



Phytogenic Synthesis of Ag Bionano-Antibiotics Against ESKAPE Drug Resistant Communities in Krasnoyarsk, Siberia

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Abstract

The present study reports synthesis of silver nano-antibiotics from aqueous extract of *H. dissectum*. The nano-antibiotics were characterized using UV–visible spectra which displayed maximum absorbance at 430 nm. The role of phytocomponents as reducing agent and stabilization of silver nano-antibiotics was depicted with Fourier-transform infrared spectroscopy which revealed presence of hydroxyl and carboxyl groups associated with silver nano-antibiotics. The crystalline nature was studied with X-ray diffraction which showed Bragg's intensities at 2θ angle which denoted (101), (111), (200), (220), (311) planes. The morphological characteristics were studied using Transmission Electron Microscopy to reveal the size ranging from 5 to 50 nm. The bactericidal activity of nano-antibiotics was studied via well diffusion and minimal inhibitory concentration assay against members of drug-resistant communities bearing resistant to more than ten standard antibiotics. Nano-antibiotics displayed highest activity against *Ps. aeruginosa* strain 55 and *Methicillin-resistant Staphylococcus aureus* with 16 mm zone of inhibition followed by *Kl. pneumoniae* strain 104 and *E. coli* strain 55. Moderate activity was observed against *Ac. baumannii* strains with 12 mm zone of inhibition. The obtained results envision the role of plant mediated nano-antibiotics as one of the best suited alternatives towards combating drug resistant pathogens.

Keywords *Heracleum dissectum* · Silver nano-antibiotics · ESKAPE · Antimicrobial-resistant · Krasnoyarsk · Siberia

Introduction

The emergence of antibiotic resistant era has resulted owing to the expansion of multi drug resistant pathogens [1]. The proliferation of antimicrobial resistance has tempered the global economy by influencing health and biomedical sectors [2]. According to the latest survey,

fatality ratio owing to drug-resistant pathogens is increasing especially in hospital-acquired infections [3, 4]. The recent studies report that 70% of hospital acquired infections are caused by pathogenic bacteria which are resistant to one or more antibiotics [5–7]. Especially, ESKAPE pathogens which includes *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter*

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species [8, 9]. These pathogens are reported to be enduring the global drug resistance and are prevalent in both developed and developing countries [8, 10]. Hence, there is great demand to develop novel antimicrobial agents which can combat the drug-resistant pathogens [11, 12]. Nano-antibiotics are the class of new antimicrobial agents miniaturized at nano-scale [13]. The recent advances in nanotechnological research have up lifted the technological aspects to synthesize nanomaterials with specific properties [14]. The physico-chemical properties of the nanomaterials make them one of the most inspiring materials in comparison to their bulk counterparts [15–18]. Scientific studies have demonstrated the effectiveness of metallic nanoparticles against wide range of pathogens. The nano-antibiotics act efficiently on pathogens by binding to the cell wall followed by depolarizing the contents of the cell wall membrane which results in the loss of cellular contents [19]. Studies also highlight that nano-antibiotics interact with the vital components of pathogens and influence the metabolic and genetic pathways, which leads to inactivation of enzymes and prevent replication [18].

In recent years, plant mediated nano-antibiotics offers facile route in contrast to conventional methods which are often associated with myriad limitations [20]. The potential of plants to synthesized multi-functional nanomaterials can be attributed towards their potential for phyto-remediation of various elements and breakdown of nutrients [21–23]. The diverse classes of phyto-constituents such as terpenoids, alkaloids, flavonoids, vitamins, polyphenols and phenolic acids are reported to interact with the metal salts and mediate the reduction process [20]. Based on these facts, in the present investigation, aqueous extract from *H. dissectum* was evaluated to synthesize silver nano-antibiotics. The selection of plant *H. dissectum* was carried out based on the ethno-pharmacological documentation which reports its usage for centuries [24]. The plant *H. dissectum* belongs to Apiaceae family which is widely distributed as perennial herb across the eastern Russia and northern part of China [25]. The traditional records report the usage of *H. dissectum* by local Siberians to treat diabetics, curing rheumatoid, and pain killer [26]. To best of our knowledge, *H. dissectum* is less explored plant species which is reported to bear significant therapeutic index. Hence in the present study, *H. dissectum* became the subject of interest to synthesize silver nano-antibiotics.

Materials and Methods

Plant Processing

To obtain the aqueous extract, plant materials were processed according to the protocol described by Syed et al.

[19]. In brief, healthy leaves and stem samples of *H. dissectum* were collected from local Siberian forest area beside Siberian Federal University, Krasnoyarsk region, Siberia, Russia. The samples were thoroughly washed under tap water to remove the soil debris followed by rinsing with double distilled water. The healthy plant materials were chopped into small segments and 20 g of finely cut materials was added to a 1-l beaker containing 500 ml of sterile distilled water [19]. The mixture was boiled for 30 min to obtained aqueous extract which was filtered and stored at 4 °C until further use.

Synthesis of Nano-Antibiotics Using *H. dissectum* and Synthesis of Chemically Derived Nanoparticles

The aqueous extract was treated with 1 mM silver nitrate solution and conversion of Ag^+ to Ag^0 was visually confirmed with the change in the color of the reaction mixture. The samples were collected periodically and analyzed with double beam UV-visible spectrophotometer. Different parameters such as temperature and pH influencing synthesis were studied. The temperature was varied from 20 to 100 °C and pH was varied from acidic to alkaline. Further, different concentration of silver nitrate was studied from 0.5 to 2 mM. The samples were drawn periodically to monitor the synthesis of nano-antibiotics and analyzed using a UV-visible spectrophotometer.

Characterization of Nano-Antibiotics

The synthesized nano-antibiotics were characterization with high-resolution transmission electron microscope (HRTEM) JEOL JEM-2100 operating at an acceleration voltage of 200 kV coupled with an energy-dispersive spectrometer Oxford Inca x-sight [27]. The possible role of the phytocomponents as a reducing agent was studied using FTIR spectroscopy. The crystalline nature was studied using X-ray diffractometer instrument operating at a voltage of 30 kV.

Multi-Drug Resistant Pathogens

The selected strains are reported to be multi-drug resistant strains bearing resistant mechanism to nearly 10 different antibiotics. The test pathogens are *Ac. baumannii* strain 210, *Ac. baumannii* strain 211, *Ps. aeruginosa* strain 215, *Ps. aeruginosa* strain 40, *Kl. pneumoniae* strain 104, *MRSA*, *E. coli* strain 55. All the test pathogens were clinically isolated from patients suffering from myriad infections. The pathogens were handled with prime care and preserved according to standard guidelines and maintained

at culture collection center of Krasnoyarsk Medical University.

Preparation of Test Bacterial Suspension

The preparation of inoculum was in accordance with the guidelines of Clinical and Laboratory Standards Institute (CLSI). The test inoculum was prepared according to the protocol described by Teh et al. [28] with slight modification. In brief, the actively growing test strains were inoculated into 10 ml sterile Mueller–Hinton broth (MHB) and incubated overnight at 37 °C. The overnight test bacterial suspensions were optically monitored and the absorbance was adjusted to 0.5 McFarland Standard with sterile Mueller–Hinton broth under aseptic conditions [28].

Antimicrobial Activity of Nano-Antibiotics

The synthesized nano-antibiotics were centrifuged at 15,000 rpm for 20 min. The obtained pellet was washed thrice with double distilled water and 5 mg/ml concentration was evaluated for antimicrobial activity via well diffusion assay. In brief pre-warmed MHA (Mueller–Hinton agar) plates were seeded with test bacterial suspension (1.5×10^6 CFU/ml) and swabbed uniformly, later by using sterile cork borer agar was punched to obtained wells and 100 μ l of nano-antibiotics were added into each well and incubated at 37 °C for 24 h. After incubation period, the zone of inhibition was measured. Similarly, broth dilution assay was carried out according to the protocol described by Baker et al. [10] with slight modification. In brief, 5 ml MHA broth was seeded with bacterial suspension (1.5×10^6 CFU/ml) followed by inoculating the test sample nano-antibiotics and incubated for 12 h. The activity was measured based on the absorbance recorded at 600 nm. The control was maintained to each test pathogens and readings were compared to evaluate bactericidal activity [10].

Minimal Inhibitory Concentration

The minimal inhibitory concentration (MIC) was determined according to the protocol described by Syed et al. [12]. In brief, the plates were prepared under aseptic conditions and volume of 100 μ l of test material (nano-antibiotics 1 mg/ml). The test material was added in the first row followed by addition of 50 μ l of nutrient broth to all other wells. Further, serial dilutions were performed using a multichannel pipette and 10 μ l of resazurin as growth indicator was seeded to each well. The final volume of the broth was adjusted with the addition of 30 μ l isosensitized broth to each well ensuring the final volume of the nutrient broth. Finally, 10 μ l of bacterial suspension

(1.5×10^6 CFU/ml) was added to each well. The plate was incubated at 37 °C for 18 to 24 h. The color change was then assessed visually from purple to pink or colorless. The lowest concentration at which color change occurred was taken as the MIC value [29].

Results and Discussion

Synthesis of Nano-Antibiotics

The aqueous extract of *H. dissectum* forms one of the facile routes to synthesize silver nano-antibiotics. In the present investigation, the synthesis was completed within 20 min of reaction under the influence of optimized parameters. The synthesis was monitored with change in the color of reaction mixture. The color intensity increased and synthesis was confirmed with spectroscopic analysis using

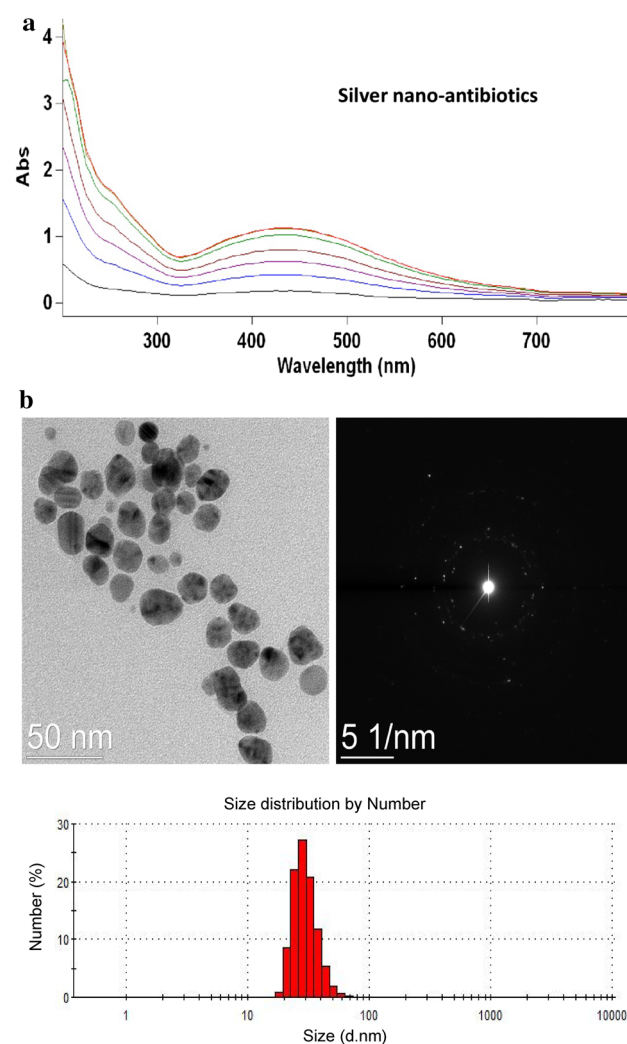


Fig. 1 a UV–visible spectra of silver bionano-antibiotics. b TEM analysis of silver bionano-antibiotics with DLS analysis

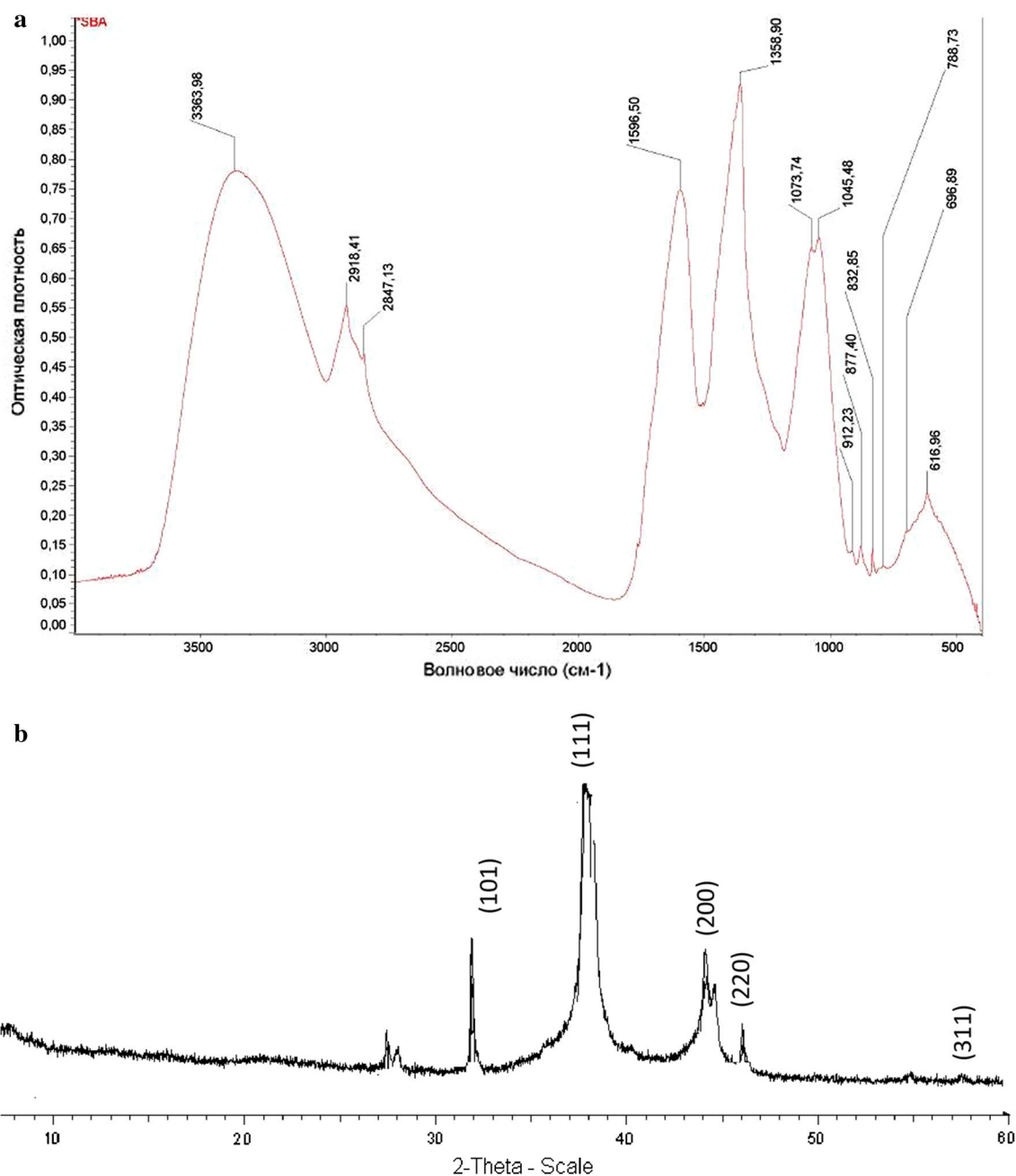


Fig. 2 **a** FTIR analysis of silver bionano-antibiotics. **b** XRD analysis of silver bionano-antibiotics

Table 1 FTIR peak position of all functional groups

FTIR	Functional group
3363	OH
2918	CH
1596	C=O
1358	C–H
1045	C–O

UV–visible spectroscopy which displayed the broad absorption between 200 and 800 nm with maximum absorption occurring at 430 nm (Fig. 1a). The UV–visible

spectroscopy forms one of the ideal and sensitive tools to confirm the formation of silver nanomaterials [30]. The increased in the intense and absorption is due to the surface plasmon resonance which describes the collective excitation of electrons [31, 32]. The excitation of electrons with change in energy levels reflects the reduction of metal ions to form nano-sized materials [33, 34]. The obtained results coincide with findings of Anandalakshmi et al. [35] which indicate the presence of phyto-components in aqueous extract mediating synthesis [35].

Fig. 3 a Influence of temperature on synthesis of silver bionano-antibiotics.
b Influence of pH on synthesis of silver bionano-antibiotics.
c Influence of metal concentration on synthesis of silver bionano-antibiotics

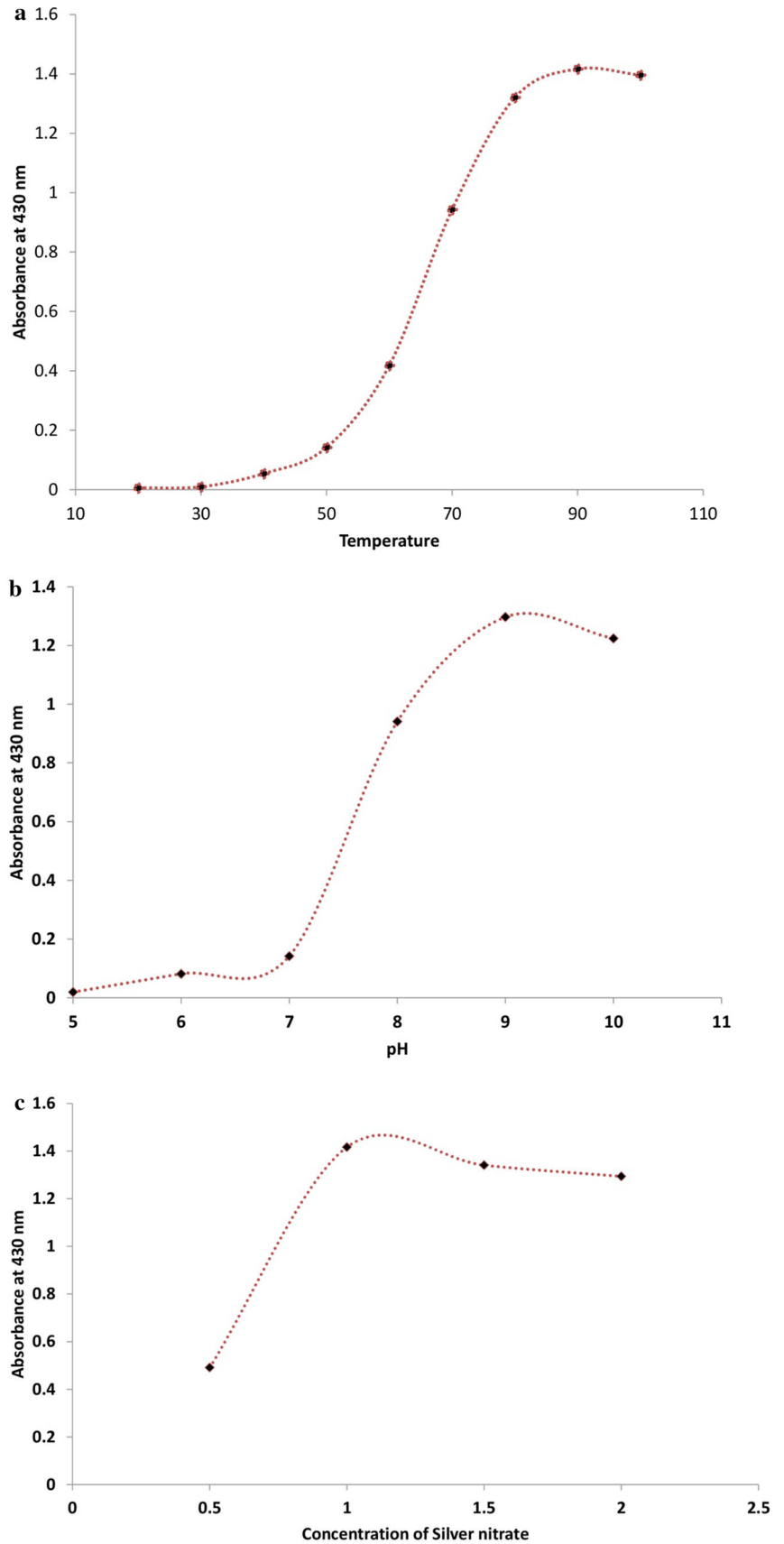


Table 2 Data on antibiotic resistance of the strains used in the work

Strain	Cep	Cez	Cef	Imp	Mer	Tic	Gen	Tob	Ami	Cip	Chl	Ctm
<i>Ac. baumannii</i> 211	R	R	R	S	R	R	R	S	R	R	R	R
<i>Ac. baumannii</i> 210	R	R	R	R	R	R	R	S	R	R	R	R
<i>Ps. aeruginosa</i> 215	S	S	S	R	R	R	S	S	S	S	R	R
<i>Ps. aeruginosa</i> 40	R	R	R	S	R	R	R	R	R	R	R	R
<i>Kl. pneumonia</i> 104	R	R	R	S	R	R	R	R	R	S	R	R
<i>E. coli</i> 55	R	R	R	S	S	R	R	R	S	R	R	R

Cep cefoperazone, *Cez* ceftazidime, *Cef* cefepime, *Imp* imipenem, *Mer* meropenem, *Tic* ticarcillin/clavulanate, *Gen* gentamicin, *Tob* tobramycin, *Ami* amikacin, *Cip* ciprofloxacin, *Chl* chloramphenicol, *Ctm* cotrimoxazole

Characterization of Nano-Antibiotics

The morphological characteristics was determined using TEM which displayed polydispersity with size ranging from 5 to 50 nm which was also confirmed with dynamic light scattering as shown in the Fig. 1b. The size and shape of nano-antibiotics can be modulated to achieve definite morphological characteristics based on the parameters such as concentration of plant extract and metal salt composition. The bio-molecular interaction between the phyto-components and silver nano-antibiotics was predicted with FTIR analysis which displayed vibrational stretches (Fig. 2a) in the IR range which corresponds to functional groups (Table 1). The influence of phyto-components in stabilization of nanomaterials has been well documented [36, 37]. The diverse classes of phyto-components like polyphenols, tannic acids, vitamins, terpenoids, alkaloids, flavonoids and saponins are reported to act as reducing agents to synthesize nanomaterials. These phyto-components are well described to stabilize the nanomaterials unlike the other conventional process wherein additional stabilizing agents are supplemented during the synthesis process. The phyto-components are also reported to adhere to nanomaterials which play vital role towards achieving specific activity. The plant mediated nanomaterials is said to have better advantageous especially in conferring biological activities like antimicrobial. The crystalline nature of nano-antibiotics was depicted by XRD analysis which displayed (101), (111), (200), (220), (311) Bragg's peaks at 2 theta angle conferring the face centric cube of crystalline silver (Fig. 2b). The obtained result is in accordance with earlier findings of Patra et al. [38].

Different Parameters Influencing the Synthesis

There are different factors which influences the maximum synthesis process. The synthesis was minimal at lower temperatures such as 20, 30 and 40 °C. Further, synthesis was moderate between 50 and 70 °C which indicated elevated temperature favoring the synthesis. The synthesis

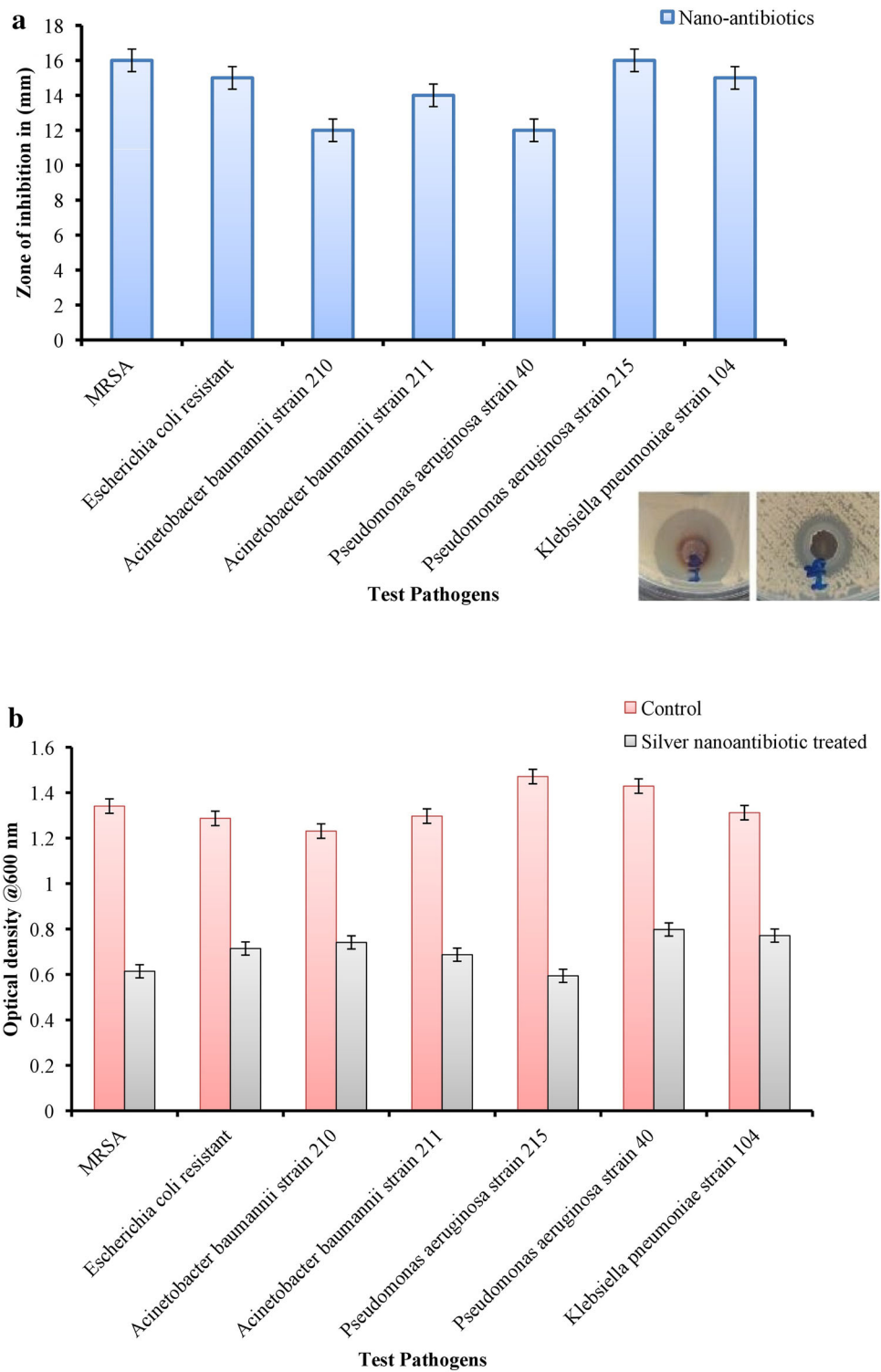
was maximum synthesis at 90 °C which was monitored by measuring the absorbance at 430 nm (Fig. 3a). Influence of higher temperature can be related to reduction kinetic and aggregation of atoms to form nuclei followed by ripening and crystal growth to achieve particle [10]. Earlier studies demonstrated that during plant mediated synthesis, size of the nanoparticles decreases with the increase in the temperature of the reaction mixture [19].

Apart from temperature, influence of pH was studied to determine its effect on rapid and maximum synthesis of nano-antibiotics. The pH was varied in the range of pH 5–10 and rate of synthesis was monitored. At acidic pH, the synthesis rate was much lower than the alkaline pH as shown in the Fig. 3b. The scientific studies demonstrated that pH play important role in the stability of nanomaterials. In the present investigation, increment in the rate of synthesis was observed at alkaline pH. The concentration of metal salts was also determined between 0.5 and 2 mM, the rate of synthesis was maximum at 1 mM concentration in comparison with other concentration (Fig. 3c). Large number of scientific studies have reported that 1 mM concentration is ideal for rapid synthesis with sufficient amount of Ag precursor available for production process [19, 22]. The influence of different parameters to mediate, stabilize and attenuate specific properties is well demonstrated [36].

Bactericidal Properties of Nano-Antibiotics

The bactericidal properties of nano-antibiotics was tested against pathogens which were recorded to have resistant for ampicillin, cefoperazone, cefepime, chloramphenicol, imipenem, meropenem, gentamicin, tetracycline, tobramycin and vancomycin antibiotics (Table 2). The activity was determined via well diffusion assay and measured as zone of inhibition across the well and statistically analyzed (Fig. 4a). Among all the test pathogens, highest activity was observed against *Ps. aeruginosa* strain 215 and MRSA with 16 mm zone of inhibition followed by *Kl. pneumoniae* strain 104 and *E. coli* strain 55. Moderate activity was

Fig. 4 a Bactericidal activity of bionano-antibiotics against multi-drug resistant pathogens via well diffusion assay.
b Bactericidal activity of bionano-antibiotics against multi-drug resistant pathogens via broth dilution assay



observed against *Ac. baumannii* strains with 12 mm zone of inhibition. The activity was in accordance with broth dilution assay which displayed decrease in the optical density of test pathogens in presence of nano-antibiotics (Fig. 4b). The activity was further confirmed with minimal

inhibitory concentration assay which displayed minimal activity obtaining between the concentration 0.625 $\mu\text{g/ml}$ to 1.25 $\mu\text{g/ml}$ (Table 3). Perusal of scientific literatures on *H. dissectum* describes scanty reports with few scientific studies working on this edible plant. Recently, a new

Table 3 Minimal inhibitory concentration of silver nano-antibiotics against multi-drug resistant pathogens

Pathogens	Silver nano-antibiotics ($\mu\text{g/ml}$)
<i>Ac. baumannii</i> strain 210	1.25
<i>Ac. baumannii</i> strain 211	1.25
<i>E. coli</i> strain 215	0.625
<i>Kl. pneumoniae</i> strain 104	1.25
MRSA	0.625
<i>Ps. aeruginosa</i> strain 40	1.25
<i>Ps. aeruginosa</i> strain 55	0.625

classes of phenylpropanoids, glycosides, coumarins and neolignans were isolated from the roots of *H. dissectum* which were reported to possess cytotoxic activity [26]. Much more studies are essential and required to reveal the untapped phyto-components from *H. dissectum*. In the present investigation, the antibacterial activity of plant mediated nanoparticles was compared with both chemically synthesized nanoparticles and the aqueous extract of *H. dissectum*. Interestingly, chemically synthesized nanoparticles had no effect on drug resistant test pathogens. The concentrated aqueous extract showed moderate activity which indicated the presence of active compounds from the plant which forms the capping across the particle to add bactericidal activity. The obtained results are promising enough for future investigation to elucidate the exact mechanism responsible synthesis and role of phyto-components in bactericidal activity. Overall, the obtained results attributes towards growing knowledge of developing new and safe antimicrobial agents. Even though considerable investigation are being carried out on different classes of nanomaterials are conducted, scanty reports are available on multi-drug resistant pathogenic microorganisms which are clinically significant and belonging to ESKAPE group. The obtained results coincides with the findings of Thiagarajan and Sangappa [39] which reports the activity of silver oxide nanoparticles against MRSA strain which was clinically isolated [39]. In the present investigation, activity was observed against both Gram -ve and Gram +ve pathogenic bacteria which indicates the broad spectrum activity of synthesized nano-antibiotics.

Possible Mechanism for Bactericidal Activity

Large number of scientific studies illustrates the antibacterial activity of silver nanomaterials against pathogenic microorganisms. The activity of nanomaterials depends on various parameters for instance, the size of the nanomaterials smaller the size, greater will be the activity. The

surface area of the nanomaterials higher the surface area, significant will be the activity of nanomaterials against targeted pathogen. Initially, the Ag^+ released binds to the membrane proteins and enzymes to form bond which results in the suppression and deactivation of the protein. Studies also confer the obstruction of respiratory enzymes by silver nanomaterials [40]. Furthermore, the source of synthesizing nanomaterials also contributes to attenuate antimicrobial activity against pathogens especially from biogenic source of synthesis of nanomaterials [41]. In the present investigation, polydispersity of nano-antibiotics play important role to suppress the growth of the test pathogens. The selected plant species to synthesize nano antibiotics is reported to have therapeutic index as per the traditional records which can also participate in antibacterial activity. The nano-antibiotics synthesized in the present study displayed significant activity against Gram +ve and Gram -ve test pathogens which are isolated from clinical samples of patients suffering from myriad infections. Further study in this area will be highly valuable to elucidate exact mechanism for antibacterial activity. The interaction of nanomaterials most of the pathogenic microorganisms have modulated the growth regulations process [42] which can be used as template based probe to identify the degree of resistance and susceptibility to design the monitoring of drug resistant pathogens [43, 44].

Conclusion

The activity obtained in the present investigation is promising enough to report the synthesis of silver nano-antibiotics using *H. dissectum*. The silver nano antibiotics displayed bactericidal activity via well diffusion assay and minimal inhibitory concentration against members of ESKAPE pathogens which are reported to be one of the leading causes of nosocomial infections. Overall the study forms initial findings which will be further evaluated for investigation to reveal the mechanism of synthesis and activity. The study also makes an attempt to evaluate nanomaterials as one of the best suited alternatives to combat drug resistant pathogens.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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