Cytotoxicity and anti-biofilm activities of biogenic cadmium nanoparticles and cadmium nitrate: a preliminary study

Mahboubeh Adeli-Sardou1,2 · Mojtaba Shakibaie3,4 · Hamid Forootanfar3,4 · Fereshteh Jabari-Morouei5 · Soudabe Riahi-Madvar6 · Sima-Sadat Ghafari-Shahrbabaki6 · Mitra Mehrabani1

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Abstract
Wild-type microorganisms have become tolerant to higher antibiotic and antimicrobial agent concentrations due to the global increase in antibiotic consumption. Green-synthesized nanoparticles (NPs) have been proposed as potential antimicrobial agents to overcome the problem. This research prepared cadmium nanoparticles (Cd NPs) using Artemisia persica extract. To clarify the biological behavior of Cd NPs and Cd (NO3)2, cytotoxicity, antibacterial, anti-biofilm, and biocompatible experiments were performed. Since Cd toxicity is associated with liver, kidney damage, and other deficits, HepG2 and HUVEC cell lines were employed as the in vitro cytotoxicity models. Cd NPs had a lower cytotoxic effect than Cd (NO3)2 against both HepG2 and HUVEC cells. The Cd NPs exhibited no hemolysis activity. The antibacterial and anti-biofilm studies were conducted using gram-positive Staphylococcus aureus and gram-negative Proteus mirabilis and Pseudomonas aeruginosa with the ability to form severe adherent biofilms. The antibacterial activity of Cd NPs against clinically isolated S. aureus, P. mirabilis, and P. aeruginosa was above 2560 µg mL−1. The Cd NPs (640 µg mL−1) decreased the biofilm formation of S. aureus, P. mirabilis, and P. aeruginosa by 24.6%, 31.6%, and 26.4%, respectively. Moreover, adding Cd NPs (100 µg/disc) to antibiotic discs increased the antibacterial activity of vancomycin, gentamicin, tetracycline, streptomycin, meropenem, and kanamycin against Methicillin-resistant S. aureus, significantly. Due to the emergence of resistant microorganisms, Cd NPs can be used as an exciting material to counterattack global health problems. Further research is needed to clarify the molecular mechanisms underlying Cd NPs’ pharmacological and toxicological effects.

Keywords Cadmium nanoparticle · Biogenic synthesis · Cytotoxicity · Anti-biofilm effect

Introduction
There has been an increasing interest in nanotechnology, which introduces the next generation of useful materials and many new technology areas in nanomedicine, biosensors, and bioelectronics (Daniel and Astruc 2004; Chung et al. 2019; Tariq et al. 2021). Nanotechnology has appeared as a multidisciplinary field in which acquiring a fundamental understanding of the electrical, optical, magnetic, and mechanical properties of nanostructures (Chari et al. 2017; Nasrollahzadeh et al. 2019; Faramarzi et al. 2020). The unique properties of nanomaterials make them an exciting subject in biological and clinical systems, as their properties differ from those of bulk materials (Khan et al. 2019; Zahin et al. 2020). Nanoparticles (NPs) have various applications in science and industry. Several publications have appeared in recent years documenting the use of
NPs in bioassay, imaging, and drug delivery (Vasudevan et al. 2015; Thovhogi et al. 2018; Uddin 2019; Sahoo et al. 2021). Several studies have demonstrated the antibacterial, antifungal, anti-biofilm, antioxidant, and anticancer potency of NPs (Anjomshoa et al. 2015; Abd et al. 2016; Khan et al. 2019; Alsaqaf et al. 2020). Although various methods have been developed and introduced to produce NPs, the green biosynthesis of metal and metalloid NPs has emerged as a noteworthy branch of nanobiotechnology because it is cost-effective, sustainable, environmentally friendly, bio-compatible, and non-toxic (Narayanan and Sakthivel 2010; Suresh et al. 2018; Aisida et al. 2020). Biological methods include the synthesis of nanoparticles by organisms such as bacteria, fungi, yeasts, and plant extracts. Different parts of plants and herbal extracts can be used to synthesize different types of metal(loid) NPs (Jayappa et al. 2020). The probable mechanism of action may be the reduction of metal(loid) ions by proteins, vitamins, and phytochemicals inside the plant parts (Salari et al. 2017; Shanthi et al. 2017; Wu et al. 2020; Rajeshkumar et al. 2021; Sahoo et al. 2021).

Among the various metal nanomaterials that exist, cadmium-based nanostructures have attracted the interest of many researchers due to their numerous biomedical applications, especially in the diagnosis, treatment, and targeted drug delivery of various types of cancers (Rodriguez-Fragoso et al. 2012; Malarkodi et al. 2014; Kominkova et al. 2017; Azizi et al. 2018; Gupta 2019; Shakibaie et al. 2021). NPs containing cadmium have been used to visualize and deliver drugs to soft tissue tumors, such as those affecting the retina and cornea (Gupta 2019). Cadmium-containing NPs such as Cd telluride (CdTe) NPs, cadmium sulfide capped with zinc (CdS: Zn 2+) NPs, CdS/ZnS quantum dots (CdS/ZnS QD), Cd oxide (Cdo), and CdS NPs are famous for their optical and electrical properties, making them suitable for use in various fields such as bio-sensing and bio-imaging, biosensor techniques, photovoltaic cell, and solar cells (Zhang et al. 2007; Muruganandam et al. 2014; Kalinowska et al. 2018; Ghotekar 2019; Dabhanie et al. 2021). Aside from these tremendous applications, Cd-containing NPs have been shown to have therapeutic applications in HepG2, HEK293T and K562, A549, MCF-7, and AGS cell lines (Zhang et al. 2007; Su et al. 2009; Shivaji et al. 2018; Gholami et al. 2020). In HepG2 cells, Cd-based NPs have increased hepatotoxicity through the extrinsic and intrinsic (mitochondria-dependent) pathways (Nguyen et al. 2013b). HepG2 cells have been used for studying cytotoxicity, oxidative stress, and mitochondrial dysfunction since it retains many specialized functions indicative of normal human hepatocytes (Nguyen et al. 2013b; Elje et al. 2020). Rodriguez et al. (2014) reported that exposure to cadmium-containing quantum dots might cause disruptions in cellular homeostatic processes, which may lead to cell death. Death can be triggered through the abrupt (necrosis) or programmed (apoptosis and autophagy) process. Early reports on including simple quantum dots in bacteria indicated that toxic ions are released when the surface of NPs is oxidized (Kloepfer et al. 2003). CdS NPs have also proven to have antibacterial and anti-biofilm properties (Rajeshkumar et al. 2014; Dhanabal and Gurunathan 2015; Abd et al. 2016; Haq Bhat and Yi 2019; Alsaqaf et al. 2020).

The literature review revealed no reports on hepatocellular toxicity, antibacterial or anti-biofilm activities associated with biologically synthesized cadmium NPs (Cd NPs). For this purpose, Cd NPs were synthesized by microwave irradiation in the presence of an aqueous extract of Artis misia persica and cadmium nitrate (Cd (NO₃)₂). In the present study, (Cd(NO₃)₂) was used to compare the biological properties of Cd NPs with their bulk form. Cytotoxicity of Cd NPs and Cd (NO₃)₂ was tested against human umbilical vein endothelial (HUVEC) and hepatocellular carcinoma (HepG2) cells. Furthermore, due to the increasing trend of drug resistance and the growing concern regarding antibiotic overuse, we evaluated antibacterial and anti-biofilm activities of Cd NPs and Cd (NO₃)₂ against clinical isolates of Staphylococcus aureus, Proteus mirabilis, and Pseudomonas aeruginosa. Additionally, the antibacterial activity of Cd NPs and Cd (NO₃)₂ was evaluated against methicillin-resistant S. aureus (MRSA) in combination with commercial antibiotics.

Materials and methods

Materials

Cd (NO₃)₂·4H₂O, Muller–Hinton broth (MHB), Agar, Tryptic soy broth (TSB), 1, 2, 3, 5-triphenyl-2 H-tetrazolium chloride (TTC), and Crystal violet were obtained from Merck Chemicals (Darmstadt, Germany). Commercial antibiotic discs including azithromycin (AZM), Ciprofloxacin (CP), ceftriaxone (CRO), Cefotaxime (CTX), erythromycin (E), tobramycin (TOB), nalidixic acid (NA), cefalexin (CN), cefixime (CMF), gentamicin (GM), tetracycline (TE), streptomycin (S), amoxicillin (AMX), Meropenem (MEM), Methicillin (ME), Levofloxacin (LEV), Kanamycin (K), and vancomycin (V) were purchased from Padtan TebB (PT Co., Iran) Company. Dulbecco’s modified Eagle medium (DMEM) and fetal bovine serum (FBS) were provided by Gibco (Life Sciences Inc., USA). 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), Penicillin–Streptomycin solution (100X), and Trypsin-EDTA (10X) were obtained from Borna Poyesh Gene Company (BP Gene Co., Iran). All solvents were of analytical grade.
Biological synthesis and characterization of cd NPs

The synthesis of Cd NPs followed the same procedure we used in our previous work (Shakibaie et al. 2021). Briefly, an aqueous extract of A. persica (0.5% w/v, 100 mL) was mixed with Cd (NO$_3$)$_2$ solution (7.7 Mm, 10 mL), and the mixture was heated three times (15 s) in a microwave oven (850 W, with 10 min rest intervals). In order to separate produced Cd NPs, the mixture was centrifuged and washed with chloroform, ethanol, and distilled water, respectively, and then autoclaved. The shape of Cd NPs was measured by a scanning electron microscope (SEM) apparatus (KYKY-EM3200). The Zeta sizer Nano S90 (Malvern) analyzed the size distribution pattern of the NPs (Shakibaie et al. 2021).

Cytotoxicity evaluation of cd NPs

To study the cytotoxicity of Cd NPs and Cd (NO$_3$)$_2$, HepG2 and HUVEC cells were applied. The Pasteur Institute (Tehran, Iran) provided these cell lines. The cells were cultured in the DMEM medium with 10% (v/v) FBS, 100 units mL$^{-1}$ penicillin, and 100 mg mL$^{-1}$ streptomycin in a CO$_2$ incubator (5% CO$_2$, 37 °C). Upon reaching 80% confluency, 10,000 cells were seeded into 96-well tissue culture plates. The following day, various concentrations of Cd NPs, Cd (NO$_3$)$_2$, and cisplatin (0-640 µg mL$^{-1}$) were added, and the cells were incubated individually for 24 and 48 h at 37 °C. Following incubation, each well was incubated with 5 mg mL$^{-1}$ of MTT solution for three hours at 37 °C. TTC solution (0.5 mg mL$^{-1}$) was then added to each sample and incubated at 37 °C for 30 min. Tetrazolium salts (TTC) are metabolically active bacteria solubilization with water, and will reduce it to a reddish formazan. The MIC value was defined as the lowest concentration that no color change was observed. Ciprofloxacin is considered the positive control (0-0.125 µg mL$^{-1}$). In the subsequent step, the disc diffusion method was used to determine the susceptibility of MRSA to antibiotics alone and when combined with the sub-inhibitory concentration of Cd NPs and Cd (NO$_3$)$_2$. Initially, the 0.5 McFarland standard of freshly cultured MRSA was spread on the surface of the MHA medium. Different antibiotic disks, the sub-inhibitory concentration of Cd NPs and Cd (NO$_3$)$_2$ coated antibiotic disks, and the sub-inhibitory concentration of Cd NPs and Cd (NO$_3$)$_2$ coated blank discs were placed on the surface of the inoculated MHA media. The growth inhibition zone diameter (mm) for each sample was measured after 24 h of incubation at 37 °C. The experiments were performed three times, and the results were reported as mean ± SD.

In vitro hemolysis analysis

According to Muzquiz-Ramos et al. (2015), the hemolysis test was performed. In brief, whole blood was collected in a K$_2$EDTA tube and centrifuged at 2500 g for 4 min at 4 ºC. After discarding the plasma, the pellet was washed with Alsever’s solution (dextrose 0.116 M, NaCl 0.071 M, sodium citrate 0.027 M, and citric acid 0.002 M, pH 6.4) three times. Afterward, the pellet was diluted with Alsever’s solution (1:10 v/v). Subsequently, 200 µL of diluted RBCs suspension was added to different Cd NPs and Cd (NO$_3$)$_2$ concentrations. Deionized water and Alsever’s solution were considered positive (100% hemolysis) and negative (0% hemolysis) controls, respectively. All samples were incubated at 37 ºC for 30 min and centrifuged. Then the Abs value of the released hemoglobin from the RBCs was determined at 415 nm. Samples with less than 5% hemolysis rate were considered negative.

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\text{Hemolysis (\%)} = \frac{(\text{Abs of sample} - \text{Abs of the negative control})}{(\text{Abs of the positive control} - \text{Abs of the negative control})} \times 100
\]

Antibacterial and Biofilm inhibition assay

The microdilution method was applied to measure the antibacterial effect of Cd NPs and Cd (NO$_3$)$_2$ (Shakibaie et al. 2019a). In summary, different concentrations of Cd NPs and Cd (NO$_3$)$_2$ (0-2560 µg mL$^{-1}$) were plated into a 96-well microplate. 10$^5$ CFU/well of clinically isolated S. aureus, P. aeruginosa, and P. mirabilis was separately added to each well. The plate was incubated at 37 °C for 24 h. TTC solution (0.5 mg mL$^{-1}$) was then added to each sample and incubated at 37 °C for 30 min. Tetrazolium salts (TTC) are widely used for determining minimum inhibitory concentrations (MICs) of bacteria. The compound is colorless upon solubilization with water, and metabolically active bacteria will reduce it to a reddish formazan. The MIC value was defined as the lowest concentration that no color change was observed. Ciprofloxacin is considered the positive control (0-0.125 µg mL$^{-1}$). In the subsequent step, the disc diffusion method was used to determine the susceptibility of MRSA to antibiotics alone and when combined with the sub-inhibitory concentration of Cd NPs and Cd (NO$_3$)$_2$. Initially, the 0.5 McFarland standard of freshly cultured MRSA was spread on the surface of the MHA medium. Different antibiotic disks, the sub-inhibitory concentration of Cd NPs and Cd (NO$_3$)$_2$ coated antibiotic disks, and the sub-inhibitory concentration of Cd NPs and Cd (NO$_3$)$_2$ coated blank discs were placed on the surface of the inoculated MHA media. The growth inhibition zone diameter (mm) for each sample was measured after 24 h of incubation at 37 °C. The experiments were performed three times, and the results were reported as mean ± SD.

The biofilm inhibition efficacy of Cd NPs and Cd (NO$_3$)$_2$ on mentioned isolates was assessed according to the previously mentioned method (Shakibaie et al. 2019b). It is noteworthy that these strains were isolated from individuals hospitalized in different hospitals (Kerman, Iran) with the ability to produce strong biofilm (Shakibaie et al. 2015). Briefly, the fresh inoculum of clinically isolated biofilm-producing strains (S. aureus, P. mirabilis, and P. aeruginosa) was prepared in a TS medium supplemented with 1% glucose (w/v). The 0.5 McFarland standard of each bacteria was prepared and further diluted to reach 10$^5$ CFU/well of the 96-well microplate. Subsequently, various
concentrations of Cd NPs and Cd (NO$_3$)$_2$ were added to each well and incubated at 37 °C for 24 h. The next day, the medium was removed, and each well was washed with sterile PBS. The formed biofilms were fixed with heating at 60 °C for 60 min and stained with crystal violet solution (0.005% w/v, 200 µL/well) for another 60 min. After gently washing and air-drying the wells, stained biofilms were dissolved in 150 µL acetic acid 33% (v/v). The absorbance was measured at 570 nm. Three sample replicates were done, and the results were reported as mean ± SD.

**Statistical analysis**

The results were analyzed by One way of ANOVA. All the experiments were done in triplicate, and all values were expressed as the mean ± standard deviation (SD). A $p$-value of less than 0.05 was considered statistically significant.

**Results**

**Biosynthesis and characterization of cd NPs**

Cd NPs were synthesized based on our previous procedures (Shakibaie et al. 2021). Reduction of aqueous Cd (NO$_3$)$_2$ ions by A. persica aqueous extract was observed by the opacification of the yellowish color of the mixture. The SEM micrograph of Cd NPs synthesized using A. Persica showed Cd NPs with some aggregation between the NPs (Fig. 1a). Hexagonal Cd NPs were characterized by a single peak in particle size distribution between 11.2 and 18.6 nm, with the most frequent size of 14.8 nm (Fig. 1b).

**Cytotoxicity of cd NPs**

To determine the effects of Cd NPs, Cd (NO$_3$)$_2$, and cisplatin on the HepG2 and normal HUVEC cells, the MTT assay was carried out. As shown in Figs. 2 and 3, the tested compounds exhibited dose-dependent effects on the mentioned cell lines after 24 and 48 h of incubation. The half-maximal inhibitory concentration value (IC$_{50}$) of biosynthesized Cd NPs, Cd (NO$_3$)$_2$, and cisplatin was 586.8 ± 1.3 µg mL$^{-1}$, 16.83 ± 0.3 µg mL$^{-1}$, and 64.2 ± 0.4 µg mL$^{-1}$, respectively after 24 h of treatment on HepG2 cells (Fig. 2a). The calculated IC$_{50}$ values of HepG2 cells after 48 h of treatment with Cd NPs, Cd (NO$_3$)$_2$, and cisplatin were 416.9 ± 1.7 µg mL$^{-1}$, 7.5 ± 0.04 µg mL$^{-1}$, and 15.4 ± 0.3 µg mL$^{-1}$, respectively (Fig. 2b). After 24 and 48 h of incubation, Cd NPs showed less cytotoxicity than Cd (NO$_3$)$_2$ or cisplatin against HepG2 cells at concentrations between 5 µg mL$^{-1}$ to 640 µg mL$^{-1}$ ($p < 0.05$). The Cd (NO$_3$)$_2$ was significantly more toxic than cisplatin when exposed to concentration ranges of 20 µg mL$^{-1}$ to 320 µg mL$^{-1}$ ($p > 0.05$), and there was no significant difference between the viability of HepG2 cells treated with 5µ mL$^{-1}$, 10 µ mL$^{-1}$ of Cd (NO$_3$)$_2$ and cisplatin after 24 h of treatment ($p > 0.05$). After 48 h of incubation, the Cd (NO$_3$)$_2$ displayed significantly higher toxicity effects on this cell line (5 µg mL$^{-1}$ to 640 µg mL$^{-1}$) compared with Cd NPs ($p < 0.05$).
In HUVEC cells, the measured 24 h IC50 value of Cd NPs, Cd (NO3)2, and cisplatin was 284.4 ± 2 µg mL−1, 12.3 ± 0.1 µg mL−1, and 26.2 ± 0.1 µg mL−1, respectively (Fig. 3a). The viability of HUVEC cells following 48 h treatment with Cd NPs, Cd (NO3)2, and cisplatin is shown in Fig. 3b, with the calculated IC50 values of 142.2 ± 0.2 µg mL−1, 3.7 ± 0.05 µg mL−1, and 5.7 ± 0.2 µg mL−1, respectively. Cd NPs showed lower toxicity than Cd (NO3)2 and cisplatin after 24 or 48 h of exposure at all concentrations (p < 0.05). Compared with cisplatin, Cd (NO3)2 was more toxic at all concentrations (p < 0.05).

As shown in Figs. 2 and 3, the cell viability of HepG2 and HUVEC cells treated with 5 µg mL−1 and 10 µg mL−1 of Cd NPs did not differ significantly from the control group (0 µg mL−1) after 24 and 48 h of treatment (p > 0.05). Substantially higher toxicity was observed at concentrations above 10 µg mL−1 (p < 0.05), and the cytotoxicity of Cd NPs and Cd (NO3)2 against these cell lines was in a dose and time-dependent manner (Figs. 2 and 3).

**Hemolysis activity**

The hemolytic properties of NPs can be measured to determine their interaction with blood components (Singh et al. 2020). A positive control (100% hemolysis) is the amount of hemoglobin released from the RBCs when water is added. As depicted in Fig. 4, at the highest concentration (640 µg...
and *P. aeruginosa* strains, were more than 2560 µg mL$^{-1}$.

Moreover, the measured MICs of Cd(NO$_3$)$_2$ against *S. aureus*, *P. mirabilis*, and *P. aeruginosa* pathogens were 1280 µg mL$^{-1}$, 1280 µg mL$^{-1}$, and 2560 µg mL$^{-1}$, respectively. Meanwhile, MICs of ciprofloxacin were 0.312 µg mL$^{-1}$, 0.312 µg mL$^{-1}$, and 0.625 µg mL$^{-1}$ against the *S. aureus*, *P. mirabilis*, and *P. aeruginosa*, respectively.

The antibacterial efficacy of commercial antibiotics alone and in combination with biosynthesized Cd NPs (100 µg/disk) and sub-MIC value of Cd(NO$_3$)$_2$ (100 µg/disk) was evaluated by disc diffusion method against MRSA strain.

mL$^{-1}$), the hemolysis rate for Cd NPS and Cd(NO$_3$)$_2$ was 0.88 ± 0.5% and 3.37 ± 0.3%, respectively.

**Antibacterial activity**

Cd NPs and Cd(NO$_3$)$_2$ were studied at different concentrations for their antimicrobial and anti-biofilm properties. A microplate serial dilution method was employed to study the MICs of Cd NPs and Cd(NO$_3$)$_2$ against various pathogenic bacteria. The calculated MIC values for Cd NPs against three clinically pathogenic strains of *S. aureus*, *P. mirabilis*, and *P. aeruginosa* strains, were more than 2560 µg mL$^{-1}$.

Moreover, the measured MICs of Cd(NO$_3$)$_2$ against *S. aureus*, *P. mirabilis*, and *P. aeruginosa* pathogens were 1280 µg mL$^{-1}$, 1280 µg mL$^{-1}$, and 2560 µg mL$^{-1}$, respectively. Meanwhile, MICs of ciprofloxacin were 0.312 µg mL$^{-1}$, 0.312 µg mL$^{-1}$, and 0.625 µg mL$^{-1}$ against the *S. aureus*, *P. mirabilis*, and *P. aeruginosa*, respectively.

The antibacterial efficacy of commercial antibiotics alone and in combination with biosynthesized Cd NPs (100 µg/disk) and sub-MIC value of Cd(NO$_3$)$_2$ (100 µg/disk) was evaluated by disc diffusion method against MRSA strain.
significantly reduced by exposure to Cd NPs as well as Cd (NO$_3$)$_2$ ($p < 0.05$). It is noteworthy that meropenem (a cell wall synthesis inhibitor) and kanamycin (a protein synthesis inhibitor) discs did not have an inhibitory effect on MRSA alone. As a result of combining these antibiotics with Cd NPs or Cd (NO$_3$)$_2$ (100 µg/disk), the MRSA growth inhibition zone was significantly increased.

**Anti-biofilm activity of Cd NPs**

The inhibitory effect of Cd NPs as well as Cd (NO$_3$)$_2$ on the biofilm formation of *S. aureus, P. mirabilis*, and *P. aeruginosa* is illustrated in Fig. 6. As mentioned previously, the sub-inhibitory concentrations of Cd NPs and Cd (NO$_3$)$_2$, (0-640 µg mL$^{-1}$) were selected for screening the formation of biofilms by planktonic cells. According to Fig. 6a, the biofilm formation of *S. aureus* decreased to 75.3 ± 9% and 23 ± 4% in the presence of Cd NPs, and Cd (NO$_3$)$_2$ (640 µg mL$^{-1}$), respectively which this reduction was significant compared to the control group (0 µg mL$^{-1}$) ($P < 0.05$). The biofilm formation by *P. mirabilis* was significantly reduced in the presence of Cd NPs, and Cd (NO$_3$)$_2$ (640 µg mL$^{-1}$), and reached 68.3 ± 2% and 74.3 ± 4%, respectively (Fig. 6b) ($P < 0.05$). *P. aeruginosa’s* biofilm formation was reduced to 73.5 ± 8% and 95.4 ± 4% when exposed to Cd NPs and Cd (NO$_3$)$_2$ (640 µg mL$^{-1}$), respectively (Fig. 6c). While the reduction in the biofilm formation of *P. aeruginosa* in the presence of Cd (NO$_3$)$_2$ was not significant ($P > 0.05$).

According to the present study, at concentrations above 5 µg mL$^{-1}$, Cd (NO$_3$)$_2$ exhibited significantly higher anti-biofilm activity than Cd NPS against *S. aureus* ($P < 0.05$).
acids, enzymes, and vitamins present in the plant parts. One proposed mechanism of NPs synthesis is the reduction of metal ions by secondary metabolites, such as flavonoids, alkaloids, polyphenols, polysaccharides, proteins, enzymes, and vitamins present in the plant parts (Sahoo et al. 2021; Shakibaie et al. 2021). A similar endorsement was made during the rapid reduction of Cd chloride using aqueous marigold and rose flower petal extract, in which most of the produced Cd NPs were spherical (Hajra et al. 2016). As mentioned in Fig. 1a, biosynthesized Cd NPs were hexagonal. Similar hexagonal CdS NPs (produced by biological or chemical techniques) have been reported previously (Martinez-Alonso et al. 2014; Srinivasa Goud et al. 2016; Kamble et al. 2020). In the study of Martinez et al. (2014), the hexagonal CdS NPs obtained by microwave heating were 9.2–11.7 nm in diameter. Additionally, Hexagonal CdS NPs with an average size of 9 nm were biologically synthesized (Srinivasa Goud et al. 2016; Kamble et al. 2020) applied the hot-injection method to prepare hexagonal-type CdS NPs (18.3–37.5 nm). Azizi et al. (2018) have found spherical Cd NPs with a diameter of 5 nm synthesized by the chemical reduction method. In another major study, Alsaggaf et al. (2020) found that CdS NPs produced by Aspergillus niger had spherical morphology with an average size of 5 nm. Malarkodi et al. (2014) reported that biogenic CdS NPs were produced with Klebsiella pneumoniae and had a spherical shape ranging from 10 to 25 nm in size. Different applied synthesis methods may contribute to the variation in the shape and size of Cd-containing NPs. Nevertheless, more researches are needed to investigate the factors affecting the size and shape of Cd NPs.

Cytotoxicity of cd NPs

There is a wide variety of areas where NPs are being used, and their applications are growing. NPs are subjected to toxicological studies before being considered for their applications. The obtained results of this study exhibited that the cytotoxicity of Cd NPs and Cd (NO$_3$)$_2$ against HepG2 and HUVEC cells was dose- and time-dependent (Figs. 2 and 3). In a study by Shikabaie et al. (2021), Cd NPs and Cd (NO$_3$)$_2$ were shown to induce a concentration-dependent response in all cell lines. The calculated IC$_{50}$ values for 3T3, MCF-7, A549, U87, and HT-29 exposed to Cd NPs were 10.6 µg mL$^{-1}$, 1.8 µg mL$^{-1}$, 47.2 µg mL$^{-1}$, 62.9 µg mL$^{-1}$, and 133.5 µg mL$^{-1}$, respectively. Furthermore, the IC$_{50}$ values of 3T3, MCF-7, A549, U87, and HT-29 exposed to Cd (NO$_3$)$_2$ were 10.5 µg mL$^{-1}$, 3.7 µg mL$^{-1}$, 25.6 µg mL$^{-1}$, 25.6 µg mL$^{-1}$, 44.4 µg mL$^{-1}$. The viability of human erythroleukemia cells (K562 cells) and human embryonic kidney cells (HEK293T cells) was decreased in a dose- and time-dependent manner after treatment with CdTe QDs.

Discussion

Biosynthesis and characterization of cd NPs

In this study, Cd NPs were successfully synthesized by A. persica aqueous extract. It has been proposed that metal ions are reduced by secondary metabolites, including flavonoids, alkaloids, polyphenols, polysaccharides, proteins, amino acids, enzymes, and vitamins present in the plant parts. One proposed mechanism of NPs synthesis is the reduction of metal ions by secondary metabolites, such as flavonoids, alkaloids, polyphenols, polysaccharides, proteins, enzymes, and vitamins present in the plant parts (Sahoo et al. 2021; Shakibaie et al. 2021). A similar endorsement was made during the rapid reduction of Cd chloride using aqueous marigold and rose flower petal extract, in which most of the produced Cd NPs were spherical (Hajra et al. 2016). As mentioned in Fig. 1a, biosynthesized Cd NPs were hexagonal. Similar hexagonal CdS NPs (produced by biological or chemical techniques) have been reported previously (Martinez-Alonso et al. 2014; Srinivasa Goud et al. 2016; Kamble et al. 2020). In the study of Martinez et al. (2014), the hexagonal CdS NPs obtained by microwave heating were 9.2–11.7 nm in diameter. Additionally, Hexagonal CdS NPs with an average size of 9 nm were biologically synthesized (Srinivasa Goud et al. 2016; Kamble et al. 2020) applied the hot-injection method to prepare hexagonal-type CdS NPs (18.3–37.5 nm). Azizi et al. (2018) have found spherical Cd NPs with a diameter of 5 nm synthesized by the chemical reduction method. In another major study, Alsaggaf et al. (2020) found that CdS NPs produced by Aspergillus niger had spherical morphology with an average size of 5 nm. Malarkodi et al. (2014) reported that biogenic CdS NPs were produced with Klebsiella pneumoniae and had a spherical shape ranging from 10 to 25 nm in size. Different applied synthesis methods may contribute to the variation in the shape and size of Cd-containing NPs. Nevertheless, more researches are needed to investigate the factors affecting the size and shape of Cd NPs.
at concentrations ranging from 3 µM to 187.5 µM (Su et al. 2009). Similarly, Zhang et al. (2007) investigated the size and time-dependent cytotoxicity of CdTe (2-6 nm) in HepG2 cells.

The cytotoxicity effect of other Cd-containing NPs, like spherical CdTe-QDs (14 nm), caused intrinsic and extrinsic apoptosis in HepG2 cells after 6 h, 12 h, and 24 h treatment (0.001-100 µM L⁻¹). This hepatocellular toxicity was time and dose-dependent (Nguyen et al. 2013b). After 2 h, 4 h, 6 h, and 24 h of treatment with these spherical CdTe-QDs, macrophages (J774A.1) and HT-29 cells showed a dose- and time-dependent reduction in metabolic activity (Nguyen et al. 2013a). The toxicity of CdTe-QDs may result from oxidative stress induction through GSH and CAT activity depletion and reactive oxygen species (ROS) formation. Other Cd-containing NPs like albumin-coated Cd NPs (Cd NPs@ BSA, 88 nm) exhibited 57 times higher toxicity than Cd NPs (spherical shape, 5 nm) against MDA-MB-231 (Azizi et al. 2018; Alsaggaf et al. 2020) reported that CdS NPs capped with A. niger proteins exhibited cytotoxicity against A549, MCF7, PC3, and cell lines with measured IC₅₀ values of 149 µg mL⁻¹, 190 µg mL⁻¹, and 246 µg mL⁻¹, respectively. The biogenic CdS NPs (40–80 nm), prepared using a biological route with Escherichia coli sulphate reductase enzyme, showed IC₅₀ values of 92.2 mM and 33.4 mM against Mus musculus skin melanoma and human epidermoid carcinoma cell lines, respectively (Shivashankarappa and Sanjay 2020). It seems that the chemical composition of Cd nanostructures, along with their synthesis routes and sizes, plays an essential role in the cytotoxicity of these Cd-containing NPs. Our study showed that Cd NPs had lower toxicity on HepG2 and HUVEC cell lines than Cd (NO₃)₂. Previously, several studies demonstrated decreasing cytotoxicity of biogenic metal(oid)-containing NPs compared with their ions (Forootanfar et al. 2014, 2015; Mohanty et al. 2014; Ameri et al. 2020). In a similar study, Forootanfar et al. (2014) found that Se NPs produced by Bacillus sp. were less cytotoxic on the MCF-7 cell line compared with selenium dioxide.

Another study revealed that tellurium nanorods (22 nm diameter, 185 nm length) display higher IC₅₀ values than potassium tellurium against A549, MCF-7, HepG2, and HT1080 cell lines (Forootanfar et al. 2015). In the study of Mohanty et al. (2014), biosynthesized tellurium nanorods (TeNRs) did not exhibit cytotoxicity to human bronchial epithelial cells (BEAS-2B) and murine macrophages (RAW264.7). The results of our recently published investigation have demonstrated a significantly higher IC₅₀ value for Cd NPs than Cd (NO₃)₂ against A549, HT-29, MCF-7, 3T3, and U87 cell lines (Shakibaie et al. 2021). It can be inferred from the literature review that Cd nanostructures induce cell death via mechanisms involved in ROS production, either through the formation of electron-hole pairs to transfer electrons to oxygen or by directly damaging the antioxidant system through the release of Cd²⁺ ions (Cho et al. 2007; Nguyen et al. 2013b; Alsaggaf et al. 2020; Shivashankarappa and Sanjay 2020). Ultimately, further research is necessary to determine the exact cytotoxicity mechanism of our Cd NPs.

**Hemolysis activity**

In order to determine whether NPs are safe and blood-compatible, hemolysis is among the fundamental tests (Singh et al. 2020). According to Fig. 4, Cd NPs were compatible with RBCs. A similar result was observed in the study of Shivaji et al. (2018), which demonstrated that the CdS quantum dots (2–5 nm) exhibited 1.83 ± 0.2% of hemolysis rate at the highest tested concentration (60 μg mL⁻¹). According to previous reports, up to 5% of hemolysis is permissible for biomaterials and considered non-hemolytic (Muzzquiz-Ramos et al. 2015; Shanthi et al. 2017). Cd NPs and Cd (NO₃)₂ exhibited no significant hemolysis at the tested concentrations (P < 0.05). In contrast, Shivashankarappa et al. (2020) reported that biogenic CdS NPs (40–80 nm) showed 33.5% hemolysis activity at 0.2 mM concentration which was noted that accumulation in cell membranes leads to toxic effects on RBCs by positively charged CdS NPs.

**Antibacterial activity**

Organic and inorganic NPs have been effective in treating several health conditions. They have been used to enhance drug delivery and bioavailability. They have also been used to treat and improve antibacterial and antifungal activities (Mba and Nweze 2021). Additionally, NPs can improve therapeutic effects when combined with antibiotics and other nanomaterials (Gounani et al. 2019). Previously, numerous metal(oid) based NPs such as ZnO, Cu₂O, and Pd have been implicated as antimicrobial agents (Suresh et al. 2018; Bezza et al. 2020; Nasrollahzadeh et al. 2020). Cd-containing nanostructures have also been found to possess antimicrobial properties (Rajeshkumar et al. 2014; Abd et al. 2016; Haq Bhat and Yi 2019; Alsaggaf et al. 2020; Shivashankarappa and Sanjay 2020) studied the antimicrobial activity of cubic CdS NPs and showed that these NPs were active against S. aureus, E. coli, Pseudomonas vulgaris, and Bacillus subtilis. Furthermore, CdO NPs synthesized by the chemical method have proven to inhibit the growth of S. aureus, P. aeruginosa, K. pneumoniae and, A. baumannii (Abd et al. 2016). Bhat et al. (2019) reported the efficacy of green synthesized CdS NPs against S. aureus and E. coli., with more sensitivity to gram-positive S. aureus. It has been proposed that the inhibition action of CdS NPs on
bacteria is related to the interaction between the NPs and thiol groups present in key bacterial respiratory enzymes (Haq Bhat and Yi 2019; Rajeshkumar et al. 2014) reported that spherical-shaped CdS NPs exhibited the maximum growth inhibition zone against the clinical strains of E. coli, Vibrio sp., Serratia nematodiphila, Klebsiella planticola, Aspergillus niger, and Aspergillus flavus. Furthermore, they indicated that CdS NPs with a positive charge interact with proteins of the microorganism’s cell membrane to disrupt them. Sekar et al. (2019) reported that CdS NPs were highly active against S. aureus and E. coli.

Unlike the previously mentioned antimicrobial activities of Cd-containing NPs, our Cd NPs biosynthesized in this study did not show antibacterial potency against the S. aureus, P. mirabilis, and P. aeruginosa strains at the tested concentrations (0-2560 µg mL⁻¹). The chemical structure of Cd-containing NPs seems to impact their antimicrobial activity significantly. Furthermore, our clinical strains of S. aureus, P. mirabilis, and P. aeruginosa have previously exhibited high ability in biofilm formation, which might be a critical factor in microbial resistance against antimicrobial agents (Shakibaie et al. 2019b).

In conjunction with other materials, NPs can be significantly enhanced in terms of activity. In a study, the spherical-shaped bismuth NPs (40–120 nm) enhanced the antibacterial effect of antibiotics that inhibit the protein and cell wall synthesis, which had no inhibitory effect on MRSA alone (Shakibaie et al. 2019b). A synergistic effect of silver NPs (Ag NPs) combined with kanamycin (a protein synthesis inhibitor) against S. aureus, E. coli, and S. typhimurium was observed in a study by Vazquez-Munoz et al. (2019). Metallic NPs have been combined with conventional antibiotics to increase antibiotic effectiveness against pathogenic bacteria (Thati et al. 2010; Nazari et al. 2014; Bankier et al. 2019). Previously it has been reported that chemically synthesized CdO NPs (32–41 nm) increased the antibacterial activity of ciprofloxacin against K. pneumoniae (Abd et al. 2016). It has been reported that the sub-inhibitory concentration of ZnO NPs (20–45 nm) increased the antibacterial activities of erythromycin, methicillin, penicillin, ampicillin, amoxicillin, streptomycin amikacin, clindamycin, oxacillin, gentamicin, cloxacillin, cefotaxime, ceftazidime, vancomycin, cephalaxin, and tetracycline against S. aureus (Thati et al. 2010).

Anti-biofilm activity of cd NPs

In this work, the antibiofilm activity of Cd NPs inhibited the biofilm formation of S. aureus, P. mirabilis, and P. aeruginosa bacteria in a dose-dependent manner. The biofilm formation of all strains successfully decreased with increasing Cd NPs concentration. Our result complies with Shakibaie et al. (2019b), who reported a notably higher anti-biofilm activity of bismuth NPs on P. aeruginosa rather than P. mirabilis and S. aureus. In a study by Dhanabal et al. (2015), hydrophilic CdS NPs in a microemulsion medium significantly reduced the biofilm formation of gram-negative E. coli. As demonstrated in Fig. 6, The anti-biofilm effect of Cd (NO₃)₂ on S. aureus was significantly higher than P. mirabilis and P. aeruginosa (P<0.05). The antibiofilm activity of Cd NPs on P. mirabilis was higher than S. aureus and P. aeruginosa, but this was not a significant effect (p>0.05). The discovery of potent anti-biofilm compounds is a challenging endeavor for biofilm eradication. Using NPs is an approach to prevent the formation of biofilms and destroy those that have formed (Shakibaie et al. 2019b). Together, our results suggest that Cd NPs may be beneficial as an antibiofilm agent against clinical strains. This study did not discuss the mechanisms relating to eradicating biofilms by Cd NPs; thus, further investigation is required.

Conclusion

The present experiment demonstrated a durable and environmentally friendly method to synthesize Cd NPs by reducing the solutions of Cd (NO₃)₂ using Artemisia persica extract. The cytotoxicity effect of synthesized Cd NPs was investigated on HepG2 and HUVEC cell lines. Aside from the non-hemolytic potency of Cd NPs, further research could be focused on conjugating or capping the Cd NPs with biological components for potential use in diagnosing, bio-labeling, in vivo-based imaging, and treating diseases. Although Cd NPs demonstrated no antibacterial activity against the isolated clinical pathogens, including S. aureus, P. mirabilis, and P. aeruginosa, these NPs could inhibit the biofilm formation produced by S. aureus, P. mirabilis, and P. aeruginosa to 24.6%, 31.6%, and 26.4%, respectively. In addition, Cd NPs enhanced the antimicrobial activity of a wide range of tested antibiotics against MRSA. Consequently, these results suggest that biologically synthesized Cd NPs could be an effective anti-biofilm agent in biomedical applications. More studies are required to determine the precise mechanisms of Cd NPs toxicity and better understand the potential factors contributing to the anti-biofilm activity of biogenic Cd NPs.

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Author contributions The authors contributed to the present work as
described below: Mahboubeh Adeli-Sardou contributed to the preparation and characterization of NPs. Mojtaba Shakibaie supervised the study, received the related grant, and was involved in purchasing materials and analyzing the obtained results. Hamid Forootanfar was involved in cytotoxicity studies, Ferehshteh Jabari-Morouei was involved in antibacterial studies, and Soudabe Rahi-Madvar supervised the hemolytic activity studies. Sima-Sadat Ghafari-Shahrbabaki involved in the anti-biofilm studies. Mitra Mehrabani was involved in statistical analysis. The authors have equally contributed to preparing and reviewing the manuscript.

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**Data Availability** All data generated or analyzed during this study are included in this published article.

**Declarations**

**Statements and declarations** The authors have no competing interests to declare relevant to this article’s content.

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**Ethical approval** This work was approved by the ethical committee of Kerman University of Medical Sciences.

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