tenue NTDM05	Ext.	Spherical	~5	-	(Mubarakali, Gopinath, Rameshbabu, & Thajuddin, 2012)
	Pseudomonas aeruginosa N6P6	-	Spherical	10	-	(Chakraborty, Mallick, Raj, & Das, 2018)
	Pseudomonas putida KT2440	Int.	-	12.5-27.5	-	(Oliva-Arancibia et al., 2017)
	Pseudomonas spp.	Int.	-	-	-	(Plaza et al., 2016)
	Pseudomonas spp.	Int.	(QDs)	10–40	-	(Gallardo et al., 2014)
	Pseudomonas spp.	Int., Ext.	Cubic	(~) 2, 16	-	(Gallardo et al., 2019)
	Psychrobacter spp.	Int.	-	-	-	(Plaza et al., 2016)
	Rhodobacter sphaeroides	Int.	Spherical	(~) 2.3, 6.8, 36.8	-	(Bai et al,. 2009a)
	Rhodopseudomonas palustris	Int.	Spherical	~8	-	(Bai et al,. 2009b)
	Shewanella sp.	Int.	-	-	-	(Plaza et al., 2016)
	Stenotrophomonas maltophilia	Ext.	Spherical	(~) 2.75, 3.04, 3.36	-	(Yang et al., 2015)
	Stenotrophomonas maltophilia	Ext.	Spherical	(~) 4.3, 4.8	-	(Yang et al., 2016)
CdSAg	*Escherichia coli* BW25113	Ext.	Spherical	6-9	Bioimaging, solar cells	(Órdenes-Aenishanslins et al., 2020)
CdS/ CdSe	*Escherichia coli* BW25114	Ext.	Spherical (Core/shell)	(~) 17	Solar cells	(Órdenes-Aenishanslins et al., 2019)

Int.: Intracellular
Ext.: Extracellular
~: Approximately

Table 2. Zinc, Lead, Silver, Arsenic, Bismuth and Cooper based S-NPs synthesized using bacteria.

Type	Bacteria	Mechanism	Shape	Size (nm)	Application	Reference
ZnS	*Clostridiaceae* sp.	Ext.	Spherical	5.95-3.34	-	(Qi et al., 2017)
	Desulfobacteriaceae	Int.	Spherical	2-5	-	(Labrenz et al., 2000)
	Desulfovibrio desulfuricans	Ext.	-	~ 2.4	-	(Murray et al., 2017)
	Desulfovibrio desulfuricans	-	Amorphous	4-12	-	(Xu et al., 2016)
	Desulfovibrio desulfuricans	Ext.	Spherical	20-30	-	(Da Costa et al., 2012)
	Klebsiella pneumoniae	Ext.	Spherical	65	Antimicrobial	(Malarkodi et al., 2014)
	Mixed SBR	Ext.	-	~ 6.5	-	(Qi et al., 2019)
	Mixed SBR	Ext.	Spherical	15	-	(Xin et al., 2008)
	Pseudomonas aeruginosa BS01	Ext.	Spherical	10-15	Cytotoxicity	(Hazra et al., 2013)
	Rhodobacter sphaeroides	Ext.	Spherical	(~) 4, 8, 30, 105	-	(Bai et al., 2006)
	Serratia nematodiphila	Ext.	Spherical	80	Antimicrobial	(Malarkodi & Annadurai, 2013)
	SRB from peatlands	Ext.		12-14	-	(Yoon et al., 2012)
	Thermoanaerobacter X513	Ext.	Spherical	2-10	bio-ink	(Moon et al., 2014)
	Thermoanaerobacter X513	Ext.	Spherical	~ 2	-	(Moon et al., 2016)
PbS	*Clostridiaceae* sp.	Ext.	Cubic	50x50x100	As(III) detection	(Yue et al., 2016)
	Clostridiaceae sp.	Ext.	Nanosheets	10	As(III) detection	(Yue et al., 2016)
	Clostridiaceae sp.	Ext.	Spherical, amorphous	60	As(III) detection	(Yue et al., 2016)
	Desulfotomaculum sp.	Ext.	Spherical, nanorods	13	-	(Gong et al., 2007)
	Rhodobacter sphaeroides	Ext.	Spherical	~ 10.5	-	(Bai & Zhang, 2009)
	Shinella zoogloeoides PQ7	Ext.	-	-	-	(Zhang & Huang, 2020)
	Stenotrophomonas maltophilia	Ext.	Amorphous	~ 3	Solar cells	(Spangler et al., 2016)

PbS/ CdS	*Stenotrophomonas maltophilia*	Ext.	Amorphous	4-5	Solar cells	(Spangler et al., 2016)
Ag2S	*Escherichia coli* BW25113	Ext.	Spherical	<15	-	(Órdenes-Aenishanslins et al., 2020)
	Pseudomonas stutzeri AG259	Int.	Triangular, hexagonal	up to 200 nm	-	(Klaus, Joerger, Olsson, & Granqvist, 1999)
	Shewanella oneidensis	Ext.	Spherical	~ 9 ± 3.5	-	(Sureshet al., 2011)
	Shewanella oneidensis MR-1	Ext.	Spherical	2-16	-	(Debabov et al., 2013)
As-S	*Desulfotomaculum auripigmentum*	Int., Ext.	Spherical	50-100	-	(Newman, Beveridge, & Morel, 1997)
	Shewanella sp. HN-41	Ext.	Nanotubes	20-100	-	(Lee et al., 2007)
	Shewanella sp.	Ext.	Nanotubes	30-70	-	(Jiang et al., 2009)
Bi2S 3	*Clostridiaceae* sp.	Ext.	Nanorods	100 D. 1000 l.	-	(Yue et al., 2014)
	Clostridiaceae sp.	Ext.	Nanoneedles	10-20 D. 5-10 l.	-	(Yue et al., 2014)
	Clostridium acetobutylicum	Ext.	Hexagonal	6-10, 440-500	-	(Kamaraj et al., 2014)
CuS	*Shewanella oneidensis* MR-1	Ext.	Nanorods	80.8 D. 17.4 l.	-	(Xiao et al., 2017)

Int.: Intracellular
Ext.: Extracellular
~: Approximately
D.: Diameter
l: Length

4.2.2 Biosynthesis using Fungus and Yeast

Fungal (and yeast) mediated NPs synthesis has been demonstrated as an attractive approach due to low cost and scalable production. In comparison with bacteria, fungi possess increased tolerance to metal ions owing to their elevated cell wall binding, allowing higher bioaccumulation of metal ions and, therefore, effective and large scale bio-production NPs (Alsaggaf et al., 2020; da Costa et al., 2016; Gahlawat & Choudhury, 2019; Singh et al., 2016). In fungi and plants, metal ions induce different mechanisms for the synthesis of metallothioneins (MTs) or Glutathione-derived peptides, called phytochelatins (PCs), thus decrease the medium toxicity (Narender & Prasad, 1990; Ortiz et al., 1995). MTs are translated from mRNA, while PCs are enzymatically derived from glutathione (GSH, γ-Glu-Cys-Gly) with a general structure $(\gamma\text{-Glu-Cys})_n\text{-Gly}$, where n=2-11 (Ortiz et al., 1995; Seregin & Ivanov, 2001). Mycosynthesis of NPs is evidenced by using several species like *Fusarium oxysporum* (Ahmad et al., 2002; Mirzadeh et al., 2013; Sandoval et al., 2017), *Coriolus versicolor* (Sanghi & Verma, 2009), *Saccharomyces cerevisiae* (Prasad & Jha, 2010; Wu, Wang, Shen, & Zhao, 2015), *Trichoderma harzianum* (Bhadwal et al., 2014), between others, to produce different sulfur based NPs as described in **Table 3**, which describes the achievements regarding the biosynthesis of S-NPs employing fungi.

The first demonstration of NPs biosynthesis using fungi was presented by Dameron et al. (1989). It was performed the synthesis of monodispersed quantum CdS crystallites employing *Candida Glabrata* and *Schizosaccharomyces pombe* yeasts (Dameron et al., 1989a). Authors found that short peptides of the form $(\gamma\text{-Glu-Cys})_n\text{-Gly}$, or phytochelatins (PCs), controlled the intracellular NPs biosynthesis, and at the same time, stabilize the NPs acting as a coat (Dameron et al., 1989a; Dameron & Winge, 1990). Similar results were reported in (Barbas et al., 1992; Dameron et al., 1989b) using just *Candida glabrata*. Here, fluorescent CdS NPs are formed intracellularly and coated by $(\gamma\text{-Glu-Cys})_n\text{-Gly}$ or γEC peptides, depending on the nutrients containing the culture medium.

Ahmed and colleagues (2002) proved that *Fusarium oxisporum*, immersed in a solution containing $CdSO_4$ as cadmium and sulfate sources, secretes sulfate reductases enzymes to produce sulfide and stabilize metal ions into CdS NPs (Ahmad et al., 2002). Similarly, Uddandarao and Mohan (2016) showed that extracellular generation of ZnS QDs using

Aspergillus flavus are stabilized and coated by protein residues, like cysteine and methionine. Also, the authors suggest that metal ions cause stress conditions to cells, which activate the assimilatory sulfate reduction (ASR) and produce ZnS NPs. Antimicrobial tests with these bio-NPs inhibited the growth of the bacteria *E. coli* due to the cell wall-NPs contact and reactive oxygen species (ROS) generation, thus declining cell viability (Uddandarao & Mohan, 2016). Biogenesis of CdS NPs without any sulfur precursor was demonstrated in (Sanghi & Verma, 2009) using fungus *Coriolus versicolor* immobilized in a continuous column. Cadmium solutions passed through the column produced yellow coloration in the fungal biomass, evidencing the formation of spherical CdS NPs with diameters of about 8-15 nm (Sanghi & Verma, 2009). The biosynthesized NPs described in these studies maintained high stability, even for months, owing to the presence of proteins and peptides attached to the crystals surface that prevented aggregation. These results are in concordance with other reports that used fungi to mediate NPs synthesis (Bhadwal et al., 2014; Chen et al., 2014; Qin et al., 2018; Seshadri et al., 2011; Uddandarao & Mohan, 2016).

NPs produced by fungal biomass have been applied for different interests, as evidenced in the following reports. In (Mareeswari et al., 2016), CdS QDs synthesized employing *Rhizopus stolonifer* fungi were used for imaging human breast adenocarcinoma MCF-7 cell lines. On the other hand, the bio-produced PbS NPs (Priyanka et al., 2017) could efficiently detect arsenic (III) in water up to 50 ppb. The sensing mechanism was due to the presence of thiol groups of cysteine residues attached to NPs that interacts with arsenic and changes the absorption spectra of NPs. Besides, Alsaggaf et al. (2020) describe the biosynthesis of CdS NPs using *Aspergillus niger* (RCMB 002002) fungi. The microorganisms were cultivated with $CdCl_2$ and Na_2S for five days to produce monodispersed fluorescent CdS QDs. Taking advantage of their size and high-surface-to-volume ratio on NPs, these were applied for antimicrobial and cytotoxicity tests showing inhibition on cell growth for bacteria and human cancer cell lines (Alsaggaf et al., 2020)

Hosseini et al. (2012) demonstrated the biological generation of CuS NPs mediated by *Fusarium oxysporum.* The nanocrystals formed have a diameter between 2-5 nm, but these values increased to 20 nm due to the formation of a shell peptide around NPs (Hosseiniet al., 2012). In a novel approach, CuS NPs were performed with the same fungi but treated with

electricity below 20 mA to prevent lethal consequences to the organisms (Hosseiniet al., 2013). Cell cultures applied electric currents presented a NP yield of about threefold in comparison with control cultures. Even though electric currents' application decreased cell growth, these produced higher amounts of protein and elevated glucose consumption. Although to understand what is happening to the cells is complex, authors speculate that electricity applied induced DNA changes to produce more protein that at the same time requires of higher energy consumption and increased cell wall permeability (Hosseiniet al., 2013). Most relevant, production of NPs were in higher rates using culture cells applied electricity than control samples (Hosseiniet al., 2013). Apart from this, few publications presented the biogenesis of Ag_2S and PbS nanocrystals using *Pleurotus ostreatus* (Borovaya et al., 2020), *Rhodosporidium diobovatum* (Seshadri et al., 2011), and *Torulopsis* sp. (Kowshiket al., 2002), as described in **Table 3**.

Biogenic NPs have been produced using yeast. For example, Krumov et al. (2007) made CdS NPs mediated by two yeasts, *Schizosaccharomyces pombe*, and *Candida glabrata*, in fed-batch conditions. Synthesis of NPs was performed intracellularly by both yeasts, but *S. pombe* could produce more synthesis than *C. glabrata*, also dependent on glucose uptake as an energy source (Krumov, Oder, Perner-Nochta, Angelov, & Posten, 2007). Using the same fungi, Al-Shalabi and Doran (2016) produced CdS QDs with diameters between 2-6 nm. In the same study, the tomato root *Solanum lycopersicum* was employed to produce bigger NPs of about 4-10 nm in size and with lower yields, compared to fungi (Al-Shalabi & Doran, 2016). *Saccharomyces cerevisiae* could biosynthesize spherical NPs with particles size between 2.5-4.5 nm (Prasad & Jha, 2010), comparable to the bio-produced NPs (Wu et al., 2015) with a diameter of about ~2 nm. The mechanism of yeast to produce NPs is the same as other fungi. Metal-sulfide NPs are formed by producing glutathione-related peptides, enzymes, and proteins, which participate in reducing stress conditions of the environment, as described previously.

Table 3. Sulfur-based nanoparticles mediated by fungi.

NP	Fungi	Mechanism	Shape	Size (nm)	Application	Reference
CdS	*Aspergillus niger (RCMB 002002)*	Ext.	Spherical	2.7-7.5	Anticancer, antibacterial	(Alsaggaf et al., 2020)
	Candida glabrata	Int., Ext.	Spherical	~ 2	-	(Barbas et al., 1992; Dameron et al., 1989a; Dameron et al., 1989b; Dameron & Winge, 1990)
	Candida glabrata	Int.	-	-	-	(Krumov et al., 2007)
	Coriolus versicolor	Ext.	Spherical	8-15	-	(Sanghi & Verma, 2009)
	Fusarium oxysporum	Ext.	Spherical	5-20	-	(Ahmad et al., 2002)
	Fusarium oxysporum f. sp. lycopersici 4287	Ext.	Spherical	2-6	-	(Sandoval et al., 2017)
	Fusarium sp.	Ext.	Spherical	80-120	-	(Reyes, Gomez, & Garza, 2009)
	Phanerochaete chrysosporium (BKMF-1767)	Ext.	Spherical	1.5-2.0	-	(Chen et al., 2014)
	Pleurotus ostreatus	Ext.	Spherical	4-5	-	(Borovaya et al., 2015)
	Rhizopus stolonifer	Ext.	Spherical	~8.8	Bioimaging	(Mareeswari et al., 2016)
	Saccharomyces cerevisiae	Ext.	Spherical	2.5-4.5	-	(Prasad & Jha, 2010)
	Saccharomyces cerevisiae	Ext.	Spherical	~ 2	Solar cells	(Wu et al., 2015)
	Schizosaccharomyces pombe	Ext.	Spherical	2-6	-	(Al-Shalabi & Doran, 2016)
	Schizosaccharomyces pombe	Int., Ext.	Spherical	~ 2	-	(Dameron et al., 1989a; Dameron & Winge, 1990)
	Schizosaccharomyces pombe	Int.	-	2-2.5	Electronics	(Kowshiket al., 2002)
	Schizosaccharomyces pombe	Int.	-	-	-	(Krumov et al., 2007)
	Trametes versicolor	Ext.	Spherical	~ 6	-	(Qin et al., 2018)
	Trichoderma harzianum	Ext.	Spherical	3–8	-	(Bhadwal et al., 2014)
ZnS	*Aspergillus flavus*	Ext.	Spherical	12-24	-	(Uddandarao & Mohan, 2016)
	Fusarium oxysporum PTCC 5115	Ext.	Spherical	42	-	(Mirzadeh et al., 2013)
	Saccharomyces cerevisiae MTCC 2918	Int.	Spherical	30–40	-	(Sandana Mala & Rose, 2014)
PbS	*Rhodosporidium diobovatum*	Int.	-	2–5	-	(Seshadri et al., 2011)
	Aspergillus flavus	-	Spherical	35-100	As detection	(Priyanka et al., 2017)
	torulopsis	Int.	Spherical	5	-	(Kowshiket al., 2002)

Ag_2S	*Pleurotus ostreatus*	Ext.	Spherical	10-15	Antibacterial, bioimaging	(Borovaya et al., 2020)
CuS	*Fusarium oxysporum*	Ext.	Spherical	2-5	-	(Hosseini et al., 2013)
	Fusarium oxysporum	Ext.	Spherical	2-5	-	(Hosseini et al., 2012)

Int.: Intracellular
Ext.: Extracellular
~: Approximately

4.2.3 Biosynthesis using Algae

Algae are unicellular or multicellular organisms belonging to four domains/kingdoms: *Bacteria*, *Plantae*, *Chromista*, and *Protozoa*, commonly found in moist freshwater surfaces, and marine water (Dahoumane et al., 2017; Rahman et al., 2020). Biogenesis of NPs using algae is a relatively new approach but a promising field in new NMs generation. The first report evidencing the formation of NPs using algae was published in 2007. In this work, Au NPs with different shapes were produced employing *Chlorella vulgaris* algae and a protein isolated (Xie et al., 2007). Since then, several authors have contributed to the understanding of this matter, reporting the synthesis of different NPs using algae (Dahoumane et al., 2012, 2017; Rahman et al., 2020). Even though it is known that the biosynthesis mechanism of algae is mediated by cell wall biomolecules, peptides, enzymes and other proteins, there is still a necessity for more research aiming at differentiating specific mechanisms and biomolecules responsible for the biogenesis of NPs and other issues (Rahman et al., 2020). Following and in **Table 4** is described the research found about the biogenesis of sulfur-based nanocrystals employing algae.

Intracellular formation of CdS NPs was possible using the green algae *Scenedesmus-24* (Jena et al., 2015). The presence of cadmium ions in the medium induced the cells' absorption/sequestration of these ions. Simultaneously, low molecular weight proteins were synthesized, like metallothioneins, phytochelatins; rich in thiol groups that interacted with Cd ions forming metal-peptide complexes to reduce toxicity. As a result of the mechanisms, CdS nanocrystals are produced, particularly with sizes ranging between 150 – 175 nm (Jena et al., 2015). The blue-green algae, *Spirulina (Arthrospira) platensis*, was reported to synthesize photoluminescent CdS NPs with spherical morphology (Mandal et al., 2016). Cadmium nitrate served as the metal source, while no sulfur source was employed. In this case, the synthesis of CdS NPs occurred extracellularly. The principal justification of nanocrystals formation was based on the binding between cadmium ions and the C-phycocyanins (CPC) biliprotein, produced by *Spirulina*, reported to bind with Hg^{2+} ions (M. Suresh, Mishra, Mishra, & Das, 2009). This was proved by observing the reduction in the intensity of fluorescence spectra of the CPC proteins while increasing cadmium nitrate concentrations in samples. In this experiment, algae cells were necessary for the biosynthesis

of NPs since CPC were released by cells in presence of cadmium ions. More interestingly, CPC served as a matrix for the formation of CdS 8-12 nm NPs, due to the ring-like shape of the CPC biomolecule (Mandal et al., 2016).

In another study, CdS NPs were bioproduced cell-free extracts of *Chlamydomonas reinhardtii* green algae (Rao & Pennathur, 2017). In this case, cadmium chloride and sodium sulfide were used as cadmium and sulfide sources, respectively, to the biosynthesis spherical CdS NP of ~5 nm in diameter. These NPs were used successfully to degrade methylene blue dye (MB), an environmental pollutant and toxic dye for humans (Rao & Pennathur, 2017). This study demonstrates that cell-free extracts from algae could be an economical and efficient alternative to produce NPs. Additionally, algae and products can be employed for bioremediation approaches such as degradation of organic dyes and metal detoxification (Rao & Pennathur, 2017).

Table 4. Biosynthesis of S-NPs employing algae.

Type	Algae	Mechanism	Shape	Size (nm)	Application	Reference
CdS	*Scenedesmus-24*	Int.	-	150-175	Bioremediation	(Jena et al., 2015)
	Spirulina (Arthrospira) platensis	Ext.	Spherical	8-12	Bioremediation	(Mandal et al., 2016)
	Chlamydomonas reinhardtii	Ext.	Spherical	~5	Bioremediation	(Rao & Pennathur, 2017)

Int.: Intracellular
Ext.: Extracellular
~: Approximately

4.3 Biosynthesis using non-living bioentities

In this section, the synthesis of S-NPs involving other bioentities apart from living organisms will be reviewed. Plants are considered in this section because the synthesis is performed by employing the extracts from a specific part of the whole organism, unlike bacteria, fungi, and algae, where the entire microorganisms participate in the synthesis (Alsaggaf et al., 2020; Bhadwal et al., 2014; Borovaya et al., 2015, 2020). In viruses, the synthesis mechanism is mainly performed by proteins and fragments, which also influences the morphology of the resulting NPs (Flynn et al., 2003; Lee, 2002; Mao et al., 2003; Shenton et al., 1999). The biogenesis of NPs using single isolated biomolecules is also important because it clarifies the mechanisms produced by other organisms for NPs biosynthesis. Additionally, biosynthesis

of NPs employing non-living bioentities can be compared to chemical routes since tiny molecules are involved, but with the advantages of being less toxic. **Table 6** summarizes the work done in the matter of biosynthesis of S-NPs using plant extracts, biomolecules and viruses.

4.3.1 Plant Extracts

The use of plants represents an alternative way to synthesize NPs with different properties. One particularity of the biosynthesis of NPs using plants is that no high accumulation of macromolecules is present on the NPs produced, different from bacteria or fungi, that use to accumulate large amounts of molecules acting as capping agents, that may affect or change particle properties (Borovaya et al., 2016). On the other hand, use of plants could easily produce NPs due to no expensive and well established process needed or simple extracts from plants (da Costa et al., 2016).

Some studies about the metal resistance of plants have suggested the mechanism related to the formation of NPs with these organisms (Ali et al., 2020; Narender & Prasad, 1990; Seregin & Ivanov, 2001). In plants, metals' presence causes the generation of ROS, associated with the dysfunction of enzymes. To overcome these conditions, plants also produce stress-related enzymes, like superoxide dismutase and other biomolecules (Seregin & Ivanov, 2001). Metals in the plant cell tissues are sequestered by low molecular weight proteins, specifically interacting with their thiol groups (S-H). These proteins have been identified as metallothioneins-like proteins belonging to phytochelatins (PCs). The general structure of these cysteine-containing peptides is described as $(\gamma\text{-Glu-Cys})_n\text{-Gly}$, where n=2-11 (Narender & Prasad, 1990; Seregin & Ivanov, 2001). Process very similar to mycosynthesis of NPs studies in a past section. Besides, more bio-compounds are linked with the synthesis of NPs such as phenols, terpenoids, ketones, carboxylic acids, aldehydes, enzymes, amides, and flavonoid (Ali et al., 2020).

In the work of Borovaya et al. (2014), CdS QDs were produced employing extracts from *Linaria maroccana* hairy root cultures. The extract's solution was supplied with $CdSO_2$ and Na_2S for specific periods and stored at 28 °C. The resulting NPs consisted of spherical CdS QD with an average particle size of 5.5-6.9 nm; no suspected synthesis mechanism is described (Borovaya et al., 2014). The same research group demonstrated the biosynthesis

of water-soluble low toxic CdS QDs using cell suspension culture of *Nicotiana tabacum*. A similar process as the previous study is performed to produce CdS in a size range of 3-7 nm. Toxicity assessment was carried out evaluating the survival of *N. tabacum* protoplasts in the presence of NPs produced at low NPs concentration, namely 0.012 mg/mL or lower, no adverse effects occurred to the protoplasts (Borovaya et al., 2016). In another approach, spherical CdS NPs were biosynthesized using pomegranate peel extract (Kaviya, 2018). This extract was rich in phytochemicals which act as capping agents and stabilizer. The produced CdS NPs demonstrated to be excellent platform biosensors for detecting Pb^{2+} ions. CdS NPs produced using tea leaf extract (*Camellia sinensis*) were also tested as antibacterial, anticancer, and bioimaging in A549 cancer cells (Shivaji et al., 2018).

Two reports present the synthesis of CdS NPs employing the hairy roots of tomato *Solanum lycopersicum*, taking advantage of their high capacity to accumulate cadmium and lead metals compared to other plant organs (Al-Shalabi & Doran, 2016; Seregin & Ivanov, 2001). In two reports, fluorescent CdS NPs in a size range of 4-10 nm, with a high photostability level, were produced (Al-Shalabi, Stevens-Kalceff, & Doran, 2014)(Al-Shalabi & Doran, 2016). The synthesis mechanism was attributed to the binding between cadmium metal ions to phytochelatins (PCs), establishing metal-PC complexes that later resulted in CdS NPs' formation (Al-Shalabi & Doran, 2016; Al-Shalabi et al., 2014). Additionally, in the work of Al-Shalabi and Doran (2016) it is compared the CdS NPs synthesis between *S. pombe* yeast and *S. lycopersicum*. In short, yeast NPs were smaller, faster and higher Cd uptake rates are observed with this organism, but cell growth decreases in the presence of Cd. Considering *S. lycopersicum*, its growth rate was relatively low in comparison with yeast. Bigger and more photostable NPs were produced (4-10 nm), cell cultures did not suffer significant changes while cultured with cadmium (Al-Shalabi & Doran, 2016).

4.3.2 Biomolecules

To study the synthesis of NPs using specific biomolecules like enzymes, RNA chains, proteins, and others, is of paramount importance since it provides a better understanding of the mechanisms of various organisms able to bioproduce NPs. In the last years, researchers have demonstrated that specific biomolecules can mediate the synthesis of NPs. For example, transfer RNAs (tRNAs) as a scaffold and ligand system were used to synthesise CdS NPs

(Ma, Dooley, & Kelley, 2006). Wild type and mutated RNAs (WT-tRNAs and MT-tRNAs, resp) were produced and faced to solutions containing cadmium and sulfide ions (Ma et al., 2006). Spherical CdS NPs have synthesized with diameters between 4-7 nm, WT-tRNAs produced smaller particles and better-defined structure than MT-tRNAs because of structural changes in this last biomolecule (Ma et al., 2006).

Thanks to some studies, it was found that specific enzymes participate in the production of NPs (Dunleavy et al., 2016; Spangler et al., 2016; Yang et al., 2016). Sometimes, these are overproduced by the organisms when metal ions are present in the growth medium (Bai et al,. 2009b; Gallardo et al., 2014). It is the case of cystathionine γ-lyase (smCSE) which appeared to participate in the CdS NPs formation in (Spangler et al., 2016; Yang et al., 2016) and was employed by (Dunleavy et al., 2016) to study its ability to crystalize NPs. Dunleavy and colleagues purified smCSE enzymes from *S. maltophilia* SMCD1, later employed to synthesize CdS QDs using cadmium acetate and L-cysteine or Na_2S. This study demonstrated that the smCSE catalyzed L-cysteine is able to produce sulfide and could template CdS formation. Additionally, it was established that the impact of sulfide source and capping agent availability on the NPs growth time, stability, and size (Dunleavy et al., 2016). A similar approach presents the biomineralization of complex QDs employing the cystathionine γ-lyase (CSE) isolated from recombinant *E. coli* cells (Spangler et al., 2017). Biocompatible $CuInS_2$, $(CuInZn)S_2$ and $CuInS_2$/ZnS core/shell QDs were biosynthesized based on the essential activity of the CSE enzyme analogous to the previous work. $CuInS_2$/ZnS core/shell QDs were conjugated to IgG antibodies and successfully applied in the bioimaging of THP-1 cells that survived after the treatment showing the biocompatibility of NPs (Spangler et al., 2017).

4.3.3 Viruses

Like many other biological entities, viruses are not the exception and can result in green approaches focused on NPs' biosynthesis. A few reports show the production of NPs using viruses or specific proteins and capsids from these (Ahiwale et al., 2017; Slocik, Naik, Stone, & Wright, 2005). Unlike bacteria, fungi, or algae, manipulating viruses demands additional specific requirements like special isolation techniques and containment infrastructures that elevate economic costs of studies, therefore negatively impacting large-scale production (da

Costa et al., 2016). Regarding S-NPs synthesis using viruses, CdS and ZnS NPs have been produced, as described next.

Shenton et al. (1999) presented CdS nanotubes' formation by the accumulation of small CdS NPs around the Tobacco Mosaic Virus (TMV). The aggregation of small particles around viruses was probably mediated by the amino acid residues of capsid's proteins, such as glutamate, aspartate, arginine, and lysine. The resulting nanotubes consisted of approximately 50 nm in width, with about 16 nm thick electron-dense outer crust and an 18 nm diameter internal core (Shenton et al., 1999). In the same report, PbS nanotubes are similarly synthesized. In this case, nanotubes had 40 nm in width (**Table 6**). The coat protein pIII of the M13 bacteriophage was found to have an affinity to ZnS in a solution. The end pIII protein is used to attach to ZnS and agglomerated with other bacteriophages into a micelle-like structure; thus, ZnS NPs are synthesized inside this arrangement with a particle size of about 2.66 nm (Lee, 2002). M13 bacteriophage viruses were genetically modified to express the protein pVIII in the capsid, which was found to aggregate CdS and ZnS from solutions, resulting in the formation of nanowires of these two semiconductors (Mao et al., 2003). The same year, nanowire structuration based on ZnS and CdS compositions were demonstrated by expressing the two protein pIII and pVIII in the same viral capsid (Flynn et al., 2003), similar to the previous studies (Mao et al., 2003) and (Shenton et al., 1999).

Next, in **Table 5**, a generalized qualitative evaluation is provided concerning the synthesis of S-NPs employing the previously studied bioentities. This evaluation is performed according to the literature reviewed and the authors' criteria of the present work. It is important to consider that the information presented in **Table 5** does not represent all the cases. The performance and success of the biosynthesis of S-NPs depend on many factors that complicate an absolute qualification. Therefore, we suggest applying multivariate statistical analysis, mathematical models, or artificial intelligence, to analyze the extended available information. These types of analysis could help in the design of better processes for the production and control of the morphology, size, of S-NPs using bioentities.

Table 5. Qualitative evaluation of five variables considering the bioentities studied in this work. The qualification goes in the numeric scale from 1 to 5 and different color intensities. 1-white) Extremely low, insignificant; 2-silver) low, minor; 3-grey) Medium, moderated; 4-sky) almost high, advantageous; 5-blue) High, excellent.

	Bacteria	Fungi	Algae	Plant Extracts	Biomolecules	Viruses
Production Cost	3	2	4	3	5	5
Yielding rate	4	5	3	2	3	1
Reaction speed	5	5	4	3	4	3
Facility	4	5	3	4	2	1
Studied	5	4	1	2	2	2

Table 6. Biosynthesis of sulfur-based nanocrystals using plant extracts, biomolecules, and viruses

PLANT EXTRACTS						
Type	**Sorurce**	**Mechanism**	**Shape**	**Size (nm)**	**Application**	**Reference**
CdS	*Linaria maroccana*	Ext.	Spherical	1.5-8.5	-	(Borovaya et al., 2014)
	Nicotiana tabacum	Ext.	Spherical	3-7	-	(Borovaya et al., 2016)
	Solanum lycopersicum	Ext.	Spherical	4-10	-	(Al-Shalabi & Doran, 2016)
	Solanum lycopersicum	Ext.	Spherical	4-10	-	(Al-Shalabi et al., 2014)
	pomegranate peel extract	Ext.	Spherical	(~) 3, 10, 25	Pb2+ detection	(Kaviya, 2018)
	Camellia sinensis	Ext.	Spherical	2−5	Antimicrobial, bioimaging, Anticancer	(Shivaji et al., 2018)
BIOMOLECULES						
Type	**molecule**	**Microorganism**	**Shape**	**Size (nm)**	**Application**	**Reference**
CdS	RNA polynucleotides	*E. coli*	Spherical	4-7	-	(Ma et al., 2006)
CdS	cystathionine γ-lyase (smCSE)	S. maltophilia SMCD1	Spherical	2-4	-	(Dunleavy et al., 2016)
CuInS2	cystathionine γ-lyase (CSE)	E. coli	Irregular	~ 2,5	-	(Spangler et al., 2017)
$(CuInZn)S_2$	cystathionine γ-lyase (CSE)	E. coli	Irregular	5	-	(Spangler et al., 2017)
CuInS2/ZnS	cystathionine γ-lyase (CSE)	E. coli	Irregular	4	Bioimaging	(Spangler et al., 2017)
VIRUSES						
Type	**Virus**	**Location**	**Shape**	**Size (nm)**	**Application**	**Reference**
ZnS	M13 Bacteriophage	Prox. end	Spherical	~2,66	-	(Lee, 2002)
ZnS	Tobacco Mosaic Virus (TMV)	Capside	Nanotube	50 w. 16 t.	-	(Shenton et al., 1999)
CdS	Tobacco Mosaic Virus (TMV)	Capside	Nanotube	40 w.	-	(Shenton et al., 1999)
CdS, ZnS	M13 Bacteriophage	Capside	Nanowire	560x20	-	(Mao et al., 2003)
CdS, ZnS	M13 Bacteriophage	Capside	Nanowire	-	-	(Flynn et al., 2003)

Int.: Intracellular
Ext.: Extracellular
~: Approximately
w.: with
t.: thick

5. CONTROL OVER NANOPARTICLE BIOSYNTHESIS

S-NPs have been biosynthesized by many organisms and other bioentities as described previously. In fact, sometimes even synthesis using the same bio-organism can lead to very different NPs, highlighting that the source is not the only parameter to consider but many factors influence NPs' production (Dahoumane et al., 2017). Slight changes in these variables can tremendously affect the resulting NPs and properties. The research over the control of NPs production via green approaches is of paramount importance since biogenerated NPs have shown many interesting properties, opening new applications that with other conventional routes are limited.

The properties of NPs highly depend on the composition, morphology, size, stability, purity, among others. Commonly, in green synthesis, NPs are formed under ambient temperatures and atmospheric pressures, whereas parameters like pH, bioentitie, salt sources, biomass, time, and external reagents, could determine the effect on the different properties of the NPs (Bruna et al., 2019; Gong et al., 2007; Yue et al., 2016; Zhang & Huang, 2020)

In terms of shape, spherical NPs seem to be easily generated since this morphology is predominant, based on the information of **Table 1**,**Table 2**,**Table 3**,**Table 4**, and **Table 6**. According to several studies, many biomolecules act as mediators in synthesizing NPs and as capping agents that template sphere like NPs (Cunningham & Lundie, 1993; Dunleavy et al., 2016; Gallardo et al., 2019; Gallardo et al., 2014; Kushkevych et al., 2020; Yang et al., 2016). Studies describe that resulting NPs adopted spherical morphologies, but in many cases, TEM or SEM images are not shown; in other cases the images show NPs to be amorphous or irregular spheres (El-Shanshoury et al., 2012; Rajeshkumar et al., 2014; Yue et al., 2016; Zhu et al., 2016)

An interesting control over the biosynthesis of NPs is described in (Bruna et al., 2019). Bruna and colleagues (2019) produced fluorescent hexagonal CdS QDs with low size polydispersity and an average size of 3.6±0.8 nm employing the halophilic bacteria *Halobacillus* sp. DS2. **Figure 3** shows TEM images and the size histogram of the hexagonal S-NPs produced by Bruna et al. (2019). Briefly, the process was performed as follows. After 28 days of growth, bacteria were isolated and suspended in buffer Tris-borax citrate 50 mM pH 8.8, supplied with cysteine and cadmium chloride ($CdCl_2$) (Bruna et al., 2019). NPs isolated shown in

Figure 3 correspond to the synthesized after after 1 hour of reaction (Bruna et al., 2019). In other study, Gong et al. (2007) evaluate the synthesis of PbS NPs employing SRB at different pHs and temperatures. With a temperature of 30 °C and 48 h of incubation, it was produced NPs with a rod to spheroidal morphologies as the pH increases in the range of 6-8, appropriate for the growth of the bacteria used (Gong et al., 2007). Meanwhile, NPs formation occurred only with temperature variations in the range of 15-35 °C, showing no differences in morphology, structure, and size (Gong et al., 2007). Changes in the morphology of NPs by pH variations are attributed to the sulfide production of the SRB, due to OH^- affects the availability of sulfate (SO_4^{2-}) decreasing sulfide excretion (Gong et al., 2007). The biosorption of metal ions by the organisms is also related to the pH of the medium. It may disturb the cell membrane conformation, increasing or decreasing its biosorption rate and capacity (Zhang & Huang, 2020). Lower pHs could protonate the cell surface, while alkalinity might cause precipitation of metal ions combined with hydroxide ions (OH^-) (Zhang & Huang, 2020). Therefore, adjusting the pH can favor or not the biosynthesis of NPs since it impacts the bio entity and reaction solution (Zhang & Huang, 2020).

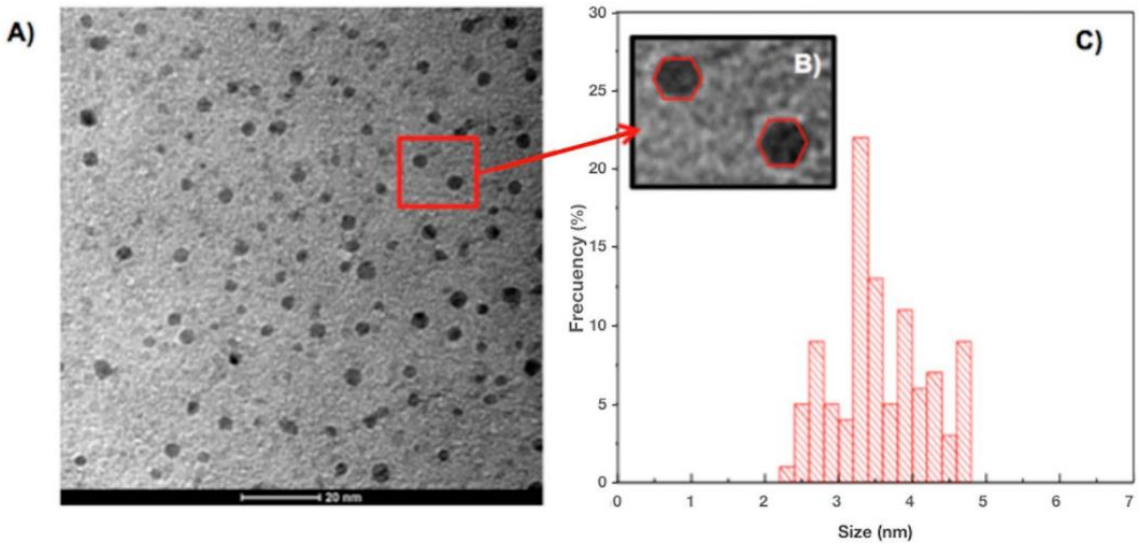

Figure 3. Example of hexagonal CdS QDs. **A**) Image from TEM analysis. **B**) Zoom from TEM image. **C**) Frequency size histogram of biosynthesized QDs. Extracted from (Bruna et al., 2019).

Sulfur source or sulfide production by the organisms is in some cases the factor for changing the morphology and size of the biogenerated NPs (Chen et al., 2014; Yue et al., 2016, 2014). To illustrate this, employing the sulfate reducing bacteria (SRB) *Clostridiaceae* sp., Yue et

al. (2016) reproduced an extracellular lead-sulfide (PbS) NPs synthesis with three different morphologies. The principle of their process was to supply the solution synthesis with polyethylene glycol (PEG) at different concentrations. 4, 12, and 20 mM of PEG were supplied to the experimental samples, resulting in the formation of cuboidal (50 x 50 x 100 nm), nanosheets (10 nm thickness), and nanospheres (60 nm), respectively, **Figure 4** shows TEM images of these shaped NPs. The synthesis was attributed to the production of sulfide (S^{2-}) ions by the bacteria, which was affected by the presence of PEG that inhibited the cell growth, upsetting the sulfur source production directly. Therefore NPs with different shapes and morphologies were produced (Yue et al., 2016).

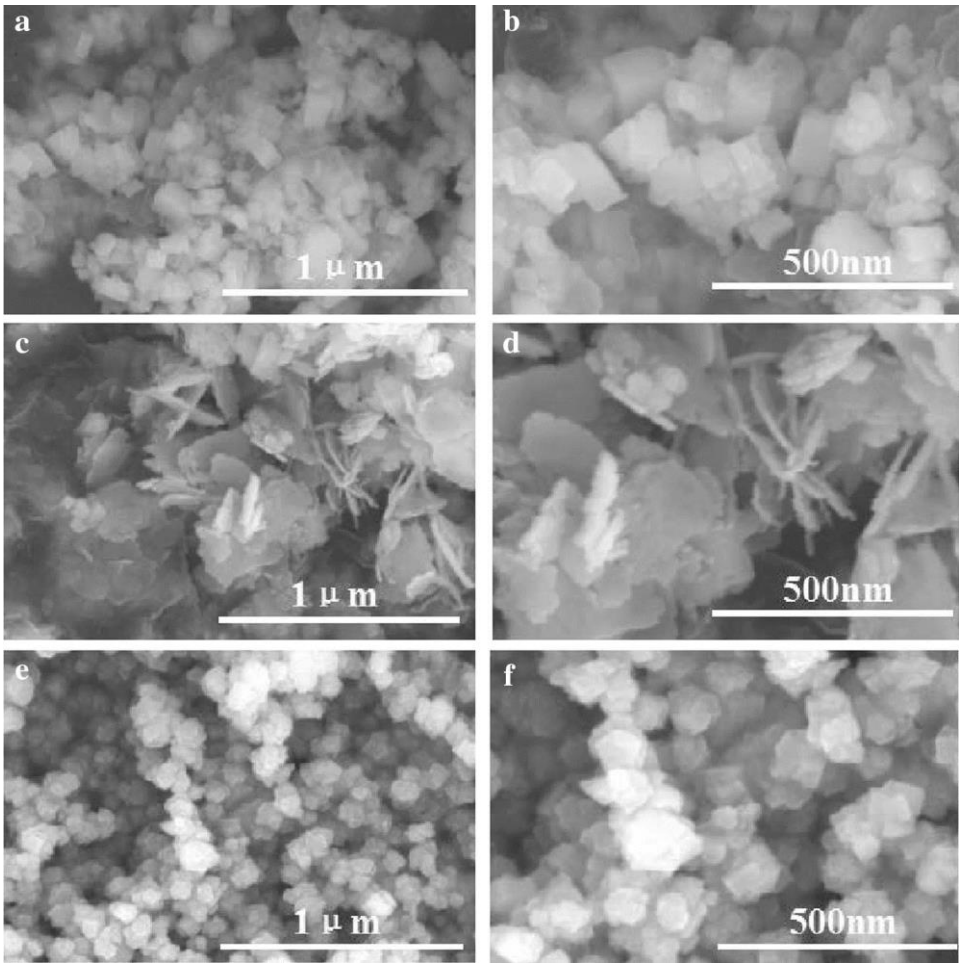

Figure 4. SEM images of biogenerated PbS NPs. a,b) Cuboidal NPs. c,d) Nanosheets. e,f) Nanospheres. Extracted from (Yue et al., 2016).

Yue et al, (2014) demonstrated the biosynthesis of Bi2S3 nanorods and nanoneedles by changing both lactic acid and Na_2SO_4 concentrations in the medium. **Figure 5** presents SEM

images of these two morphologies produced by changing lactic acid and Na_2SO_4 concentrations. High doses of these two reagents (0.3 mol/L) lead to the formation of nanorods, contrary to nanoneedles which were synthesized at lower doses (0.1 mol/L) (**Figure 5**). The process was performed using the water-oil two-phase system; particularly, the synthesis was executed in the water phase. Probably, the morphology difference was because the concentrations of lactic acid and SO_4^{2-} (from Na_2SO_4) promoted different speed rates generation of S^{2-} (Yue et al., 2014). Chen et al. (2014) present a size-controlled biosynthesis of CdS NPs using white-rot fungal strain *P. chrysosporium* (BKMF-1767). Here, NPs with sizes in the range of 1.5-2.0 nm were produced (average of 1.96 ± 0.1 nm). Thioacetamide (TAA, 99%) as S precursor, Cadmium nitrate tetrahydrate (99%) for Cd, pH of 9, 10, and 11, temperature 37°C, constantly stirred for 12 h. Proteins could be an important factor for forming, stabilizing, not agglomeration, and size controlling (Chen et al., 2014).

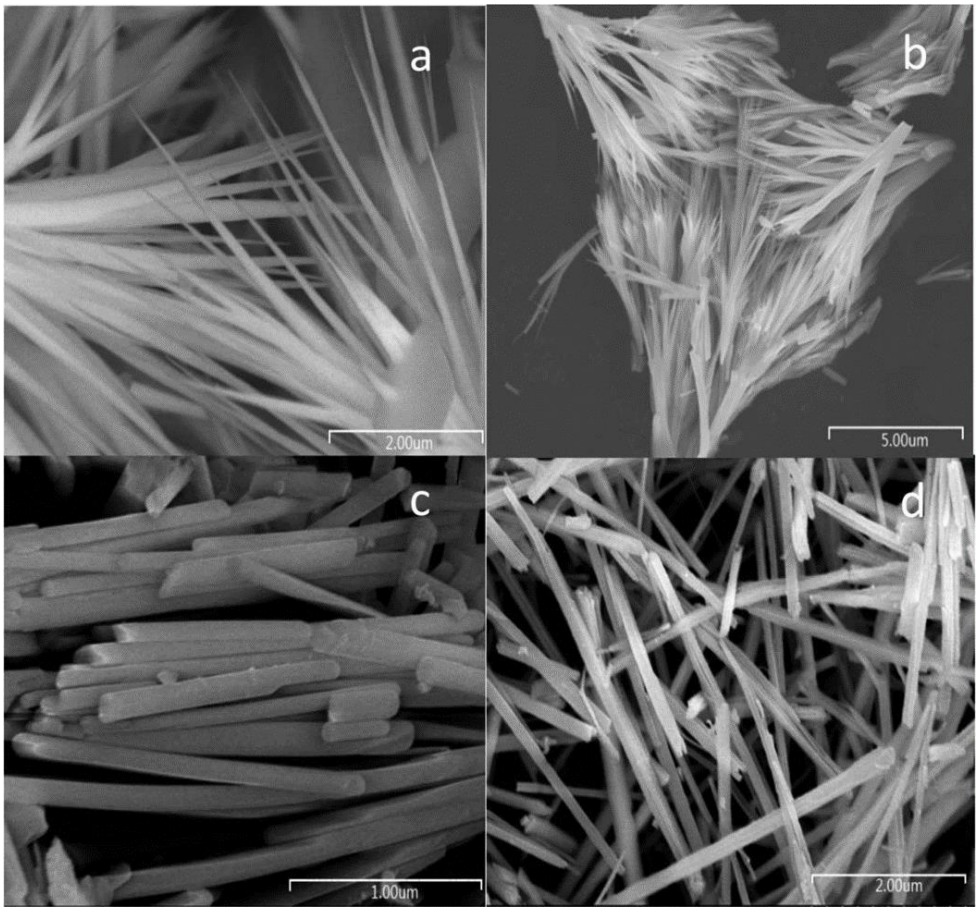

Figure 5. SEM images of Bi2S3 NPs changing both lactic acid and SO_4^{2-} concentration after 20 days of incubation. **a, b)** Nanoneedles formed at low concentrations. 2 and 5 μm scale bar respectively. **c, d)** Nanorods formed at high doses. 1 and 2 μm scale bar respectively. Taken from (Yue et al., 2014).

In another study, crystalline phases of the ZnS NPs varied in dependence of hydroxypropyl starch (HPS) concentration, at low concentrations (0.4 g/L or lower), wurtzite ZnS nanocrystals were formed with a hexagonal phase (Qi et al., 2017). In contrast, with high HPS concentrations (0.8 g/L or higher), sphalerite ZnS cubic phase crystals were produced. According to the TEM results, QDs formation occurs inside cavities of columnar structures held by HPS (Qi et al., 2017). The size of ZnS NPs was also inversely influenced by HPS, given that the particle increases or decreases in size with low and high HPS concentrations, respectively. QDs with the average particle size of 5.95 ± 1.13 nm were detected at an HPS concentration of 0.2 g/L, and meanwhile, at 1.6 g/L, the APZ was 3.34 ± 0.65 nm (Qi et al., 2017).

A great advantage of the green production of NPs is the high stability they achieve. This feature is attributed to the mechanisms performed in which several biomolecules participate in overcoming toxicity and the production and stabilization of the NPs. One of the biomolecules most commonly found on NPs' surface is L-cysteine, produced especially by bacteria and fungi (Dunleavy et al., 2016; Lei et al., 2020; Yang et al., 2015). In addition to its function as a capping agent, it is the source of sulfur through the catalytic activity of enzymes such as cysteine desulfhydrase, cysteine synthase, and cystathionine γ-lyase (smCSE) (Cunningham & Lundie, 1993; Dunleavy et al., 2016; Gallardo et al., 2019; Gallardo et al., 2014; Kushkevych et al., 2020; Yang et al., 2016)

Dunleavy et al. (2016) showed that the growth and stability of QDs also depend on the concentration of sulfide source and available capping agents. The production of CdS NPs was mediated by the single enzyme cystathionine γ-lyase (smCSE), catalyzing sulfide from L-cysteine and serving as a capping agent in periods no longer than 4 hours, CdS gets precipitated into bulk form if this time is exceeded. The addition of glutathione in the enzymatic medium allowed the NPs formation for longer times, especially at the glutathione concentration of 10 mM, reaching the maximum production at 24 hours of reaction (Dunleavy et al., 2016). In this case, sulfide was directly extracted from L-cysteine through

enzymatic activity, whereas glutathione increased the capping agent availability, thus increasing NP formation in concentration and stability in time. Furthermore, the addition of glutathione caused the formation of smaller NPs due to its capping role of these biomolecules (Dunleavy et al., 2016).

Many studies demonstrate that time is an essential factor for the growth of NPs and size increase. As a consequence of particle size variation, the NPs' optical properties change (Bruna et al., 2019; Órdenes-Aenishanslins et al., 2020; Qin et al., 2018); this can be confirmed with the evaluation of fluorescence emission spectra and UV-Vis emission spectra. Gallardo et al. (2019) showed an increase in the size of CdS NPs extracellularly synthesized. Cell-free growth medium from *P. fragi* GC01 was supplied with Cys 2 mM and $CdCl_2$ 20 μg mL^{-1}, sample fluorescence changed the coloration to green, yellow, and orange after 1, 2, and 3 hours of experiment, respectively. The average diameters of these QDs measured using TEM were 2.31 ± 0.51, 2.59 ± 0.71, and 2.59 ± 0.78 nm, in the same order. In the report of Yang et al. (2016), the sizes of CdS NPs changed from 2.75 nm to 3.36 nm after reaction times of 60 min and 300 min, respectively (Gallardo et al., 2019). Similarly, in Yang et al. (2015), the NPs' peak of absorption spectra increased from 312 nm to 378, and emission spectra changed from 460 nm to 562 nm as the reaction time increased (Yang et al., 2015). Similarly, Órdenes-Aenishanslins et al. (2020) produced spherical CdS QDs using the bacteria *E. coli* BW25113 changing the particle size by time control. **Figure 6** shows supernatant samples containing synthesized NPs emitting different fluorescent colors depending on the incubation time, shifting from green to yellow and red.

Metal and sulfur concentration also plays an important role in the size of the NPs. Yang et al. (2016) demonstrated that by changing the S:Cd ratio, the NPs size is affected notably, and optical properties changed. High concentration rates could affect the stability of NPs. It promotes aggregation between NPs or formation of bigger ones with low stability, also related to the capping agent's availability, such as L-cysteine (Yang et al., 2016). The same study presented the impact of pH on NPs biosynthesis and correspondent optical properties. It demonstrated that the biogenesis of NPs is strongly affected by changing the pH due to the appropriate conditions for the organisms or impact on biomolecules participating (Bruna et al., 2019; Ulloa et al., 2016; Yang et al., 2016).

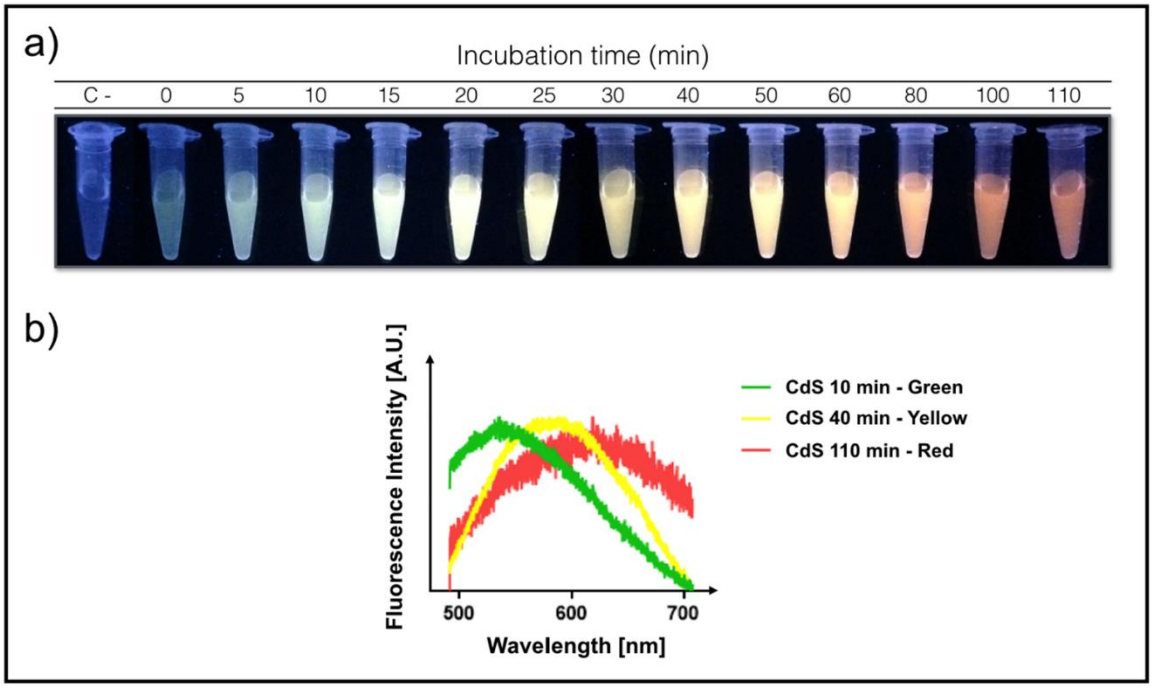

Figure 6. Changes in optical properties of CdS NPs produced at different times. a) Fluorescence emissions recorded at different incubation times. b) Fluorescence emission spectra at 10, 40 and 110 min. Taken from , (Órdenes-Aenishanslins et al., 2020)

To sum up, **Figure 7** describes specific factors that are significantly linked to the properties of biosynthesized S-NPs. For the size of the NPs, reaction time plays a relevant role. It has been demonstrated that synthesis occurs after some minutes, hours and even days, also dependent on other factors such as organisms or biomolecules. Generally, smaller particle size is achieved right after the synthesis begins, whereas bigger particles are formed in prolonged reaction times. Consider that prolonged reaction can produce aggregation followed by precipitation and loss of NPs stability (Dunleavy et al., 2016), being necessary to stop the bioentity activity mediating the biosynthesis and isolate the NPs.

Apart from that, morphology is another determinant property of NPs for their applications. Perhaps, spherical-shaped NPs are easier to produce, but it is possible to produce S-NPs with interesting morphologies such as cubic, nanoneedles, nanorods, nanotubes, nanowires, and others. Although it is not defined, it can be deduced that the bioentity used impacts the shape of the NPs, as well as the use of external reactants such as lactic acid (Yue et al., 2014) and PEG (Yue et al., 2016), and the concentrations of biomass, sulfur, and metal sources. Finally,

capping agents in the reaction solution are the main agents to provide stability to the NPs, also serving as matrices and templates to form NPs with distinct shapes and sizes.

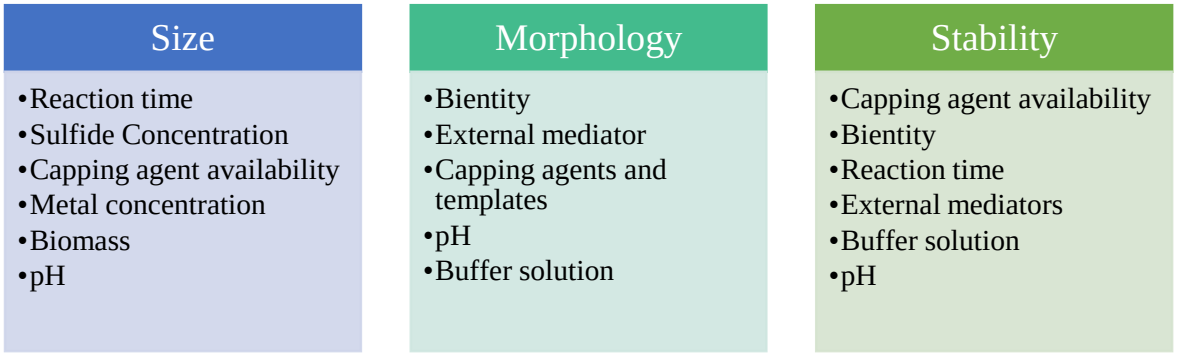

Figure 7. Principal factors affecting the size, morphology and stability of the biosynthesized S-NPs.

6. CHARACTERIZATIONS.

Once S-NPs are obtained, it is necessary to determine the physicochemical properties, which are obtained through characterization techniques such as X-ray diffraction (XRD), transmission electron microscopy (TEM), scanning electron microscopy (SEM), X-ray photoelectron spectroscopy (XPS), Ultraviolet-visible (UV-Vis) spectroscopy, Fourier-transform infrared (FTIR) spectroscopy and color change. This part focuses on explaining what information can be obtained from each technique.

6.1 XRD

One of the most used characterization techniques that provide the study material's crystallographic structure is X-ray diffraction, or XRD (Kamaraj et al., 2014). XRD measures the X-rays' intensities and scattering angles that leave the material after being irradiated by the X-rays (Artioli, 2017; Stanjek, 2004). These intensities are given in the form of diffraction peaks, which are indexed to different phases that correspond to the crystalline structures that the material forms (Artioli, 2017; Stanjek, 2004). For instance, the crystalline nature of CdS, ZnS, Ag_2S, PbS, Bi_2S_3 show characteristic diffraction peaks indexed to different planes such as cubic (Alsaggaf et al., 2020; Benavente et al., 2019), hexagonal (Kowshiket al., 2002), crystalline (Borovaya et al., 2016), amorphous (Newman et al., 1997), wurtzite (Sweeney et al., 2004; Yoon et al., 2012), sphalerite (Labrenz et al., 2000; Qi et al., 2017), among others (Lee et al., 2007; Sweeney et al., 2004; Yue et al., 2014). Additionally, identification of crystallinity phase allows to confirm or predict the morphology of the NP, also used to calculate the crystalline grain size (Bakhshi & Hosseini, 2016; Malarkodi et al., 2014; Murray et al., 2017; Tripathi et al., 2014; Zhang & Huang, 2020).

6.2 TEM and SEM

TEM and SEM techniques have been widely employed to study the resulting biosynthesized NPs. Although these techniques produce different type of images, in general they allow to detect-visualize the produced NPs, in that way analyze the size, morphology, dispersion and other properties of the samples (Hazra et al., 2013; Mourdikoudis et al., 2018; Uddandarao & Mohan, 2016). Particularly, since SEM consists on producing images from the reflection of electrons, it provides information about dispersion of the NPs (Mourdikoudis et al., 2018),

capping, agglomeration (Hazra et al., 2013; Uddandarao & Mohan, 2016), and size on NPs if these have larger particle size, such as S-NPs presented in the **Figure 4** and **Figure 5**, which particle size is around 60 nm and 100 nm respectively (Yue et al., 2016, 2014). On the other side, TEM images result by passing electrons through the sample (Mourdikoudis et al., 2018). This technique facilitates to observe internal structure of the NPs and crystallinity as well (Priyanka et al., 2017), measure particle size and visualize the shape on these (Bruna et al., 2019; Carrasco et al., 2021; Kamaraj et al., 2014), as the CdS NPs shown in **Figure 3** with an average particle size of 3.5 ± 0.8 nm, allowing also establish a frequency size histogram (Bruna et al., 2019).

6.3 UV-Vis

To identify the nature and to confirm the formation of S-NPs, quantitative measurements of the amount of radiation absorbed by the NPs are required, carried out using ultraviolet-visible spectroscopy (UV-Vis) (Hosseini & Sarvi, 2015; Yadav, 2005). This technique provides valuable information about optical properties, size, concentration, agglomeration state, and hints on NP shape (Borovaya et al., 2015; Mourdikoudis et al., 2018). **Table 7** presents examples of UV-Vis absorption wavelengths, morphology and size of some S-NPs. Absorption wavelengths are also dependent on the particle size and morphology (Al-Shalabi et al., 2014; Spangler et al., 2017). Thus, in the characterization of CdS NPs and ZnS NPs, strong absorption peaks of approximately 280 to 450 nm (Bruna et al., 2019; El-Shanshoury et al., 2012; Gallardo et al., 2019), and 205 to 420 nm (Hazra et al., 2013; S. Qi et al., 2017; Uddandarao & Mohan, 2016), have been identified in the UV spectrum, respectively, confirming the formation of CdS and ZnS NPs. In the same way, for PbS, CuS and Ag2S NPs, absorption peaks of 325, 320 and 295 to 400 nm have been obtained, respectively (Hosseiniet al., 2012, 2013; X. Liu et al., 2015; Seshadri et al., 2011; Sureshet al., 2011; Yue et al., 2014)..

Table 7. UV-Vis absorption wavelengths, morphology and size of different S-NPs.

Type	UV-Vis absorption λ (nm)	Morphology	Size (nm)	Reference
CdS	419.5, 381.5, 362.5	Spherical	2.5-5.5	(El-Shanshoury et al., 2012)
	360	Cubic	(~) 2.31	(Gallardo et al., 2019)
	370	Cubic	(~) 2.59	

	380	Cubic	(~) 16	
	360	Hexagonal	2-5	(Bruna et al., 2019)
	394-475	Spherical	5-200	(Smith et al., 1998)
	280-300	Spherical	4-10	(Al-Shalabi et al., 2014)
	453	Spherical	4-5	(Borovaya et al., 2015)
	368	Spherical	(~) 5.1	(Tripathi et al., 2014)
ZnS	205	Spherical	(~) 5.16	(Qi et al., 2017)
	210	Spherical	(~) 5.95	
	210	Spherical	(~) 3.34	
	220	Spherical	(~) 4.29	
	320-340	Spherical	12-24	(Uddandarao & Mohan, 2016)
	250-330	Spherical	10-15	(Hazra et al., 2013)
	280-320	Spherical	42	(Mirzadeh et al., 2013)
PbS	300	Spherical	35-100	(Priyanka et al., 2017)
	348	Spherical	(~) 3.8	(Bai & Zhang, 2009)
	535	Spherical	(~) 10.8	(Bai & Zhang, 2009)
CuS	400	Spherical	2-5	(Hosseiniet al., 2012)

6.4 FTIR

For the study on NMs, FTIR technique allows the acquisition of information about the surface composition and ligand binding present in the NPs (Mourdikoudis et al., 2018). Therefore this technique is widely utilized for the characterization of NPs generated by means of biological systems (Bhadwal et al., 2014; Priyanka et al., 2017; Uddandarao & B, 2016). FTIR helped to analyze the composition and surface chemistry of the biosynthesized S-NPs, at the same time allowing to identify specific biomolecules in the process of biosynthesis (Priyanka et al., 2017; Qin et al., 2018). Therefore, the most detected absorbance bands in CdS NPs correspond to bond stretching such as carboxyl-amine (-OH, -NH) (Bhadwal et al., 2014; Chen et al., 2014; Tripathi et al., 2014), carbon-isonitrile (-C≡C, -N=C) (Sanghi & Verma, 2009; Tripathi et al., 2014), amine II (-NH) (Chen et al., 2014a; Malarkodi et al., 2014; Tripathi et al., 2014), ether-ester (-CO) (Bhadwal et al., 2014; Sanghi & Verma, 2009; Tripathi et al., 2014), carbon-hydrogen (-CH) (Bhadwal et al., 2014; Tripathi et al., 2014), Sulfur bonds (-CS, -SH) (Sanghi & Verma, 2009), and -CI (Sanghi & Verma, 2009; Tripathi et al., 2014). **Table 8** presents the wavenumber peaks (cm^{-1}) of chemical species found on

the surfaces of different types of S-NPs. To illustrate, Bruna et al. (2019) were able to identify covalent bonds between thiol groups and the metal of the NPs, similar to Uddandarao et al. (2016) confirmed the presence of cysteine and methionine residues in the surface of ZnS NPs, justifying the participation of biomolecules in the synthesis of S-NPs (Bruna et al., 2019; Qin et al., 2018; Uddandarao & B, 2016).

Table 8. Different FTIR peaks found on biogenerated S-NPs.

NP	Chemical species	Molecule	Wave number (cm^{-1})	References
CdS	-OH, -NH	Carboxyl, amine	3920-3217	(Bhadwal et al., 2014; Bruna et al., 2019; Chen et al., 2014; Tripathi et al., 2014)
	-C≡C, -N=C	Carbon, isonitrile	2190-2105	(Sanghi & Verma, 2009; Tripathi et al., 2014)
	-N-H	Amine II	1560-1536,1008,780	(Bai et al,. 2009b; Chen et al., 2014; Malarkodi et al., 2014; Sanghi & Verma, 2009; Tripathi et al., 2014)
	-C-H	-	141-1365	(Bhadwal et al., 2014; Sanghi & Verma, 2009; Tripathi et al., 2014)
	-C-O	Ether and ester	1286-1072	(Bhadwal et al., 2014; Sanghi & Verma, 2009; Tripathi et al., 2014)
	-C-H	Tyrosine, tryptophan	825,742	(Sanghi & Verma, 2009)
	-C-S, -S-H	Cysteine, methionine	921,715,663	(Sanghi & Verma, 2009)
	-C-I	-	500-322	(Sanghi & Verma, 2009; Tripathi et al., 2014)
CdS, ZnS, Ag2S	-CH	Phenols, alcohols	3434-2357	(Bhadwal et al., 2014; Malarkodi & Annadurai, 2013; Sanghi & Verma, 2009; Sureshet al., 2011)
	-C=O	Amine I	1735-1640	(Bhadwal et al., 2014; Bruna et al., 2019; Chen et al., 2014; Chelladurai Malarkodi & Annadurai, 2013; A. K. Suresh et al., 2011)
	C=C, -C-N	Aromatic amine	1536-1382	(Bai et al,. 2009b; Chen et al., 2014; Malarkodi et al., 2014)
	-C-N	Aliphatic amine	1309-1040	(Bai et al,. 2009b; Bhadwal et al., 2014; Chen et al., 2014; Malarkodi et al., 2014; Malarkodi & Annadurai, 2013; Sanghi & Verma, 2009)
	-N-H	Amine II	1560-1536	(Malarkodi et al., 2014; Sureshet al., 2011)
	-C-Cl	-	711,619	(Malarkodi et al., 2014; Tripathi et al., 2014)
	-C-Br	Bromoalkane	592-505	(Bhadwal et al., 2014; Malarkodi & Annadurai, 2013; Tripathi et al., 2014)
Ag2S	-	Amine III	1355-1243	(Sureshet al., 2011)

6.5 Color

According to several authors, one of the indicators of metallic sulfide NPs' production is a physical change (color) that occurs at the moment of the reaction. Basically, the coloration produced corresponds to the complementary wavelength absorbed in the UV-vis tests (Abd Elsalam et al., 2018; M. Borovaya et al., 2015; Sandoval et al., 2017; Spangler et al., 2016; Zhang & Huang, 2020). The color changes according to the type of biosynthesized NPs. Thus, in the biosynthesis of CdS NPs, a color variation from orange to yellow is evidenced, and ZnS NPs production, the color differs from yellow to white (Abd Elsalam et al., 2018; M. Borovaya et al., 2015; Murray et al., 2017; Sandoval et al., 2017). On the other hand, for the generation of NP from CuS, Ag_2S and As_2S_3, color changes of greenish-black, dark brown and yellow are evidenced, respectively (Hosseiniet al., 2012, 2013; Jiang et al., 2009; Lee et al., 2007; Sureshet al., 2011). Moreover, in biosynthesized Bi_2S_3 NPs and Fe_3S_4 NPs, a dark brown color was observed (Bharde et al., 2008; Kamaraj et al., 2014). **Table 9** presents various coloration changes observed in the reaction solution during the formation of different S-NPs

Table 9. Visual characterization of the S-based nanoparticles formation

Nanoparticle	Color	Reference
CdS	Orange / Yellow	(Abd El-Raheem R. El-Shanshoury, 2012; Abd Elsalam et al., 2018; Borovaya et al., 2015; Prasad & Jha, 2010)
	Yellow	(Ahmad et al., 2002; Borovaya et al., 2014; Chen et al., 2014; Cunningham & Lundie, 1993; Malarkodi et al., 2014; Mandal et al., 2016; Sandoval et al., 2017; Sanghi & Verma, 2009)
PbS	Brown	(Spangler et al., 2016)
	Black	(Zhang & Huang, 2020)
ZnS	Yellow / White	(Malarkodi et al., 2014; Malarkodi & Annadurai, 2013; Murray et al., 2017)
Fe_3S_4	Dark brown	(Bharde et al., 2008)
Ag_2S	Deep brown	(Sureshet al., 2011)
As_2S_3	Yellow	(Jiang et al., 2009; Lee et al., 2007)
Bi_2S_3	Dark brown	(Kamaraj et al., 2014)
CuS	Greenish black	(Hosseiniet al., 2012, 2013)
$CuInS_2$	Yellow, orange, red	(Spangler et al., 2017)
$(CuInZn)S_2$	Yellow	(Spangler et al., 2017)

6.6 Other techniques of characterization

More techniques of characterization are employed with the purpose of obtaining more information about the composition, shape, dispersion, size distribution, surface chemistry and confirm the biosynthesis of S-NPs (Mourdikoudis et al., 2018). For example, Photoluminescence spectroscopy (PL) is highly applied to characterize QDs and measure optical properties and therefore apply the S-NPs, such as for fluorescence-based biosensors (Priyanka et al., 2017). Chemical composition of the CdS NPs and their capping was characterized by Bruna et al. (2019) emproying the X-ray photoelectron spectroscopy (XPS) (Bruna et al., 2019). In another work, Energy-dispersive X-ray spectroscopy (EDS or EDX) was used to confirm the chemical composition of CdS QDs (Giovanni Ulloa et al., 2018). Apart from TEM, Ulloa et al. (2016) used the Dynamic light scattering (DLS) technique to identify the size of CdS NPs in different ranges in agreement with TEM (G. Ulloa et al., 2016).

7. BIOMEDICAL APPLICATIONS

NMs have shown to be highly beneficial in medicine and are successfully used for biomedical applications. Some NPs have already been approved to treat, cure, or diagnose diseases for clinical uses, while many other NPS continue to emerge in research stages (Ventola, 2017). There are many fields in which NPs have shown promising results, for example, tumor research (McHugh et al., 2018; Miyashita et al., 2016; Owais et al., 2011), bioimaging (Gao et al., 2005; Yue et al., 2016), drug delivery (D. Yang et al., 2016), photodynamic therapy (Fakayode, Tsolekile, Songca, & Oluwafemi, 2017), and antimicrobial activity (Abd Elsalam et al., 2018). Among the S-based NPs described here, several reports describe the use of these bio-products for specific bioapplications, being almost all NPs classified as QDs. QDs are three-dimensional fluorescent semiconductor NPs with diameters ranging between 1-10 nm and spherical morphology. These particular NPs have been successfully applied in optoelectronic devices, sensors, and photocatalysts, for example. In the last decade, research interest has been focused on using QDs in the biomedical field (Abdel-Salam et al., 2020).

For medical applications, the NPs have to overcome strict requirements. Water solubility, or hydrophilicity, is essential in these materials because it will interact with aqueous systems in the body (animal or human) and disperse to target tissues. Surface chemistry, functional groups, and charge are fundamental to avoid being recognized by the immune system and being eliminated. Additionally, functional groups directly affect NPs' stability, it is imperative to consider the nature of ligands, such as hydrophobicity, hydrophilicity, or amphiphilicity, to avoid NPs aggregation and improve stability (Fakayode et al., 2017; McHugh et al., 2018). Studies published during the last years have demonstrated promising biosynthesized S-bases NPs applied in biomedical fields, especially for cancer research (Alsaggaf et al., 2020; Shivaji et al., 2018), bioimaging (Borovaya et al., 2020; Qi et al., 2016), antimicrobial activity (Gahlawat & Choudhury, 2019; Uddandarao & Mohan, 2016; Wang et al., 2017), and bioremediation (Mashkoor & Nasar, 2020; Rao & Pennathur, 2017).

7.1 Research in Cancer Treatment

Cancer is a disease resulting from the uncontrollable cell growth that can invade many parts of the body (McHugh et al., 2018). This disease has been investigated worldwide for a long time, despite that, there is still no effective cure developed, therefore cancer research is highly

necessary for the design of new technologies to treat, diagnose and cure cancer (McHugh et al., 2018). It has been observed that drug accumulation in target cancer sites of common treatments can reach less than 0.01% while employing NPs this value could increase to 1% to 5% (Wolfram et al., 2015). Available drugs that employ nanotechnology (nanodrugs) have been demonstrated to be efficient and with potential safety benefits because of enhanced drug administration to target tissues (Ventola, 2017). For example, Doxil ® is the first nanodrug approved by the Food and Drug Administration (FDA) for the treatment of Kaposi's sarcoma in patients with human immunodeficiency virus (HIV), although many adverse effects have been registered, after than 20 years from its approval it is still used for the original indication and other types of cancer (Ventola, 2017). Similarly, there are other nanodrugs approved with increased benefits than typical drugs such as Abraxen for breast cancer treatment and Rapamune as an immunosuppressant (Ventola, 2017).

The studies of Shivaji et al. (2018) and Alsaggaf et al. (2020) are the only ones which present approaches for cancer treatment using S-NPs (Alsaggaf et al., 2020; Shivaji et al., 2018). In the work of Shivaji et al. (2018), cytotoxicity tests were performed using the human lung alveolar basal epithelial cell line (A549) treated with the biosynthesized CdS QDs and cisplatin, a standard drug used to treat different cancers like testicular cancer, ovarian cancer, cervical cancer, breast cancer, bladder cancer, and others (Shivaji et al., 2018). The cell viability of A549 treated with CdS QDs and cisplatin at concentrations of 10, 20, 30, 40, and 50 μg/mL after 24 h were evaluated, at 20 μg/mL or higher concentrations, unlike cisplatin, QDs produced more significant cell inhibition (Shivaji et al., 2018). Shivaji and colleagues (2018) stated that QDs could affect DNA replication, at the same time, inhibit the enzyme function causing cell apoptosis. Different fluorescence colors were recorded with cells treated with 0, 10, 25, and 50 μg/mL of CdS after the test (Shivaji et al., 2018). Green fluorescence belonged to non-treated cells, while yellow, red, and orange colors appeared in cells treated with higher concentrations (Shivaji et al., 2018). In a similar approach, Alsaggaf et al. (2020) determined the inhibitory concentration IC50 for three carcinogenic cell lines: MCF7, PC3, and A549, being 190 $\mu g \cdot mL^{-1}$, 246$\mu g \cdot mL^{-1,}$ and 149 $\mu g \cdot mL^{-1}$, respectively. They established that inhibitory response is due to the oxidative environment produced by the release of metal ions from CdS NPs (Alsaggaf et al., 2020).

7.2 Bioimaging

In the bioimaging field, QDs are preferred because of the superior fluorescent properties (Abdel-Salam et al., 2020). Fluorescence of QDs can reach intensities more than ten times greater than traditional fluorescent dyes, besides presenting higher brightness and improved photostability due to lower photobleaching compared to organic dyes (Abdel-Salam et al., 2020; McHugh et al., 2018). In that sense, QDs have been extensively utilized for biomedical interests, principally in the bioimaging field (Feng et al., 2018; Órdenes-Aenishanslins et al., 2020; Shivaji et al., 2018). These NPs present a wide emission range of visible and infrared wavelengths depending on the size, shape, and composition, which favors the application in this field (Gao et al., 2005). Following are described a few approaches of biogenerated S-based NPs for bioimaging.

Some reports show that biosynthesized NPs can be used to visibly detect certain specific organisms and even plant cells. As follows, Qi et al. (2016) developed a specific method for specific bacteria detection. The organisms used were *P. aeruginosa*, *E. coli*, *S. aureus*, *V. alginolyticus*, and SRB, and for each culture, cadmium ions were introduced, and fluorescence analysis was performed after two days (Qi et al., 2016). Their results indicate that no obvious fluorescence emission was detected for bacteria, except for SRB, in which high fluorescence intensity was detected. SRB was able to produce CdS NPs that tend to accumulate at their cell wall, in that way contributing to the SRB detection using fluorescence (Qi et al., 2016). Imaging plant tissues using bioproduced S-based NPs is also possible. For example, Borovaya et al. (2020) demonstrated the imaging of *Allium cepa* epidermal root cells employing biproduced Ag_2S NPs. The cells treated with these NPs produced luminescence in the visible green spectrum (520-550 nm) (Borovaya et al., 2020).

Moving forward, many reports presented in the past sections have shown that biogenerated S-based NPs can be applied successfully for *in vitro* bioimaging of specific cells. To illustrate this, it was possible to image human breast adenocarcinoma cell line (MCF-7) thanks to the optical properties of CdS and CdTe QDs produced using *Rhizopus stolonifer* fungi (Mareeswari et al., 2016). Similarly, it was possible to produce ternary QDs (CdSAg) employing *E. coli* and used for labeling HeLa human cells, which provided fluorescence responses in the near-infrared region, allowing to visualize cells without evoking morphology

changes (Órdenes-Aenishanslins et al., 2020). In a novel approach, $CuInS_2$/ZnS core/shell QDs biosynthesized utilizing the single enzyme cystathionine γ-lyase (CSE) were functionalized and used for bioimaging. Core/shell NPs demonstrated excellent photoluminescence, later conjugated with IgG antibodies for specific binding to epidermal growth factor receptor (EGFR) of the THP-1 leukemia cells (Spangler et al., 2017). Functionalized QDs bound to specific sites of the THP-1 cells after incubation of 1 h, unlike non-conjugated QDs, in which no specificity in binding was seen in confocal microscope images (Spangler et al., 2017). Besides, the quality of living cells was evaluated every 20 min for 6 hours, observing that the imaging process or QDs did not cause adverse or toxic effects on THP-1 cells (Spangler et al., 2017).

7.3 Antimicrobial Activity

Standard antimicrobial tests performed with NPs are the agar-disk diffusion method and the agar well diffusion method (Abd Elsalam et al., 2018; Alsaggaf et al., 2020; Malarkodi et al., 2014). Both methods are based on the culture of the microorganism to be evaluated in agar plates (Balouiri, Sadiki, & Ibnsouda, 2016). In the first case, filter paper disks containing the test compound (NPs) at a certain concentration are placed on the agar surface, whereas in the second, holes are purchased from the agar where the test compound will be placed (Balouiri et al., 2016). The mechanisms for antimicrobial activity start with the interaction of NPs with the cell wall of the microbes (Borovaya et al., 2020; Malarkodi et al., 2014; Rajeshkumar et al., 2014). At this level, electrostatic interactions occur by the differences of electrical charges of the negatively charged cell membrane and NPs. This interaction produces conformational changes on the cell membrane, therefore affecting permeability and other vital metabolisms pathways (Borovaya et al., 2020; Rajeshkumar et al., 2014). It has been shown that NPs can enter inside the cells, producing adverse effects on the cells' enzyme function and over genetic material (Shivaji et al., 2018; Wang et al., 2017). Consequently, protein translation from DNA is irreversibly affected, resulting in cell death (Wang et al., 2017). Besides these, NPs can release metal ions to the environment, which also can enter the cell, inducing the formation of free radicals like reactive oxygen species (ROS) producing lethal conditions (Gahlawat & Choudhury, 2019; Uddandarao & Mohan, 2016; Wang et al., 2017).

NPs have been widely used as antimicrobial agents (Wang et al., 2017). This approach is particularly promising due to the potency to inhibit the growth of the organisms and as a substitute of antibiotics (Tripathi & Chung, 2019; Wang et al., 2017). Thus, the application of NPs could reduce the economic costs associated with cleaning, disinfection, sterilization methods, and antibiotics, therefore preventing undesired adverse effects. As presented in this section, biogenerated S-base NPs have also been applied *in vitro* for antimicrobial studies, showing favorable results (Alsaggaf et al., 2020; Rajeshkumar et al., 2014; Shivaji et al., 2018; Uddandarao & Mohan, 2016).

Rajeshkumar et al. (2014) performed antibacterial tests with the bioproduced CdS and ZnS NPs against four oral pathogens: *Streptococcus* sp. *Staphylococcus* sp. *Lactobacillus* sp., and *Candida albicans* (Rajeshkumar et al., 2014). The well diffusion method was implemented, and the diameter zone of inhibition around wells containing NPs was measured to interpret the antibacterial activity of NPs (Rajeshkumar et al., 2014). In general, CdS and ZnS produced considerable zones of inhibition without exception; these diameters varied between 10-25 mm depending on the concentration of NPs and pathogens (Rajeshkumar et al., 2014). According to Rajeshkumar and colleagues, the NPs get impregnated to the pathogen cell membrane which at the same time discharge toxic ions to the cell and interrupt important proteins for their metabolism, thus inhibiting cell growth (Rajeshkumar et al., 2014). Another study demonstrated that ZnS NPs biosynthesized by Uddandarao and Mohan B (2016), produced apoptosis to *E. coli* bacteria. The mode of action to produce this effect starts in the releasing of metal ions from NPs, which interact with cells and produce ROS causing lethal conditions and consequently cell death (Uddandarao & Mohan, 2016).

Although it is known that the primary mode of action of antimicrobial activity is produced by NPs, detailed mechanisms are not yet completely understood. It appears that some organisms have better resistance than others, or particular species are not affected. For instance, synthesized fungus-mediated CdS NPs inhibit the cell growth principally on gram-negative bacteria (*E. coli* and *Proteus vulgaris*) and gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*), while no affection was seen against *Candida albicans* yeast (Alsaggaf et al., 2020). Comparable with Borovaya et al. (2020), their biosynthesized Ag_2S NPs produced higher antibacterial activity against gram-negative bacteria *E. coli* (90 %) and low

inhibition against gram-positive bacteria *B. thuringiensis* (70%). It is believed that bactericidal effects are caused by free radicals present on the NPs surface, producing functional abnormalities in the bacterial membrane (Borovaya et al., 2020). In other work, CdS NPs synthesized by a plant extract demonstrated to be effective for growth inhibition against Gram-positive (*S. pyogens* and *S. aureus*) and Gram-negative (*E. coli*, *S. marcescens*, *K. pneumoniae*) bacteria. According to the authors, small particle size favored bacteria cell wall penetration and absorption, producing lethal effects to the cells around wells charged with NPs (Shivaji et al., 2018).

7.4 Other Applications

Besides the previous bio-applications, some studies tested the biogenerated S-NPs to be utilized in other fields. Some S-NPs have demonstrated excellent electric properties; therefore, exciting results have been used in solar cells (Carrasco et al., 2021; Órdenes-Aenishanslins et al., 2019; Wu et al., 2015) or diode fabrication (Meenal Kowshik et al., 2002). For instance, CdS/CdSe Core/Shell QDs synthesized employing *E. coli* were tested in solar cells as photosensitizer materials and compared with other QDs. Core/shell QDs with an average size of 16.7 nm demonstrated improved photovoltaic parameters compared to CdS, and CdTe QDs produced by biological and chemical routes, respectively (Órdenes-Aenishanslins et al., 2019). The previous and other studies suggest that core/shell NPs produce better results than simple S-based NPs as photosensitizers in solar cells (Carrasco et al., 2021; Órdenes-Aenishanslins et al., 2019; Spangler et al., 2016). Even though these NPs worked effectively, the efficiencies are not comparable to materials currently used in the electronic field.

S-NPs could sense metal ions in aqueous solutions, like Pb^{2+}, and arsenic ions. CdS QDs synthesized using pomegranate peel extract demonstrated a selective detection of Pb^{2+}. NPs fluorescence was redshifted in the presence of Pb^{2+} ions and at different concentrations. It is believed that Pb ions interacted with capping agents on the NPs surface, therefore aggregating at this place and producing optical changes in samples (Kaviya, 2018). Similarly, biogenerated PbS NPs could detect elevated concentrations of As (III), even in the presence of other metal ions at reduced concentrations. Results suggest that As bound to cysteine thiol

groups present on the NPs surface (Priyanka et al., 2017). These reports open future utilization of biosynthesized NPs as biosensors for metal ions detection in water.

Furthermore, biogenerated S-based NPs have been studied for their potency to remove contaminants in water. Nanocrystals have shown the capacity to catalyze methylene blue dye (MB), a dangerous chemical highly utilized and released into the environment, causing severe ecosystem and health problems (Mashkoor & Nasar, 2020). Different NPs shapes produced by Yue et al. using *Clostridiaceae* sp. SRB were tested to degrade MB by photocatalysis using UV light. Cuboidal NPs performed the best catalytic activity removing the dye completely within 20 hours of UV light irradiation. Surface, size, and shape played essential roles in this study (Yue et al., 2016).

Another work also demonstrated that biogenerated CdS NPs were able to reduce the concentration of MB in water. These NPs mediated hydroxyl radicals' production from water that acts as oxidizing agents converting methylene blue into a harmless form (Rao & Pennathur, 2017). In addition to this, the process of generating NPs using bacteria, fungi, and algae represents a natural bioremediation mechanism. In this sense, through the action of enzymes, amino acids, and other biomolecules, the microorganisms interact with metals in the environment, converting them into S-based NPs with reduced toxicity, overcoming stress conditions, and cleaning the environment. Coming up next, in the **Figure 8** are summarized the fields in which biosynthesized S-NPs have been applied and relevant properties to consider.

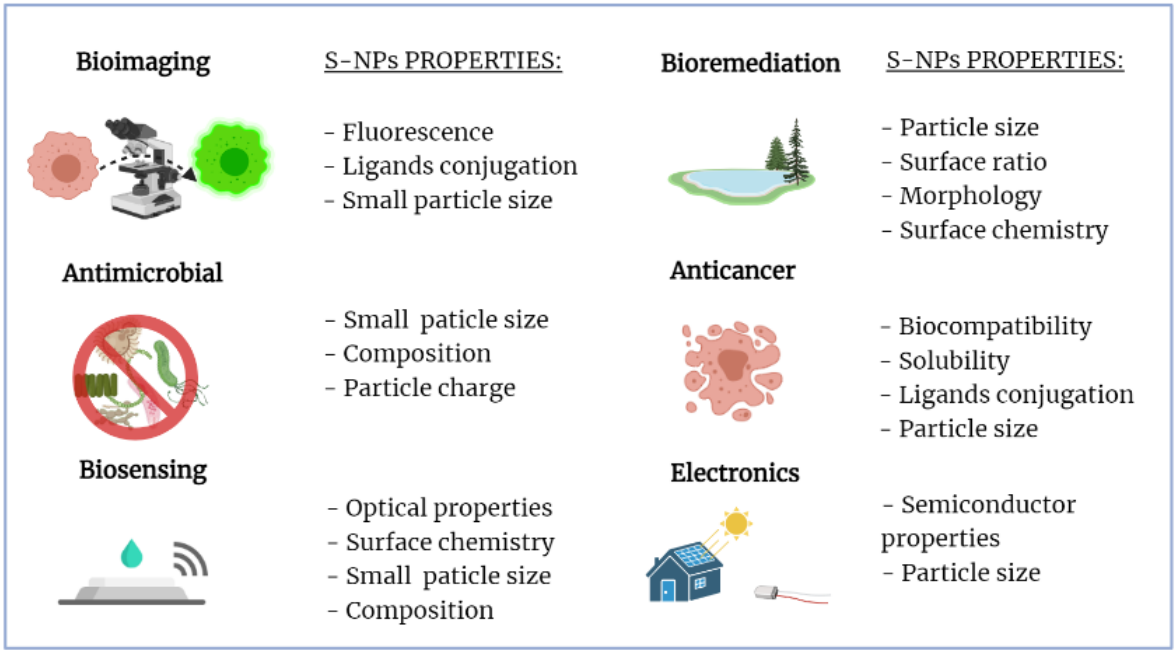

Figure 8. Applications of biosynthesized S-NPs and their properties to consider for being utilized in each field. Created in BioRender.com

8. CONCLUSIONS

To conclude, it has been shown that the biosynthesis of S-NPs can be mediated by several biological systems, which in this work have been classified as living organisms and nonliving organisms. In many cases, the biosynthesis of S-NPs has occurred without the use of sulfide salts because it can be synthesized from certain pathways, enzymatic activity, and the participation of peptides rich in cysteine and thiol groups. In living organisms, synthesis can occur within cells (intracellular) or outside cells (extracellular). The extracellular biosynthesis of S-NPs proves to be economically favorable because the process can occur using cell-free extracts, and the cellular biomass can be reused. On the other hand, intracellular synthesis is a process in which biomass cannot be reused since the NPs purification process requires cell lysis. The use of non-living organisms is also essential for a better comprehension of the processes for the biosynthesis of S-NPs, which also opens up more future research using bioentities not yet applied.

The literature reviewed here has shown successful biosynthesis of S-NP using single biomolecules, confirming the participation of these bioentities in the synthesis of NPs. In particular, the enzyme cystathionine γ-lyase enzyme stands out for producing monodispersed and complex quantum dots with smaller sizes (**Table 6**), and for its function as a template, capping agent and stabilizer (Dunleavy et al., 2016; Spangler et al., 2017). This approach could be applied with other biomolecules related to the synthesis of S-NPs using microorganisms, such as phytochelatins and phycocyanins (Dameron et al., 1989a; Dameron & Winge, 1990; Suresh et al., 2009). Phycocyanins served as mediators, template, and stabilizer of NPs in the work of (M. Suresh et al., 2009). Biotechnology could be an alternative to design organisms capable of overproducing biomolecules whose activity have been linked to the synthesis of S-NPs. Therefore, these biomolecules could be isolated and used for biosynthesis of NPs without possible interference from other biomolecules normally excreted by the cells. This method would also provide knowledge of the capping agent's composition, giving a more accurate perspective of its possible uses of the NPs produced.

The biosynthesis of S-NPs depends on several factors involved to obtain NPs with different properties. Short reaction times are associated with smaller particles, while in some cases, extended times can produce bigger NPs, aggregation, and loss of stability. In the same way,

attention must be paid to the concentration relationship between biomass, sulfur resources, and metal sources, since it also impacts NPs' size. On the other hand, it is necessary to establish optimal pH conditions favorable for both the bioentity and the solution and avoid other compounds' precipitation. Regarding NPs morphology, this is highly dependent on the type of biomass used, concentrations, external mediators and templates like hydroxypropyl starch (HPS) (Qi et al., 2017). Although achieving stability of the biosynthesized NPs using microorganisms is relatively easy, it has been seen that when using isolated biomolecules, this property can be affected because of capping agents' availability, being necessary to relatively high concentrations of this compound. Numerous factors impact the biosynthesis of NPs, so it is still a challenge to biosynthesize S-NPs with specific properties and on large scales. Perhaps, applying statistics, mathematical models, or artificial intelligence, would allow analyzing in a better way the impact of all of these factors listed in **Figure 7**, therefore establish favorable methodologies for the controlled biosynthesis of S-NPs

The study of the properties of NPs is significant to know their potential applications. The most used techniques are XDR, UV-Vis, TEM, SEM, and FTIR, due to the well-known operating procedures and acquisition information regarding the composition, optic properties, crystallography, morphology, size, and organic structures attached to the surface of the NPs. Furthermore, other techniques are used to confirm or extract more information from NPs, such as XPS, DLS, EDS and Photoluminescence spectroscopy (PL). Appreciation of coloration changes of the reaction solutions can be considered a technique to identify events occurring in the reaction. As **Table 9** shows, in many cases, the color of the reaction solution changes at the same time that the biosynthesis of S-NPs occurs.

The S-NPs have been experimentally applied for research in cancer treatment, bioimaging, antimicrobial activity, biosensing, bioremediation, and for building electronic devices. The application of the NPs used in these fields largely depends on their properties, such as particle size, optical properties, toxicity, surface envelope, morphology, and solubility (Alsaggaf et al., 2020; Borovaya et al., 2020; Kowshiket al., 2002; Mareeswari et al., 2016). For example, for cancer treatment, NPs must be soluble stable at physiological pH and with small particle sizes. For bioimaging and biosensing, the S-NPs used have shown interesting optical properties, in addition to the presence of functional ligands on their surface. It has been

possible to produce fluorescent S-NPs to imaging cells without inducing adverse effects after treatment (Spangler et al., 2017). The most common materials applied in these fields are quantum dots due to their small size (1-10 nm) and fluorescence capacity. Since QDs have the ability to fluoresce in prolonged times after being excited, these NPs could be used for surgical interventions, being helpful for the surgeon to identify targeted tissues of interest, whether to be removed or to avoid operating. Although numerous publications have reported interesting achievements and discoveries, more research is still needed to determine the exact mechanisms for the S-NPs biosynthesis, therefore controlling NP properties and producing at industrial scales.

Finally, the present bibliographic review work provides an extensive update of all the publications on biosynthesis of S-NPs of the last thirty years. The synthesis method and results of several outstanding works are briefly disclosed. Likewise, the factors involved in biosynthesis and the impact on the properties of the resulting S-NPs, such as reaction time, bioentity, biomass and precursors concentrations, external agents, among others, are also analyzed. On the other hand, it is examined the most used characterization techniques that confirm the synthesis of S-NPs and provide information regarding the properties of the produced S-NPs. Finally, the applications achieved with these NPs are presented considering the unique properties provided by the different biosynthesis mechanisms. In this way, a work focused on several edges on the biosynthesis of S-NPs is presented, demonstrating that biosynthesis is a promising route for the generation of new NMs with unique properties that can expand their application to various scientific areas.

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