

1 Revisiting the mechanistic pathways for bacterial mediated synthesis 2 of noble metal nanoparticles 3

4 **Jafar Ali^{1,2}, Naeem Ali^{*3}, Lei Wang¹, Hassan Waseem³, and Gang Pan^{*1,4}**

6 ¹ *Key Laboratory of Environmental Nanotechnology and Health Effects, Research Center for Eco-
7 environmental Sciences, Chinese Academy of Sciences, 18 Shuangqing Road, Beijing 100085, P. R.
8 China.*

9 ² *University of Chinese Academy of Sciences, Beijing 100049, P. R. China*

10 ³ *Department of Microbiology, Quaid-i-Azam University Islamabad, Pakistan*

11 ⁴ *School of Animal, Rural and Environmental Sciences, Nottingham Trent University, Brackenhurst
12 Campus, NG25 0QF, UK*

14 * Corresponding authors: gpan@rcees.ac.cn & naemali95@gmail.com

15 **Abstract:** Synthesis and application of reliable nanoscale materials is progressive domain and
16 limelight of modern nanotechnology. Conventional physicochemical approaches for the
17 synthesis of metal nanoparticles have become obsolete owing to costly and hazardous
18 materials. There is a need to explore alternative, cost-effective and eco-friendly strategies for
19 fabrication of nanoparticle (NPs). Green synthesis of noble metal nanoparticles has emerged
20 as a promising approach in the last decade. Elucidation of the molecular mechanism is highly
21 essential in the biological synthesis of noble metal nanoparticles (NPs) for the controlled size,
22 shape, and monodispersity. Moreover, mechanistic insights will help to scale up the facile
23 synthesis protocols and will enable biotransformation of toxic heavy metals hence also
24 providing the detoxification effects. Therefore, the current review article has primarily targeted
25 the mechanisms involved in the green synthesis of metal NPs, which have been reported during
26 the last few years. Detailed mechanistic pathways have highlighted nitrate reductase as a
27 principle reducing agent in the bacterial mediated synthesis and stabilization of NPs.
28 Furthermore, we have highlighted the potential implications of these mechanisms in

29 bioremediation and biomineralization processes, which can play a critical role in
30 biogeochemical cycling and environmental impacts of heavy metals. We anticipate that this
31 review article will help researchers to address the challenges of bioremediation and modern
32 nanotechnology.

33 **Keywords:** Green synthesis, Mechanism, Nitrate reductase, Biomineralization, Metal-
34 nanoparticle

35 **1. Introduction**

36 Nanotechnology has emerged as a progressive and interdisciplinary science during the last few
37 decades. The prefix “nano” indicates one billionth or 10^{-9} units. It is widely known that
38 nanoparticles (NPs) range in size from 1 to 100 nm (Jafar Ali and Ali, 2015). Nanomaterials
39 usually display unique biological, physical and chemical properties compared to their bulk
40 matter (Ahmad et al., 2013, Wang et al., 2018). Synthesis of noble metal NPs has drawn the
41 much attention due to potential applications in electronics, photonics, catalysis, nanomedicine,
42 biofuel cells, biomedical engineering and biological recovery of metals (Daraee et al., 2016,
43 Park and Na, 2015, Rana et al., 2017, Wang et al., 2015). Remarkably, silver nanoparticles
44 (AgNPs) possess inhibitory and bactericidal effects. Antibacterial characteristics of AgNPs
45 have enabled to minimize the antibiotic resistance, which has emerged as a major health
46 problem in recent years (Jain et al., 2009, Musarrat et al., 2010, Prabhu and Poulouse, 2012).
47 Recently there has been an upsurge of interest in the microbial reduction of metallic ions to
48 metal nanoparticles (NPs). Significant applications of the nanomaterials are usually size
49 dependent, thus controlled size synthesis of nanomaterials is highly desired (Jiang et al., 2008,
50 Narayanan and Sakthivel, 2010, Wang et al., 2017).

51 Various physical and chemical strategies could be employed to synthesize well-defined
52 nanomaterials (Daraee, Eatemadi, Abbasi, Fekri Aval, Kouhi and Akbarzadeh, 2016, Shah et
53 al., 2019). But these conventional synthesis protocols are not preferred due to high cost and
54 involvement of hazardous materials (Jha et al., 2009, Narayanan and Sakthivel, 2010,
55 Starowicz et al., 2006). Moreover, the large scale synthesis also face many issues such as low
56 stability and less monodispersity (Manoj et al., 2018). Henceforth there is a growing demand
57 for the employment of environmentally benign processes for the synthesis of stable NPs (Fayaz
58 et al., 2010). In this regard elucidation of molecular mechanisms may play a critical role in the
59 green synthesis of noble metal NPs with controlled dimensions and high monodispersity (Ali
60 et al., 2016). Various mechanistic theories about bio-synthesis of NPs have been presented in
61 literature (Ali et al., 2017, Ali, Hameed, Ahmed, Ali, Zainab and Ali, 2016). Majority of studies
62 have speculated the nitrate reductase as a principle reducing agent along with its stabilizing
63 feature. However, a plausible bio-synthesis mechanism may involve more than one cellular
64 components. Pathways involved in the green synthesis of nanomaterials are of prime
65 importance for commercialization of nanotechnology and also for environmental sustainability.

66 Synthesis mechanisms will also improve the bioremediation and biomineralization processes
67 for environmental contaminants. Biomineralization is the utmost process of controlling the
68 ultimate fate in biogeochemical cycling and ecological impacts of heavy metals (Diaz et al.,
69 2015). A better understanding of microbial transformation pathway at the genetic level may
70 lead to develop new genetic tools for accelerating the bioremediation strategies (Kang et al.,
71 2017, Wu et al., 2016). Assumably, biological transformation pathways of heavy metals can
72 be explored further. An escalating number of publications about nanomaterials during the last
73 decade illustrates the potential of this active domain. A thorough and comprehensive review of
74 literature is needed to provide facts about the green synthesis. The fundamental insight of
75 enzyme-metal interaction is elaborated here which, will enable the biotransformation of toxic

76 heavy metals hence providing the detoxification effect (Liu et al., 2016, Venkatachalam et al.,
77 2017).

78 Although several detailed reviews about the synthesis and applications as antimicrobial agents
79 have been published (Davis and Shin, 2008), but very few studies have focused on mechanistic
80 pathways involved in the green synthesis of NPs (Zhao et al., 2013). We have tried to
81 summarize the mechanisms for green synthesis of NPs which have been reported during the
82 last few years. Moreover, we have highlighted various biomolecules involved in the reduction
83 of metals into their NPs. We have also described the potential remedial prospects based on
84 these mechanisms. It is anticipated that the current study will improvise the understandings of
85 molecular routes involved in biochemical processes at complex interfaces.

86

87 **2. Mechanisms for the synthesis of noble metal nanoparticle**

88 The specific mechanisms of NPs formation varies from organism to organism. However, the
89 synthesis of NPs follows a generalized scheme wherein; metal ions are either entrapped into
90 the microbial cells or on the microbial surface in the presence of an enzyme, metal ions get
91 reduced to NPs (Yin et al., 2016). Initially, algal biomass of *Verticillium* sp. formulated the
92 intracellular NPs of gold and silver, the exact pathway was not identified but NPs synthesis on
93 the mycelial surface have demonstrated that electrostatic forces of attraction are responsible
94 for the entrapment of metal ions on the fungal cell wall, mainly due to negative charge of
95 carboxylate group of enzymes. Next reduction of metal ions by the enzymes to form nuclei of
96 noble metals, which later on grow through further accumulation and reduction (Fig.1)
97 (Mukherjee et al., 2002).

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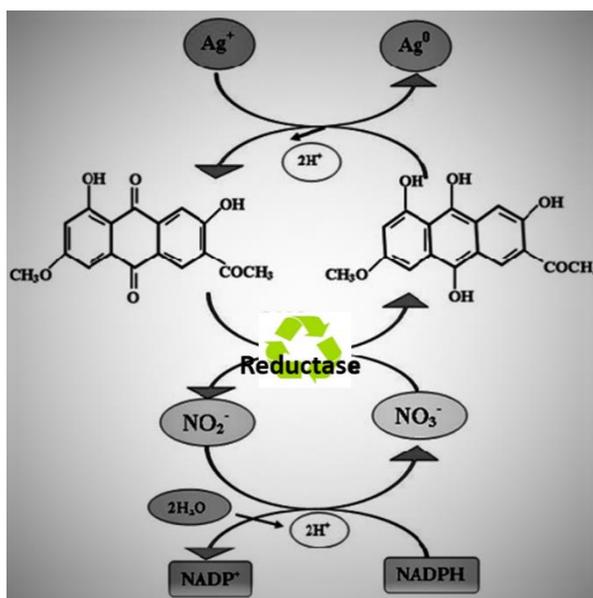


Figure 1: Extracellular reduction of silver ions and the transfer of electrons

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101 2.1 Mechanisms of silver nanoparticle synthesis

102 Among all the noble metals silver has been studied comprehensively, for biological synthesis

103 of metal nanoparticles due to enormous applications. In this regard, Kalishwaralal *et al.*,

104 (Kalimuthu *et al.*, 2008, Kalishwaralal *et al.*, 2010) investigated the participation of the nitrate

105 reductase enzyme in the synthesis of AgNPs by *Bacillus licheniformis*. Authors proposed that

106 nitrate ions may help for the induction of enzyme, which reduces the Ag^+ to Ag^0 . The probable

107 mechanistic pathway assisting the reduction of metallic ions is the enzymatic reduction process

108 by electron shuttle (Fig. 2). Cofactors like NADH in NADH-dependent nitrate reductases

109 enzymes are required for generating metal NPs. *B. licheniformis* releases cofactors NADH and

110 NADH-dependent enzymes, along with some other factors especially nitrate reductase the

111 possible reason toward the bio reduction of Ag^+ to Ag^0 (Durán *et al.*, 2011, Li *et al.*, 2011).

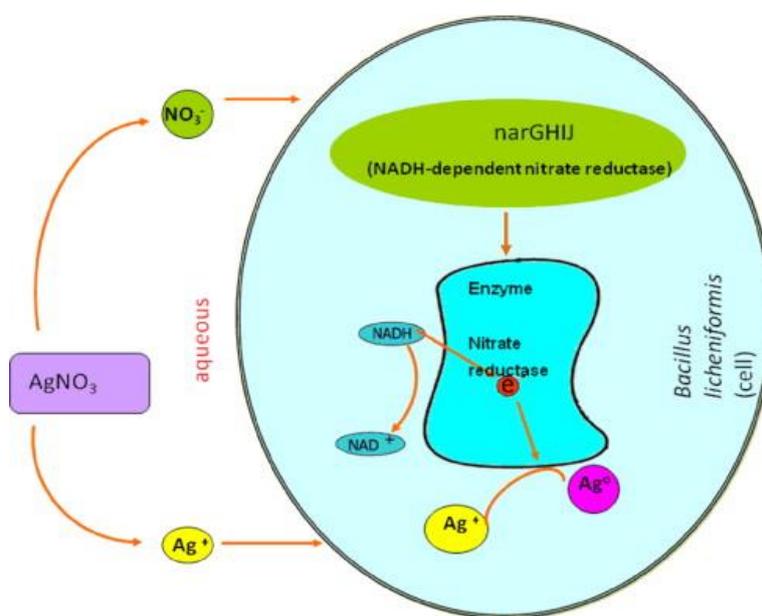
112 Sintubin and colleagues hypothesized another mechanism of AgNPs synthesis by

113 *Lactobacilli*, (Sintubin *et al.*, 2009) according to which pH upsurge is directly correlated with

114 competition for the negatively charged binding site between metal ion and protons (Sintubin,

115 De Windt, Dick, Mast, van der Ha, Verstraete and Boon, 2009). Lin and coworkers (Li *et al.*,

2011) further investigated that biosorption of silver ions on the culture of *Lactobacillus* A09 with the sudden fall in pH due to the interaction of between metal ions and protons. The ring structure of monosaccharides was catalyzed by high pH and reducing power is provided by aldehydes. In the presence of metal ions, the aldehyde got oxidized into respective carboxylic acid, and metal ions get reduced. However, which cellular component is mainly involved in biosorption and reduction is still needs further evaluation. *Lactobacillus* mediated synthesis of AgNPs from probiotic tablets and yoghurt has also been reported. Lactate from NADH depending lactate dehydrogenase and pyruvate generated two protons involved in the synthesis process alongside thioredoxin systems and glutathione. Conclusively, all components work in coordination to facilitate the synthesis of AgNPs (Nangia et al., 2009). Effect of visible light on the production of AgNPs was studied, especially when the culture of *Klebsiella* and silver nitrate was exposed to visible light resulted in variable synthesis rate (Mokhtari et al., 2009).



128
 129 **Figure 2:** Enzymatic reduction of silver in the presence of coenzyme by *Bacillus licheniformis*
 130 adopted from (Kalimuthu, Babu, Venkataraman, Bilal and Gurunathan, 2008) with permission
 131

132 Klaus et al., (Klaus et al., 1999) proposed that silver accumulation outside the cellular
 133 membrane of bacteria was associated to reacting potential with H₂S gas turning it non-toxic to

134 itself in case of *Pseudomonas*. The bio-reduction of the ionic silver into AgNPs was due to the
135 cofactor and nitrate reductase enzyme secreted by *Bacillus licheniformis*. Optimization in
136 activity and production reconfirmed the hypothesis that there is involvement of catalytic
137 proteins in reduction and synthesis. (Vaidyanathan et al., 2010). However, bacterial interaction
138 with different metals is not yet completely understood. A protein assay was performed to
139 confirm the involvement of catalytic proteins in AgNPs synthesis by *Fusarium oxysporum*.
140 Authors identified that protein was NADH-dependent reductase responsible for reducing the
141 silver nitrate solution and subsequent formulation of AgNPs. It was also observed that the
142 NADH-dependent reductase enzyme was not present in all fungi, because *Fusarium*
143 *moniliforme* was unable to synthesize intracellular and extracellular NPs (Ahmad et al., 2003).
144 In another study, extracellular synthesis of AgNPs was carried out using the *Fusarium*
145 *oxysporum*, in this work a mechanistic approach was taken into account. The verification of
146 reduction (metal ions) through extracellular shuttle quinone and nitrate-dependent reductase
147 was done by fluorescence spectra, Uv-vis and especially by enzyme activity.

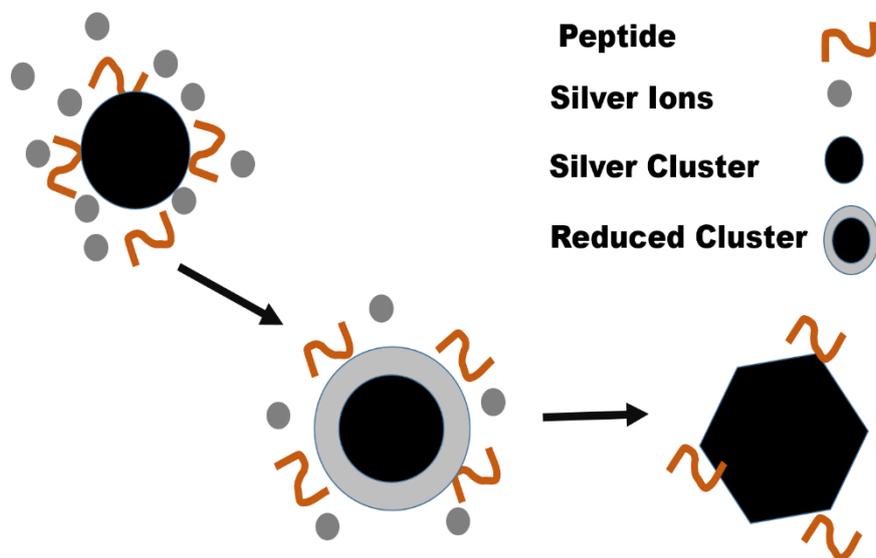
148 Synthesized AgNPs from *F. oxysporum* were stabilized by proteins (Durán, Marcato, Durán,
149 Yadav, Gade and Rai, 2011). The additional evidence to the Duran et al., (Durán, Marcato,
150 Durán, Yadav, Gade and Rai, 2011) findings was provided by Ingle et al., (Ingle et al., 2009).
151 Through a comparative study of nitrate reductase from the fungal filtrate and commercially
152 available nitrate reductase discs. Along with the synthesis of NPs authors also pointed out that
153 there was a close association in the synthesis process and reductase enzyme. *F. moniliforme*
154 has the nitrate reductase but unable to perform the synthesis process due to lack of
155 anthraquinone. These findings clarified the understanding of synthesis mechanism that not only
156 nitrate reductase was essential, but an electron shuttle is also required for reduction of metals.
157 Similarly, Durán et al. (Durán, Marcato, Durán, Yadav, Gade and Rai, 2011) results were
158 confirmed by Kumar et al., (Kumar et al., 2007) wherein, in vitro synthesis of AgNPs was

159 carried out by a purified enzyme nitrate reductase and a cofactor (NADPH). The stabilizing
160 agent was provided externally in the form of, 4-hydroxyquinoline and phytochelatin. In the
161 absence of enzyme and cofactor, synthesis of AgNPs was entirely inhibited hence confirming
162 the participation of nitrate reductase enzyme in the synthesis of AgNPs. Naik et al. (Naik et al.,
163 2002) established the synthesis process of AgNPs using peptides attached to the surface of
164 AgNPs. According to his findings reduction of silver ions was accelerated when peptide
165 adhered to the nanoclusters or nuclei.

166 A mechanistic model was proposed that explained how peptides were added to the solution of
167 silver ions, and they reacted with preformed metal ions nuclei and created a reducing vicinity
168 around the metal nanocluster (Fig. 3). Due to this interaction reduction process was catalyzed
169 and distribution of shape, size (60–150 nm) was observed. Peptides with special amino acid
170 like cysteine, methionine, arginine, and lysine may attach on the surfaces of nuclei and can be
171 used in the production of AgNPs (Selvakannan et al., 2013). In this way, the silver and peptide
172 interaction was examined in detail (Balachandran et al., 2013, Naik, Stringer, Agarwal, Jones
173 and Stone, 2002). Tyrosine amino acid under alkaline conditions acts as a reducing agent.
174 Indeed it is the phenolic group of tyrosine that can reduce silver and later on modifying itself
175 into a semi-quinone structure. Tyrosine-based synthesis was preferable because newly
176 synthesized NPs were easily achievable through centrifugation (Dubey et al., 2015,
177 Selvakannan et al., 2004). Furthermore, they also observed that tyrosine has also the potential
178 for reducing gold. Free N terminus of peptides with metal surface provide the stabilization. A
179 tripeptide containing tyrosine residue at C terminus to reduce the gold ions and free N terminus
180 to stabilize and attach with GNPs (Bhattacharya and Gupta, 2005, Shankar et al., 2015). While
181 the oligopeptide holding tyrosine can also be used in a gel-network structure for reducing
182 metals and synthesizing GNPs and AgNPs (Daima et al., 2014, Jones et al., 2008). It was also
183 demonstrated that the peptides lacking the specific tyrosine residue were failed to perform

184 reducing activity. These findings were in accordance with idea that tyrosine plays a key role
185 for in situ reduction. At alkaline pH, tryptophan can also be used to formulate the metal NPs.

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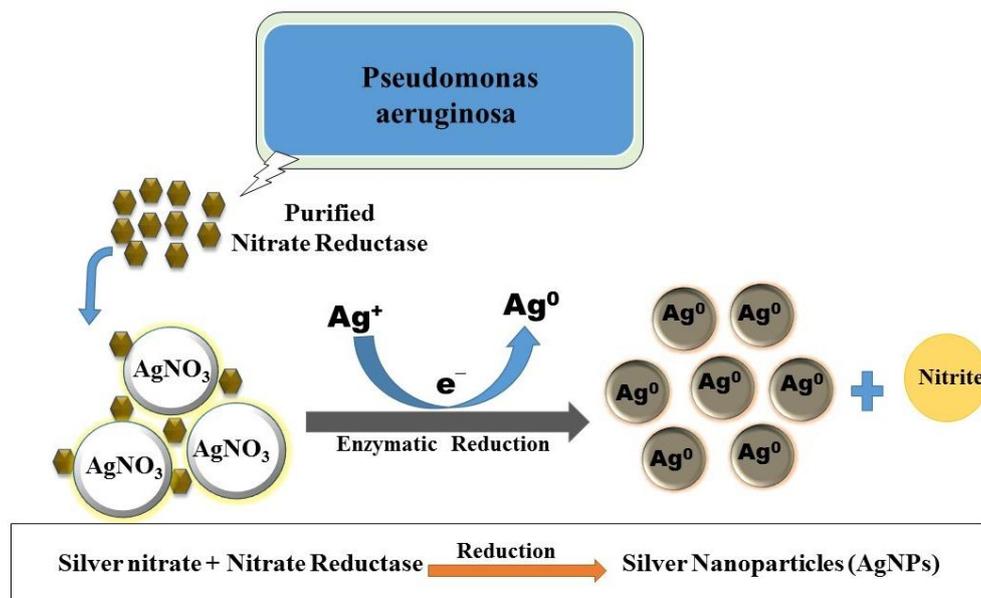


187
188 **Figure. 3:** Model presenting the silver crystal formation by silver-binding peptides. Adopted from
189 (Naik, Stringer, Agarwal, Jones and Stone, 2002) with permission

190

191 Another mechanism was proposed by Si and Mandal, (Si and Mandal, 2007) describing the
192 reductive properties of tryptophan moieties. This study demonstrated that initially tryptophan
193 is changed into tryptophol radical which can donate electrons to the metal ions and
194 subsequently forming metal NPs. Because this radical can act as a fluorescent agent
195 (ditryptophan), in the kynurenine form, hence attachment of peptide can be analyzed by
196 fluorescence spectroscopies and UV-vis techniques (Si and Mandal, 2007). In ambient light
197 aspartic acid and glutamic acid can produce AgNPs in the presence of carboxylic groups of
198 short peptides of yeast can support the synthesis process. Recently a study has reported the eco-
199 friendly fabrication of AgNPs using the supernatant of *Pseudomonas aeruginosa* JP1 culture
200 which was isolated from a metal contaminated soil. Authors have linked the nitrate reductase
201 with AgNPs synthesis through retreating the nitrate reductase with purified protein (Fig. 4)

202 (Ali, Ali, Jamil, Waseem, Khan and Pan, 2017). However, another study has also reported that
 203 superoxide dismutase is responsible for the extracellular synthesis of AgNPs by *Fusarium*
 204 *oxysporum* (Yin, Yang, Hu, Tan, Zhao, Zhang, Liu and Jiang, 2016). Broadly, the enzymes
 205 involved in the synthesis of metal NPs are nitrate reductases for which NADH act as a
 206 coenzyme.



207

208 **Figure 4:** Extracellular and nitrate reductase-mediated synthesis of AgNPs by *Pseudomonas*
 209 *aeruginosa* JP1. adopted from (Ali, Ali, Jamil, Waseem, Khan and Pan, 2017) permission

210 Mostly, assimilatory type of nitrate reductases are metalloproteins having the molybdenum
 211 ions as cofactor and catalyzes the several reactions in nitrogen, carbon and sulfur cycle.
 212 Through different mechanistic approaches, it can be concluded that enzymes may play a critical
 213 role in the reduction of metal salts subsequently formulating the metal NPs. Thus the
 214 optimization of different parameters for its maximum activity and production can enhance the
 215 AgNPs synthesis process. Moreover, by controlling the mechanistic steps monodispersity and
 216 uniformity are attainable. Different types of enzymes involving NPs synthesis with their sizes
 217 are mentioned in Table 1.

218

219 *2.2. Mechanism of gold nanoparticle synthesis*

220 Discussion about the bacteriogenic synthesis mechanism of gold nanoparticle (GNPs) was
221 started when a closely resembled mechanistic process was elaborated for the extracellular
222 synthesis of GNPs by using the culture of *Rhodopseudomonas capsulate* (He et al., 2007).
223 Different cofactors like NADH or NADH-dependent enzymes are also released extracellularly.
224 In the reduction process, the initial step is the transfer of an electron from NADH through an
225 electron carrier (NADH-dependent reductase), while in next step electrons are transferred to
226 gold ions (Au^{3+}) and got reduced to elemental gold (Au^0) or GNPs. The mechanism of GNPs
227 synthesis by a bacterium *Stenotrophomonas maltophilia* was proposed by Nangia et al.,
228 (Nangia, Wangoo, Goyal, Shekhawat and Suri, 2009). Authors have suggested the involvement
229 of NADPH-dependent reductase enzyme in the reduction of Au^{3+} to Au^0 and stabilization via
230 capping molecules. Das et al. (Das and Marsili, 2010) have reported GNPs were synthesized
231 extracellularly using *Rhizopus oryzae*. The FTIR spectrum of the reaction mixture containing
232 AuCl_4^- showed the presence of different amides like amide I (primary), II (secondary) and
233 amide III and vanishing carboxylic group, indicating the involvement peptides or proteins in
234 the reduction of gold ions. The involvement of the phosphate bond was revealed by the peak
235 shifting from $1,034\text{ cm}^{-1}$ to $1,025\text{ cm}^{-1}$. Thus it was concluded that GNPs could be synthesized
236 by surface bounded molecules which also act as stabilizing agent (Singaravelu et al., 2007).

237 *2.3. Mechanism of palladium nanoparticle synthesis*

238 Palladium is another precious metal commonly used in electrochemical catalysts and refining
239 industries as well as an important catalytic converter in automobiles to lower the emission of
240 dangerous pollutants. The high consumption rates of Palladium has outperformed the
241 production rates during the last few years. Although, some chemical practices are being

242 employed for the bulk recovery of palladium from the waste streams, there is a need to develop
243 sustainable and more efficient strategies. Microbial reduction of soluble Pd(II) to Pd(0) to
244 recycle precious metals and synthesize catalytic nanoparticles has proven as an effective,
245 sustainable method (Ahmed et al., 2018). Several studies have reported the palladium reduction
246 to palladium nanoparticles (PdNPs) through bacteria along with diverse applications.
247 Extracellular reduction of palladium to PdNPs by *Geobacter sulfurreducens* was reported as a
248 sustainable method to recover precious metal catalysts (Yates et al., 2013). Another recent
249 investigation pointed out the selective electrocatalysis of biofuel molecular oxidation using
250 palladium nanoparticles generated on *Shewanella oneidensis* MR-1 (Wu et al., 2018).

251

252 2.4. Mechanism of platinum nanoparticle synthesis

253 Earliest microbial mediated synthesis of platinum nanoparticles was achieved by the reduction
254 of Pt (IV) via hydrogenase enzyme extracted from sulphate-reducing bacteria (SRB) (Fig. 5)
255 (Martins et al., 2017). Since then a diverse range of microbes has served as nanofactories for
256 platinum nanoparticles (PtNPs). Although fungal based synthesis is reported in most of the
257 studies, *Desulfovibrio vulgaris* opted a bioreduction mechanism to formulate the spherical
258 PtNPs in periplasmic spaces. However, an enzymatic reduction was also reported for the
259 intracellular synthesis of monodispersed cuboidal PtNPs (5 nm) by *Acinetobacter*
260 *calcoaceticus* (Gaidhani et al., 2014). Similarly, a reductive decomposition channel was used
261 by *Shewanella* strain to synthesize the intracellular PtNPs which were located inside the
262 periplasmic membranes (Martins, Mourato, Sanches, Noronha, Crespo and Pereira, 2017).

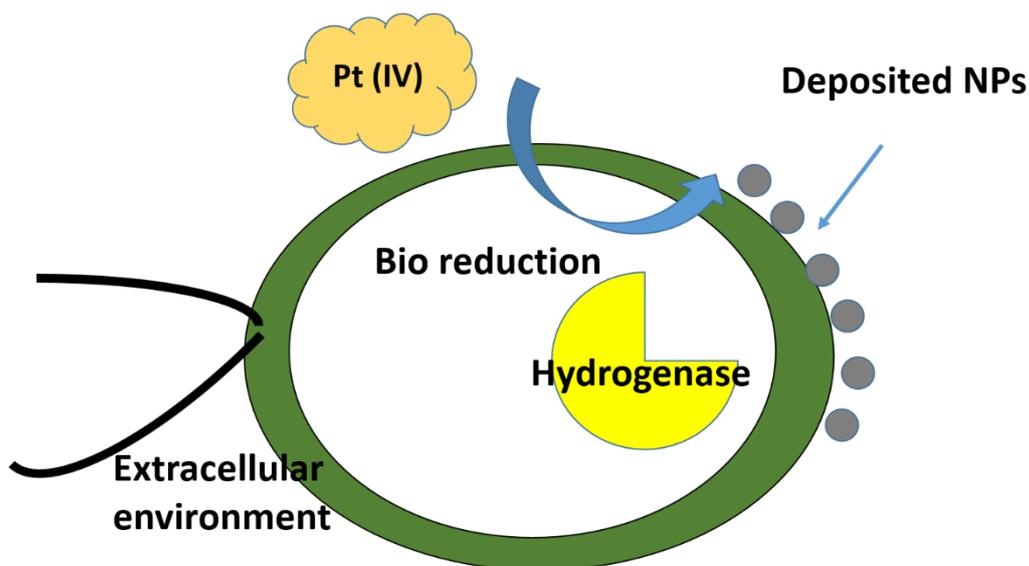


Figure 5: Extracellular synthesis mechanism of platinum nanoparticles

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266 2.5. Mechanisms of non-noble metal nanoparticle synthesis

267 Metal NPs formulation can be linked with the fact that metallophilic microbes evolve genetic
 268 and proteomic reaction in response to toxic environments (Casals et al., 2012). Heavy metal
 269 ions such as Hg^{2+} , Ni^{2+} , CrO_4^{2-} , Ag^+ , Co^{2+} , Cu^{2+} , Cd^{2+} , Zn^{2+} and Pb^{2+} can hinder the growth
 270 of organisms. In order to alleviate the toxicity and regulate the metal homeostasis
 271 microorganisms have developed proteomic and genetic responses (Sinha et al., 2014).
 272 Numerous metal resistance genes or gene clusters can reside in microorganisms which enables
 273 them to detoxify metals through a series of mechanisms such as efflux, complexation, or
 274 reductive precipitation efflux. In this way, metallophilic bacteria flourish in environments
 275 harboring ions of heavy metals, like efflux streams of metal processing plants, mine waste
 276 rock piles and naturally mineralized zones (Reith et al., 2013). Another study revealed the
 277 active and passive mechanisms used for the magnetite synthesis from *Shewanella oneidensis*
 278 (Perez-Gonzalez et al., 2013). When ferrihydrite is utilized as a final electron acceptor by
 279 bacteria, the pH around the cell raised which results in active production of Fe^{2+} ions. Later on,
 280 localized concentrated ions of Fe_2^{2+} and Fe_3^{3+} at cell wall increase in supersaturation state of the
 281 cell through the passive mechanism. Biomineralization of bacterial magnetite particle (BacMP)

282 is speculated to be a multistep process. The invagination of the cytoplasmic membrane is the
283 first step, and newly organized vesicles act as precursor BacMP membrane. It is believed that
284 vesicle formation in magnetotactic bacteria resembles with GTPase mediated study in
285 eukaryotes. Then vesicles are joined in chains along with cytoskeletal filaments. The
286 assemblage of Fe^{+2} inside the vesicles by siderophores molecules (iron transporters), is the next
287 step of BacMP biomineralization. Oxidation-reduction firmly control the internal iron. Finally,
288 proteins attached to BacMP initiate nucleation and also regulate the morphology of magnetite
289 crystals. Several proteins attached to the BacMP membrane play an important role for the
290 generation of magnetite (Arakaki et al., 2008).

291 Sangha et al., (Sanghi and Verma, 2009) have also investigated the synthesis of cadmium
292 sulfide NPs. They proposed disulfide bonds of cysteine are involved in NPs formation which
293 can be assigned to breakage of S–H bond and creation of new bonds, which is Cd-thiolate (Cd–
294 S– CH_2COOH) complex on the surface of NPs. The carboxylic group (COOH) of the cadmium-
295 thiolate complexes interact with hydrogen bond instead of reacting with the amino group of
296 proteins. Therefore, the hydrogen bond is responsible for amino group binding with capped
297 CdS. Beveridge et al., (Beveridge et al., 1997) have explained the mechanisms that were under
298 consideration for the biosynthesis of nanomaterials including alteration of toxicity and
299 solubility, bioaccumulation, oxidation, reduction, biosorption, efflux systems precipitation and
300 extracellular complexation of metals. Cell wall has a significant influence on the intracellular
301 synthesis of NPs. The positively charged metallic ions electrostatically attached toward the
302 negatively charged wall. Small diffused NPs are obtained as a result of reduction through the
303 enzymes present in the cell wall (Jager et al., 2018).

304 Mukherjee et al., (Mukherjee, Senapati, Mandal, Ahmad, Khan, Kumar and Sastry, 2002)
305 described the intracellular synthesis of NPs takes place through a step-by-step mechanism in

306 case of *Verticillium* species. The mechanism contains two stipulating steps mainly,
 307 bioreduction and synthesis. A similar mechanism was also found in fungus for the synthesis of
 308 NPs. Moreover, Nair and Pradeep (Nair and Pradeep, 2002) observed that firstly metal ions
 309 nucleate; thus nanoclusters formation is the result of electrostatic interaction between the
 310 bacterial cell and metal clusters. Subsequently, the small nanoclusters get diffused through the
 311 bacterial cell wall. The same mechanism was witnessed in the case of Actinomycete (Sastry et
 312 al., 2003). Extracellular bacterial synthesis of NPs has been presented through nitrate-
 313 reductases reducing metal ions into nanocomposites (Ali, Hameed, Ahmed, Ali, Zainab and
 314 Ali, 2016, Jain et al., 2011).

315

316 Table 1: Different sizes of enzymes or biomolecules involved in metal nanoparticles synthesis
 317

Serial #	Microorganism	Nanoparticle type	Biomolecules/enzyme involved	Molecular Size	Reference
1.	<i>Enterobacter cloacae</i>	AgNPs	Nitrate reductase	-	(Shahverdi et al., 2007)
2.	<i>Pseudomonas aerogenosa</i> JP2	AgNPs	Nitrate reductase	66 kDa	(Ali, Ali, Jamil, Waseem, Khan and Pan, 2017)
3.	<i>Pseudomonas aerogenosa</i> JP1	AgNPs	Nitrate reductase	65 kDa	(Ali, Hameed, Ahmed, Ali, Zainab and Ali, 2016)
4.	<i>E. coli</i>	AgNPs	Nitrate reductase	-	(Huang et al., 2015)
5.	<i>Bacillus subtilis</i>	AgNPs	proteins	66-116 kDa	(Reddy et al., 2010)
6.	<i>Verticillium sp.</i>	Magnetite	protein	55- and 13- kDa	(Bharde et al., 2006)
7.	<i>Shewanella oneidensis</i>	AgNPs	C-type cytochromes	-	(Law et al., 2008)
8.	<i>S. maltophilia</i>	AgNPs	Chromium reductase	-	(Oves et al., 2013)

9.	<i>Tetrathiobacter</i>	SeNPs	-	90-kDa protein	(Hunter and Manter, 2008)
10.	<i>Sclerotium rolfsii</i>	AuNPs	NADPH-dependent enzyme	28.7&19.5	(Narayanan and Sakhivel, 2011)
11.	<i>D.desulfuriacans</i> ATCC 29577	PdNPs	Hydrogenase and cytochrome C ₃	-	(Mabbett et al., 2004)
12.	<i>M. psychrotolerans</i> 53	Ag-nanoplates	Ag-reductases	-	(Ramanathan et al., 2010)
13.	<i>Aspergillus flavus</i> NJP08.	AgNPs	Protein fragment	32 & 32 kDa	(Jain, Bhargava, Majumdar, Tarafdar and Panwar, 2011)
14.	<i>Penicillium fellutanum</i>	AgNPs	-	70 KDa protein	(Kathiresan et al., 2009)
15.	<i>F. oxysporum</i>	AgNPs	α -NADPH-dependent nitrate reductase and phytochelatin	(44 kDa)	(Kumar, Abyaneh, Gosavi, Kulkarni, Pasricha, Ahmad and Khan, 2007)
16.	<i>Fusarium oxysporum</i>	AuNPs	protein	66- and 10-kDa	(Mukherjee, Senapati, Mandal, Ahmad, Khan, Kumar and Sastry, 2002)

318

319 *- : no information found

320

321 3. Conclusion

322 Green synthesis of metal NPs has resulted in efficient, cost-effective and eco-friendly
323 fabrication methodologies. Applications of nanomaterials are highly size dependent. Exploring
324 the underlying molecular mechanism of NPs formation is very necessary for controlled size
325 synthesis and enhanced applications. Although several studies have presented the underlying
326 mechanisms of NPs formulation, generally nitrate reductase is considered as principle reducing

327 agent. Role of catalytic proteins and stabilizing agents will undoubtedly provide sufficient
328 information to control the morphology and crystallinity of nanomaterials. Moreover, Pathways
329 involved in the green synthesis of nanomaterials are not only of prime importance for
330 commercialization but also for environmental sustainability. Synthesis mechanisms will also
331 improve the bioremediation and biomineralization processes for environmental contaminants.
332 Future research on the microbial mediated biological synthesis of nanoparticles with unique
333 optoelectronics, physicochemical and electronic properties are of great importance for
334 applications in the areas of chemistry, electronics, medicine, and agriculture.

335 **4. Future prospects**

336 Nanotechnology has emerged as a promising domain of modern science. Enzymatic pathways
337 are mainly contributing to the biosynthesis of metal NPs. Mechanistic insights will accelerate
338 the synthesis processes of controlled morphology, stabilized nanomaterials for enhanced
339 applications. Biological synthesis of metal NPs has also contributed to remediate the
340 environment contaminants (Prabhu and Poulouse, 2012). Heavy metals contamination has
341 become a significant concern due to non-biodegradable nature and hazardous environmental
342 impacts (Pejman et al., 2015). Bioremediation is preferred over chemical remedies
343 (electrochemical treatment and chemical precipitation) due to economic reasons, simple nature
344 and high efficiency (Masood and Malik, 2013). Combination of microbial physiology,
345 metabolic and genetic engineering tools can offer innovative bio-based clean-up processes.
346 Interestingly, microbes have evolved the several mechanisms for metal resistance (Wu, Huang,
347 Ling, Yu, Jiang, Liu and Li, 2016). Metal-reducing microbes act as geochemical agent and
348 promote the transformations, precipitations, and dissolutions of minerals (Diaz, Swart, Eberli,
349 Oehlert, Devlin, Saeid and Altabet, 2015). Enzymatic reduction mechanism has provided a new
350 platform to explore biomineralization activity in detail. Biomineralization is the utmost process

351 of controlling the ultimate fate in biogeochemical cycling and environmental impacts of heavy
352 metals (Engel, 2017).

353 The fundamental insight of enzyme-metal interaction is elaborated here which will enable the
354 biotransformation of toxic heavy metals hence providing the detoxification effect (Liu, Zeng,
355 Niu, Liu, Zhou, Jiang, Tan, Xu, Zhang and Cheng, 2016). Nitrate reductase producing microbes
356 can potentially enhance the efficiency of bioremediation strategies. Nitrate reductase and other
357 enzymes have been investigated for improving the remediation of heavy metals and toxic
358 contaminants (Noor Afifah et al., 2016, Wang et al., 2018). Metal microbe interaction and role
359 of secreted enzymes still needs further annotation (Neumann et al., 2017). A better
360 understanding of microbial transformation pathway at the genetic level will lead to develop
361 new genetic tools for accelerating the bioremediation (Kang, Qu, Alvarez and Zhu, 2017).
362 Whereas, these mechanisms may also assist in elucidating the antibiotic resistance phenomena
363 (Engel, 2017, Waseem et al., 2019). The worldwide upsurge in antibiotic resistance has become
364 a severe concern for modern medicine (Goossens et al., 2005, Neu, 1992, Yelin and Kishony,
365 2018). One of the promising approaches for overcoming bacterial resistance is the use of
366 metallic nanoparticles in combination with antibiotics (Ghosh et al., 2012). However, recently
367 co-occurrence of metal resistance genes and antibiotics resistance genes have been reported
368 (Jang et al., 2018). Therefore metal transforming microbes may have a critical role in the
369 production of superbugs (Lindsay and Holden, 2004). Moreover, the metal reducing microbes
370 and extracellular electron transfer mechanism may have implications in electro-
371 microbiological applications for renewable energy (Ali et al., 2018, Jackson and Mantsch,
372 1995).

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383

384 **Conflict of Interest**

385 Authors declare the no conflict of interest

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