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Actinomycetes mediated biogenic synthesis of metal and metal oxide nanoparticles: Progress and challenges

Actinomycetes mediated synthesis of nanoparticles

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Abstract

Actinomycetes mediated biogenic synthesis of metal nanoparticles and their antimicrobial activities are well documented. Actinomycetes facilitate both intracellular and extracellular metal nanoparticles synthesis and are efficient candidates for the production of polydispersed, stable and ultra-small size metal nanoparticles. Secondary metabolites and new chemical entities derived from actinomycetes have not been extensively studied for the synthesis of metal/ metal

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oxide nanoparticles. The present review focuses on biogenic synthesis of metal nanoparticles from actinomycetes and the scope for exploring actinomycetes derived compounds (enzymes, organics acids and bioactive compounds) as metal and metal oxide reducing agents for the synthesis of desired nanoparticles. This review also focuses on challenges faced in the applications nanoparticles and the methods to synthesise biogenic metal nanoparticles with desired physiochemical properties such as ultra-small size, large surface to mass ratio, high reactivity etc. Methods to evade their toxicity and unique interactions with biological systems to improve their chance as an alternative therapeutic agent in medical and pharmaceutical industry are also discussed.

Keywords: Actinomycetes, Antimicrobials, Biopharmaceuticals, Pharmaceuticals, *Streptomyces*.

Introduction

Nanoparticles have attracted great attention in the recent past due to their fascinating properties. Nanoparticles offer advantages such as high surface area, increased reactivity, surface plasmon resonance (SPR), enhanced Rayleigh scattering and surface enhanced Raman scattering (SERS) over their bulk material (Daniel and Astruc 2004; Kim et al. 2007). Nanoparticles are widely used in varied applications such as drug delivery, nanoantibiotics, pharmaceutical nanoengineering, catalysis, sensor development, electronics and related fields (Chau et al. 2007). The application of nanoparticles is influenced by their size, stability, shape and dispersive nature (Narayanan and Shaktivel 2010). Nanotechnology offers us the opportunity to synthesize nanoparticles of desired characteristics so as to facilitate their use in various applications. Nanoparticles can be synthesized using two approaches namely top-down approach and the

bottom-up approach (Fendler 1998). In the top-down approach bulk materials are broken down to nano sized materials and in the bottom-up approach atoms and molecules are assembled to molecular structures in nanometer range. The chemical and biological methods use the bottom-up approach for the synthesis of nanoparticles (Pattekari et al. 2011). Chemicals such as reducing agents, organic solvents and non-biodegradable stabilizing agents are also used to synthesize nanoparticles. Though these methods are very popular in the synthesis of nanoparticles, the use of hazardous chemicals limits their use in medical and clinical fields (Li et al. 2011). Another challenge is to synthesize monodispersed nanoparticles with different shape and size. The high cost involved in the physical and chemical methods also contributes to the search of alternative methods to synthesize nanoparticles (Ingle et al. 2008).

Biosynthesis of nanoparticles involving biological system is a rapid, clean, simple, nontoxic, inexpensive and eco-friendly technology. Biosynthesis of nanoparticles is used to obtain high range of chemical composition, size/shape, high monodispersity and large-scale production. Biogenic nanoparticles are advantageous in the fact that they are water soluble and biocompatible. Synthesis of nanoparticles using microorganisms, enzymes and plant extracts has been suggested as possible biological methods to synthesize nanoparticles (Song and Kim 2008). Biologically synthesized nanoparticles have proved to be more efficient than the traditionally synthesized nanoparticles. The proteins present in the biological source act in a synergistic way by capping the nanoparticles thereby increasing their efficiency (Kumar et al. 2013). Among biological system microbes owing to their diversity emerge as a promising option for nanoparticle synthesis (Plaza et al. 2014). Biosorption, bioaccumulation, biodetoxification and biomineraization of metals by microorganisms also make them a suitable biological source to

synthesize nanoparticles (Dickson 1999). A few microbes have the ability to selectively reduce certain metal ions by electron transfer. An example is the hydroquinone released by certain microorganisms which can reduce ions to nanoparticles (Baker and Tatum 1998). The nanoparticle biosynthetic process is controlled by the biochemical and the genetic nature of the microbe that is used for the biosynthesis (Naveen et al. 2010). Bacteria can be easily handled and manipulated and this makes it an easier choice to design specific nanoparticles based on their shape, size and their application (Zonooz and Salouti 2011).

Synthesis of nanoparticles using bacteria, yeast and fungi

Many successful attempts have been made in the synthesis of nanoparticles using bacteria, fungi, and yeast. Nanoscale gold particles are readily precipitated within bacteria when they are incubated with Au^{3+} ions (Beveridge et al. 1980). The environment from which the microorganism was isolated influences the formation nanoparticles. An example would be *Pseudomonas stutzeri* AG259 isolated from silver mine which when placed in a solution of $AgNO_3$ was able to reduce Ag^+ ions and form silver nanoparticles within the periplasmic space of the bacteria (Klaus-Joerger et al. 2001). Synthesis of gold and silver nanoparticles was reported within lactic acid bacteria present in buttermilk after exposure to corresponding metal ions (Nair and Pradeep 2002). Other bacteria such as *Pseudomonas aeruginosa*, *Morganella* sp., *Bacillus subtilis*, *Bacillus licheniformis*, *Rhodopseudomonas capsulate* and *Brevibacterium casei* mediate intracellular and extracellular synthesis of nanoparticles (Hazra et al. 2013; Saifuddin et al. 2009; Vaidyanathan et al. 2010; Kiran et al. 2010). It would be interesting to investigate the potential of eukaryotes to synthesize nanoparticles as their genetic makeup and characteristics vary from prokaryotes which would result in nanoparticles with fascinating

characteristics and applications. Few genera of fungi have been studied for their synthesis of nanoparticles and it was observed that they are good candidates for producing gold and silver nanoparticles (Mukherjee et al. 2001; Mukherjee et al. 2002). Actinomycetes are microorganisms which share important characteristics of fungi and prokaryotes such as bacteria and are known for their ability to produce secondary metabolites with varied biological activities (Vimal et al. 2009).

Synthesis of biogenic nanoparticles from actinomycetes

Actinomycetes are capable of synthesizing intracellular and extracellular nanoparticles. Intracellular synthesis occurs on the surface of the mycelia due to the electrostatic binding of Ag^+ ions to the negatively charged carboxylate groups in the enzyme present on the cell wall of mycelia. The Ag^+ ions are then reduced by the enzymes in the cell wall forming silver nuclei. The accumulation of the silver nuclei leads to formation of nanoscale silver particles (Sunitha et al. 2013). Novel alkalotolerant actinomycetes, *Rhodococcus* sp. was used to synthesize gold nanoparticles. The results from trasnsmission electron microscopic (TEM) image showed the presence of nanoparticles on the walls of the actinomycetes confirming the intracellular synthesis of gold nanoparticles (Ahmad et al. 2003). Intracellular synthesis of silver nanoparticles using *Rhodococcus* NCIM 2891 was reported (Otari et al. 2012). Wet biomass of *Streptomyces hygroscopicus* was exposed to $HAuCl_4$ and at 72 hours the yellow colored biomass turned pink indicating the formation of extracellular gold nanoparticles (Waghmare et al. 2014). *Streptomyces* sp. HBUM171191 was reported to produce silver, manganese and zinc nanoparticles when the wet biomass was exposed to the corresponding metal solutions. The color

change of the biomass from light yellow to brown, dark yellow and dark yellow indicates the formation of silver, manganese and zinc nanoparticles (Waghmare et al. 2011).

Extracellular synthesis of nanoparticles can be attributed to the enzymes that are involved in nitrogen cycle. They may be responsible for the electron shuttle enzymatic metal reduction process (Karthik et al. 2014). The α-NADH dependent nitrate reductase plays an important role in the reduction of Ag^+ ions to silver nuclei. Actinomycetes mediated the extracellular synthesis of nanoparticles using *Streptomyces glaucus* 71MD (Tsibakhashvili et al. 2011). Pure culture of *Streptomyces* sp. ERI-3 reduced colorless silver nitrate solution to a reddish brown color within 12 hours (Zonooz and Salouti 2011) indicating the formation of silver nanoparticles.

Metal and metal oxide nanoparticles from actinomycetes as nanoantibiotics

Antibacterial activity of nanoparticles from actinomycetes

Silver has been used as antimicrobial agent since ancient times. Silver is also known for its catalytic activity, chemical stability and good conductivity. Silver in minute quantities are not toxic to human health. These properties make silver an excellent choice to synthesize silver nanoparticles for biomedical applications. Actinomycetes are well known for their ability to produce secondary metabolites/new chemical entities, which serve as antibiotics. Since actinomycetes are primary source for antibacterial substances there are numerous reports of actinomycetes mediated metal and metal oxide nanoparticle synthesis and their antimicrobial activity. Silver nanoparticles produced from actinomycetes have been shown to possess significant antibacterial activity. Silver nanoparticles synthesized using *Streptomyces* sp. BDUKAS10, showed 16 mm, 15 mm and 13 mm zones of inhibition against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacillus cereus* respectively (Sivalingam et al. 2012).

Silver nanoparticles were synthesized extracellularly from *Streptomyces rochei* using 10^{-3} $AgNO_3$ and 10^{-4} $AgNO_3$ and were used to evaluate the antibacterial activity. Zones of inhibition of 28 mm, 22 mm, 21 mm, 25 mm and 31 mm against *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis* and *Staphylococcus aureus* (Selvakumar et al. 2012). Synthesis of silver nanoparticles using *Streptomyces* sp. & *Rhodococcus* sp. and their antibacterial potential with the zone inhibition of 26 mm against *Pseudomonas aeruginosa* followed by *Staphylococcus aureus* (23 mm), *Klebsiella Pneumoniae* (21 mm), and *E. coli* (19 mm) was reported (Sukanya et al. 2013). Extracellular silver nanoparticles synthesized from *Streptomyces parvulus* SSNP11 exhibited zone inhibition of 30 mm, 26 mm, 21 mm and 26 mm against *Bacillus subtilis*, *Salmonella typhi*, *Pseudomonas putida* and *Klebsiella pneumoniae* respectively (Prakasham et al. 2014). Intracellular gold nanoparticle synthesized from *Streptomyces viridogens* HM10 showed 14 mm and 16 mm zones of inhibition against *Staphylococcus aureus* and *Escherichia coli* (Balagurunathan et al. 2010). Antibacterial activity of metal nanoparticles from actinomycetes species are given in Table 1.

Antifungal activity of nanoparticles from actinomycetes

The biologically synthesized silver nanoparticles using *Streptomyces* sp. JAR1 inhibited *Fusarium* sp. and *Aspergillus terrus* JAS1 with zones of inhibition of 21 mm and 16 mm respectively for 100 µl of nanoparticles (Chauhan et al. 2013). Silver nanoparticle synthesized from *Streptomyces* sp. VITBT7 showed selective inhibition against *Aspergillus fumigatus* (MTCC3002) and *Aspergillus niger* (MTCC1344) with 20 mm and 22 mm which were better than the activity of the cell free supernatant (Subashini et al. 2013). Silver nanoparticles synthesized from *Streptomyces* sp. VITSTK7 showed antifungal index of 75% against

Aspergillus fumigatus, 67% against *Aspergillus niger* and 62% against *Aspergillus flavus* (Thenmozhi et al. 2013). Silver nanoparticles synthesized using *Streptomyces* sp.VITPK1 showed potential anti-candidal activity against *Candica albicans*, *Candida tropicalis* and *Candida krusei* with zones of inhibition of 20 mm, 18 mm and 16 mm respectively (Sanjenbam et al. 2014). Gold nanoparticles synthesised using *Streptomyces* sp. VITDDK3 exhibited antifungal activities against *Microphyton gypseum* and *Tricophyton rubrum* with zones of inhibition of 10 mm and 13 mm respectively (Gopal et al. 2013). Nanoparticles were also found to be potentially active against various human pathogenic fungi such as *Candida albicans, C.tropicalis, C.krusei, Saccharomyces cerevisiae* and different species of the genus *Aspergillus which include A.niger, A. fumigatus, A. flavus, A. terreus* and *A. brasiliensis.* Synthesised nanoparticles also showed activity against dermatophytes like *Trichophyton rubrum* and *T. tonsurans*, *Scedosporium* sp., and *Ganoderma* sp. (Chauhun et al. 2013; Manivasagan et al. 2013).

Antiparasitic activity of nanoparticles from actinomycetes

Silver nanoparticles synthesized from actinomycetes (*Streptomyces* sp.), has also been reported to possess antiparasitic activity against *Rhipicephalus microplus and Haemaphysalis bispinosa* (Karthik et al. 2014).

Biological applications of nanoparticles from actinomycetes

Antioxidants neutralize free radicals thereby protecting cell damage. Metal and metal oxide nanoparticles are effective free radical scavengers and thus play an important role in biomedical applications (Hamasaki et al. 2008). Free radicals initiate lipid peroxidation which is

the oxidative degradation of lipids which incurs cell damage. Gold nanoparticles synthesized from *Streptomyces* sp. NK52 exhibited 47% inhibition of lipid peroxidation (Prakash et al. 2013). Silver nanoparticles synthesized from *Nocardiopsis* sp. MBRC-1 showed cytotoxic activity against human cervical cancer cell line and it caused 50% inhibition to cell viability at 200 µg/mL of the nanoparticle (Manivasagan et al. 2013). Gold nanoparticles produced by marine *Nocardiopsis* sp. MBRC-48 showed better reducing potential than standard ascorbic acid. It exhibited 69% of DPPH free radical scavenging activity at 300 µg/mL (Manivasagan et al. 2015).

Nanoparticles synthesized from actinomycetes having antimicrobial properties are used in fabric industry. Copper and zinc nanoparticles synthesized using *Streptomyces* sp. were coated on to 100% cotton fabric by pad-dry-cure-method. The processed fabric was placed on to a bacteriostasis agar plate swabbed with the bacterial inoculums. Copper nanoparticles synthesized showed a zone of bacteriostasis of 30 mm and 27 mm after 24 hours for *Staphylococcus aureus* and *Escherichia coli* respectively. The synthesized zinc nanoparticles showed a zone of bacteriostasis of 24 mm and 21 mm after 24 hours for *Staphylococcus aureus* and *Escherichia coli* respectively. These fabrics can be used in hospitals to prevent or minimize infection (Usha et al. 2010). Silver nanoparticles (25 µg) synthesized from *Streptomyces* sp. showed 22 mm zone of inhibition against extended-spectrum beta-lactamases (ESBL) pathogen *Klebsiella pneumoniae* (ATCC 700603) (Subhashini et al. 2014). Gold nanoparticles synthesized from *Streptomyces* sp LK-3 was used to treat *Plasmodium berghei* ANKA (PbA) infected mice and it was observed that the survivability increased up to 85% when compared to the control whose survivability was 50% on 8 days post infection (Karthik et al. 2013). Table 2 summarizes other applications (excluding antibacterial activity) of nanoparticles from actinomycetes

Synthesis of biogenic nanoparticles from actinomycetes derived compounds

Very few reports are available on the synthesis of biogenic nanoparticles from actinomycetes derived compounds. A blue pigment, actinorhodin produced by *Streptomyces coelicolor* was separated from the cells by centrifugation and was used to synthesize silver nanoparticles by photo-irradiation method. The synthesized nanoparticle was tested for antibacterial activity against Methicillin-resistant *Staphylococcus aureus* (MRSA) (Manikprabhu and Lingappa 2013). Gold and silver nanoparticles were produced using methyl esters of myristate, palmitate and stearate (thermostable glycolipid) extracted from *Gordonia amicalis* HS-11, cultivated on a medium containing n-hexadecane as the sole source of carbon. The glycolipid mediated synthesized gold and silver nanoparticles exhibited 89.8 and 94.85% hydroxyl radical scavenging activity respectively. The gold and silver nanoparticles mediated by the purified glycolipid exhibited 74 and 67.25% nitric oxide radical scavenging activity respectively (Sowani et al. 2016). The increase in efficiency of nanoparticles synthesized using actinomycetes derived compound is evident from the above reports. Each actinomycetes strain had the genetic potential to synthesis 10-20 secondary metabolites (Lam 2006). The metal and metal oxide reducing potential of actinomycetes derived compounds for biogenic synthesis of nanoparticles and the possible mechanism involved in the synthesis need to be explored. Such nanoparticles would have better bioactive efficiency than conventional nanoparticles.

Challenges of using metal and metal oxide nanoparticles

Even though biogenic NPs find extensive applications in various fields, they have few shortcomings which prevent their use in medical and other related applications. Effective stabilization is necessary to prevent agglomeration of nanoparticles due to the high-surface

energy and protect the properties of the synthesized nanoparticles. Biodistribution of nanoparticle is affected by interaction with proteins through a process called opsonisation and these alter the properties of the nanoparticles (Sanvicens and Marco 2008). Mononuclear phagocyte system also called as reticuloendothelial system (RES) composed of monocytes and macrophages also interacts with nanoparticles. Several approaches have been tried to evade the unwanted interactions of NPs during delivery. One such approach is coating the nanoparticles with polymers. Coating of nanoparticles using polyethylene glycol (PEG) minimizes unwanted recognition and thereby increases the circulation half-life of nanoparticles (Owens and Peppas 2006). Multi walled carbon nanotubules (MWCNT) when coated with ammonium/chelator functional group evades uptake by RES (Singh et al. 2006). Water soluble, thiol-stabilized gold nanoparticles were synthesized using monohydroxy (1-mercaptoundec-11-yl) tetraethylene glycol for better medical applications. The hydrophilic tetraethylene glycol group makes the nanoparticles water soluble and the hydrophobic carbon chain confers stability to the nanoparticle (Li et al. 2002). Water solubility of the nanoparticles increases its biocompatibility. The toxic effect of nanoparticles has to be taken in to account when they are used for *in vivo* applications. Nanotoxicity is related to (i) the possible release of (toxic) ions from metallic nanoparticles and (ii) the oxidative stress due to the intrinsic characteristics of the nanoparticle (morphology, surface charge, size and chemical surface composition) (Seabra and Duran, 2015). None of the nanoparticles synthesized using actinomycetes were tested extensively for toxicity. Element specific toxicity due to the core metal or metal oxide and at certain instances toxicity caused by surface coating contributes to nanotoxicity of nanoparticles. Other desired property would be the specificity which can be achieved by adding aptamers, peptide etc. which recognizes a prostate-specific membrane antigen (Farokhzad et al. 2006). The mechanism of

interaction between the nanoparticle and the cells are not clearly understood and this would help the researchers to synthesize desired metal and metal oxide nanoparticles with better efficiency. Use of magnetic nanoparticles and quantum dots facilitate real time imaging and biodistribution of nanoparticles (Derfus et al. 2007).

The main challenges related to green synthesis of NPs can be summarized as (i) limitations related to the scaling up the syntheses processes; (ii) the reproducibility of the biogenic processes needs to be improved; (iii) the mechanism of nanoparticle formation are not completely elucidated; (iv) the control over nanoparticle size and distribution needs to be enhanced; (v) mechanism of action metal/ metal oxide NPs on targets need to be studied. In addition, the potential toxic effects of biogenically synthesised nanoparticles need to be studied further. Therefore, there is a need for further studies on biogenic synthesis of metal and metal oxide nanoparticles from actinomycetes/ actinomycetes derived secondary metabolites for stability, toxicity, specific size, shape and composition to make it as effective bioactive nanoparticles for therapeutic applications.

Conclusion

New therapeutic agents are the need of the hour as microbial pathogens develop resistance to the available antimicrobial agents. Actinomycetes have been extensively studied for their ability to produce secondary metabolites with varied biological applications. Biogenic synthesis of nanoparticles mediated by actinomycetes has great scope for developing nanoantimicrobials and nanoantibiotics which could be used as alternative therapeutic agents. Though there are several reports of biogenic nanoparticle synthesis from actinomycetes, studies

on synthesis of metal nanoparticles using actinomycetes derived bioactive compounds are scanty and needs to be studied further. Targeted drug delivery needs to be improved in such a way they distinguish microbes and infectious cells from healthy cells. Bio compatible nanoparticles should be developed so as to use them in medical and pharmaceutical fields. The fate of biogenically synthesised nanoparticles on human tissues needs to be studied further. All these factors should be taken into account while synthesizing biogenic nanoparticles for *in vivo* use as therapeutic agents.

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Conflict of Interest

The authors declare no conflict of interest.

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Table 1: Antibacterial nanoparticles synthesized from actinomycetes

Actinomycetes	**Type of NPs**	**References**
Streptacidiphilus durhamensis	Silver	Buszewski et al. 2016
Streptomyces graminofaciens	Siver	Kamel et al. 2016
Streptomyces rochei MHM13	Silver	Abd-Elnaby et al. 2016
Streptomyces sp.VITPK1	Silver	Sanjenbam et al. 2014
Actinomycetes sp.	Silver	Sunitha et al. 2014
Streptomyces sp. LK3	Silver	Karthik et al. 2014
Streptomyces sp.	Silver	Abdeen et al. 2014

Streptomyces sp. VDP-5	Silver	Singh et al. 2014
Streptomyces- MS 26	Silver	Zarina and Nanda, 2014
Streptomyces parvuus SSNP11	Silver	Prakasham et al. 2014
Streptomyces sp. JAR1	Silver	Chauhun et al. 2013
Thermoactinomyces sp.	Silver	Deepa et al. 2013
Nocardiopsis sp. MBRC-1	Silver	Manivasagan et al. 2013
Streptomyces sp. VITBT7	Silver	Subashini and Kannabiran 2013
Streptomyces sp. I & II, *Rhodococcus* sp.	Silver	Sukanya et al. 2013
Rhodococcus sp.	Silver	Otari et al. 2012
Streptomyces rochei	Silver	Selvakumar et al. 2012
Nocardia farcinica	Gold	Shah et al. 2012
Streptomyces glaucus 71MD	Silver	Tsibakhashvili et al. 2011
Streptomyces sp. ERI-3	Silver	Zonooz and Salouti 2011
Streptomyces sp. HBUM171191	Zinc/manganese	Waghmare et al. 2011
Streptomycetes viridogens HM10	Gold	Balagurunathan et al. 2011
Rhodococcus sp.	Gold	Ahmad et al. 2003
Streptomyces sp.	Zinc/copper	Usha et al. 2010

Table 2: Biomedical application of nanoparticles synthesized from actinomycetes

Actinomycetes	Type of NP	Size(nm)/ Shape	Bioactivity/Target Area	References
Rhodococcus sp.	Gold	9/ spherical	Antifungal, catalysis and synthesis of coating for electronic applications	Ahmad et al. 2003
Rhodococcus sp.	Silver	10/ spherical	Varied applications – catalysis, biological labeling, optoelectronics etc.	Otari et al. 2012
Streptomyces sp.	Zinc	Spherical	Antibacterial nanopackaging	Usha et al. 2012
Streptomyces sp JAR1	Silver	68.13	Antibacterial and antifungal	Chauhan et al. 2013
Streptomyces sp. NK52	Gold	10-100/ various shapes	Anti-lipid peroxidation activity	Prakash et al. 2013
Nocardiopsis sp. MBRC-1	SIlver	45/ spherical	Antifungal and cytotoxitic activity against HeLa (human cervical cancer cell line)	Manivasagan et al. 2013
Streptomyces sp.	Silver	20-60/	Anti-*Aspergillus* activity	Thenmozhi et al.

VITSTK7		spherical		2013
Actinorhodin from *Streptomyces coelicolor*	Silver	28-50/ irregular	Anti-MRSA activity	Manikprabhu and Lingappa 2013
Streptomyces sp. VITBT7	Silver	20-70/ spherical	Antifungal and antibacterial activity	Subhashini et al. 2013
Streptomyces sp. VITPK1	Silver	20-45	Anticandidal activity	Sanjenbam et al. 2014
Streptomyces sp.	Silver	20-70/ spherical	Anti-ESBL activity	Subhashini et al. 2014
Gordonia amicalis HS-11 (methyl esters of myristate, palmitate and stearate)	Silver, gold	5-25/ spherical	Free radical scavenging activity	Sowani et al. 2016