RESEARCH ARTICLE

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Biosynthesis of silver nanoparticles from *Arum dioscoridis* plant leaf aqueous extract: anticancer and antimicrobial properties

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Abstract

This study was carried out to synthesize silver nanoparticles (AgNPs) from *Arum dioscoridis* (AD) leaf extract and to investigate the cytotoxic and antipathogenic effects of them. The plant material had a reducing and stabilizing effect on the synthesized nanomaterial. During the plant-mediated synthesis of nanomaterials, no substances that would cause environmental pollution were used. For the structural characterization of AD-AgNPs, Ultraviolet-visible (UV-vis) Spectroscopy, Field Emission Scanning Electron Microscopy (FE-SEM), Electron Dispersive X-ray (EDX) Spectroscopy, Fourier Transform Infrared (FT-IR) Spectroscopy, Transmission Electron Microscopy (TEM), X-ray Diffractometer (XRD), Atomic Force Microscopy (AFM) and Zetasizer analyses were performed. The produced AgNPs showed maximum surface plasmon resonance at 431.67 nm and had mostly spherical morphology. The zeta potential value of the nanomaterial was -9.76 mV and the average powder crystal size was 31.48 nm. The minimum inhibitory concentration (MIC) values (mg/L) of AD-AgNPs on *Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa*, and *Candida albicans* were 0.25, 2.00, 0.125, 4.00, and 1.00, respectively. After 24 and 48 hours of application by MTT [3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolium bromid] assay, the half-maximal inhibitory concentrations (IC_{50}: µg/mL) of AD-AgNPs on human colon adenocarcinoma cell (CACO-2), human breast cancer cell (MCF-7), glioblastoma multiforme cell (T98-G), and healthy human umbilical vein endothelial cell (HUVEC) lines were determined as 2.977, 2.801, 5.694, 4.392; 2.115, 2.300, 2.612, 4.091, respectively.

Keywords: AgNPs, *Arum dioscoridis* extract, Cytotoxicity, Green chemistry, Pathogen microorganism

INTRODUCTION

Plant-based metallic nanoparticles (NPs) synthesis has risen dramatically over the last few decades (Song and Kim, 2009; Philip, 2011; Kanniah et al., 2020). Metallic NPs are more advantageous than bulk materials due to their unique size (1-100 nm), morphology, and surface distribution, as well as optoelectronic, physicochemical, and magnetic attributes (Fahmy et al., 2019; Jamkhande et al., 2019). These NPs have also been evaluated in recent years for usage in water treatment, diagnostic, cancer therapy, cell labeling, antimicrobial agent, drug delivery, and biomarker applications (Dikshit et al., 2021; Salem and Fouda, 2021; Singh et al., 2018).

The NPs are produced according to chemical, physical, and biological perspectives (Zhang et al., 2016). In a physical perspective, various methods such as microwave irradiation, ultra-sonication, and physical adsorption are used to synthesize NPs.

In a chemical perspective, decreasing agents like sodium citrate, elemental hydrogen, cetyltrimethylammonium bromide (CTAB), ascorbate, sodium hydroxide (NaOH), sodium borohydride (NaBH4), polyol process, N,N-dimethylformamide (DMF), and tollens reagent are used. Since the aforementioned approaches necessitate the use of environmentally harmful toxic chemicals or non-biodegradable agents (Gour and Jain, 2019; Heuer-Jungemann et al., 2019), scientists have adopted to produce nanoparticles by biological methods, also called "green synthesis" (Baran et al., 2022; Gur et al., 2022; Keskin et al., 2022).

Not only plants (Palithya et al., 2021), but also natural resources such as bacteria (Patil et al., 2019), fungi (Abdelkader et al., 2022), algae (Chaudhary et al., 2020), and seaweeds (Dixit et al., 2019) are frequently utilized in the biological generation of NPs. In recent years, herbal nanoparticle synthesis studies with silver metal have attracted attention (Alkhulaifi et al., 2020; Baran et al., 2021; Zubair et al., 2022). As is common knowledge, silver (Ag) plays an important role in limiting bacterial growth. Because Ag ions can interrupt DNA duplication and cell division. On the other hand, AgNPs attach to cell membrane proteins thanks to their ultra-mini dimension and trigger the manufacturing of reactive oxygen species (ROS) in the bacteria. This condition creates oxidative stress, which leads to cell death (Baran et al., 2022).

Arum dioscoridis, one of the 26 species belonging to the genus *Arum* L. of the Araceae family, is disseminated in Western Asia, North Africa, Europe, and the Mediterranean region. The distribution area of this plant, which grows wild in the natural environment, in Türkiye, is Eastern Mediterranean and Southwestern Anatolia (Yabalak, 2018). *A. dioscoridis*, which is called "Yılanyastığı" and "Gavur Pancarı" in Türkiye, is used in making "Tirşik soup" and the "pastry" in Kahramanmaraş, Kilis, Osmaniye, and Adana provincials (Çeçen et al., 2020; Sökmen et al., 2023). Since the leaves of this plant contain toxic alkaloids and can cause food poisoning when consumed without cooking, it is not considered suitable to be consumed raw (Kozuharova et al., 2020).

This work was fulfilled to synthesize AgNPs from AD leaf extract and to research the cytotoxic and antipathogenic effects of them. In the research, in which no environmentally harmful substances were used, the aqueous synthesis and stabilization of AgNPs were carried out by reducing silver nitrate ($AgNO_3$) aqueous solution with *A. dioscoridis* leaf extract. After the structural characterization of the obtained AgNPs, their cytotoxic effects in some cell lines as well as their antipathogenic activities against pathogenic yeast and bacteria were revealed.

MATERIALS AND METHODS

Material

Arum dioscoridis leaves obtained from Alatepe Village in Kilis (Türkiye) were used in the study. GPS location: 36°47'13" N, 37°11'57" D. The plant was diagnosed by Dr. Cumali Keskin, a plant taxonomist from Mardin Artuklu University (Mardin, Türkiye). $AgNO_3$ (99.8% purity), vancomycin, fluconazole, penicillin, streptomycin, colistin, fetal bovine serum (FBS), Mueller Hinton Broth (M-H Broth), and Roswell Park Memorial Institute-1640 (RPMI-1640) were obtained from Sigma-Aldrich (Germany). Dulbecco's modified eagle medium (DMEM) was acquired from Gibco (UK). [3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolium bromid] (MTT) was purchased from Thermo Fisher Scientific (USA). *Candida albicans* (ATCC® 10231™), *Staphylococcus aureus* (ATCC® 29213™), *Escherichia coli* (ATCC® 25922™), *Pseudomonas aeruginosa* (ATCC® 27853™), and *Bacillus subtilis* (ATCC® 11774™) utilized for antipathogenic activities of the AgNPs. CACO-2, MCF-7, T98-G lines, and HUVEC were used for the cytotoxic tests of the AgNPs.

Arum dioscoridis leaf extract preparation

The green leaves of *A. dioscoridis* were cleaned with pure water and dried at room conditionss. 5 g of the dried leaves were boiled with 0.5 L of pure water and cooled. Then, it was processed via Whatman filter papers and maintained at +4 °C for the production of AgNPs.

Manufacturing of the nanoparticles

A 30 mM $AgNO_3$ aqueous solution was adjusted from solid $AgNO_3$ for the production of AgNPs. The extract and solution at a ratio of 3:2 were left to react in a beher. The dark solution resulting from the reaction was centrifuged (6000 rpm, 5 minutes). The granular portion produced at the conclusion of the centrifugation was cleaned numerous times with pure water, and the resultant leftover (AgNPs) was maintained in a furnace at 65 °C for 24 hours to dry. The dried material was preserved for characterization processes.

Characterization of the nanoparticles

UV-vis. spectrophotometer (CARY 60, Agilent, USA) spectra of the synthesized AgNPs were ascertained in the 300-800 nm wavelength range. The size, morphology, crystallite, and surface distribution of AD-AgNPs were determined by FE-SEM (Quanta, FEG240, USA), TEM (JEM-1010, JEOL, USA), XRD (RadB-DMAX II, Rigacu, Japan), EDX spectroscopy (Quanta, FEG 240, USA), and Zetasizer (Malvern, Mastersizer 3000, UK). Debye-Scherrer equation was applied to reckon the crystal size of AD-AgNPs (Hatipoğlu, 2021a). FT-IR spectroscopy (CARY 630, Agilent, USA) was utilized to recognize the functional units in the leaf extract as well as the functional units causing the decrease at the conclusion of the reaction. AFM (Park NX10, South Korea) analysis was used to ascertain the exterior topology of the produced AgNPs.

Antipathogenic activity of the nanoparticles

The microdilution technique was utilized to assess

MIC of AgNPs against *C. albicans*, *P. aeruginosa, E. coli*, *B. subtilis,* and *S. aureus*. The wells were filled with M-H Broth medium for bacteria and RPMI-1640 for yeast. The microplates containing the medium and bacteria were treated with an AgNPs solution. Each time, 100 L was drawn from these wells and transferred to the next well. The microplates were then filled with microplate solutions arranged and regulated due to 0.5 McFarland. It was incubated for a day at 36 °C. The MIC value was calculated after incubation by ascertaining the least concentration without proliferation. Moreover, the antipathogenic activities of the AgNPs on the pathogen microorganisms were evaluated using a 30 mM $AgNO_3$ solution containing the commercial antibiotics vancomycin, colistin, and fluconazole.

MTT test to assess the cell viability

The cell viability test was performed at Dicle University Veterinary Faculty Cell Culture Laboratory. RPMI-1640 medium was used for HUVEC and CACO-2 cell lines, and DMEM was used for T98-G and MCF-7. All the cell lines were incubated in T75 culture flasks at 37 °C in 5% CO_2. 10% FBS, 100 U/mL penicillin, and 100 U/mL streptomycin were supplemented to both mediums. When the cells reached 80-90% confluence, they were taken from the flasks, and their numbers were determined by the hemocytometric method. The counted cells were inoculated into 96-well plates in 90 µL of the medium, with $7.5x10^3$ cells for HUVEC, 8 $x10^3$ cells for CACO-2, $5x10^3$ cells for MCF-7 and T98-G in each well. The cell inoculations were performed in triplicate and two plates (to perform two different time treatments, 24 and 48 hours). The AgNPs synthesized at diverse doses (500, 250, 125, 62.5, 31.25, and 15.625 µg/mL) were applied to the plates that were inoculated the next day. Ultrapure water was applied to the cells in the control group. At 24 and 48 hours after the application, an MTT test was conducted in the dark to ascertain the changes in the cell viability (Irtegun Kandemir and Ipek, 2023).

RESULTS AND DISCUSSION

UV-vis analysis

After allowing the plant extract and $AgNO_3$ solution to react, the color change was detected. The UV-vis spectra of AD-AgNPs at 30-120 minutes of the reaction are shown in Figure 1. The color shift in the suspension assisted in identifying the presence of synthesized AgNPs. In other words, UV-vis revealed the manufacturing of plant-based AgNPs by converting Ag^+ ions to Ag^0 ions (Garibo et al., 2020). As is known, free electrons in AgNPs are in charge of the surface plasmon resonance (SPR) absorption band of the nanomaterial (Alias Antonysamy et al., 2017). AD-AgNPs showed maximum absorbance at 431.67 nm. It was reported that the maximum absorbance of the AgNPs based on various plants varied between 420-480 nm (Shruthi et al., 2017; Pallela et al., 2018; Mariadoss et al., 2019; Aryan et al., 2021).

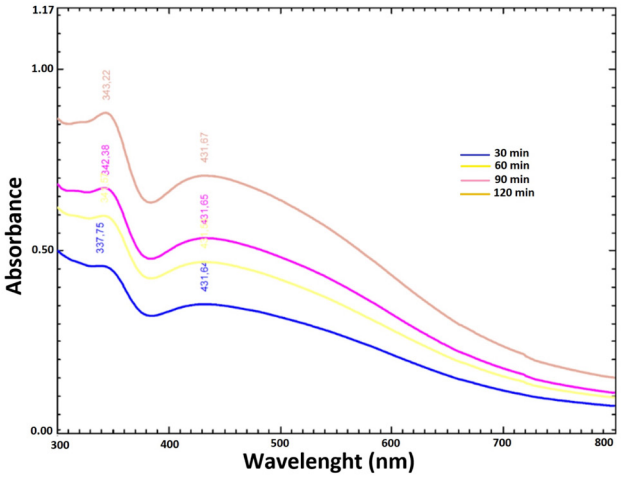

Figure 1. Time-based UV-vis absorption spectra of AD-AgNPs

EDX analysis

The EDX spectrum of AD-AgNPs verified the incidence of sharp spectral signals at nearly 3 keV for the absorption of nanocrystals in the silver area owing to surface plasmon resonance (Figure 2). This characteristic peak (3 keV) is consistent with the results of many studies with different plants (Hatipoğlu, 2022b; Ali et al., 2023; Baran et al., 2023). Other absorption peaks that emerged were due to phytochemicals in *A. dioscoridis* leaf extract. EDX analysis clearly indicated the existence of fundamental silver indicators.

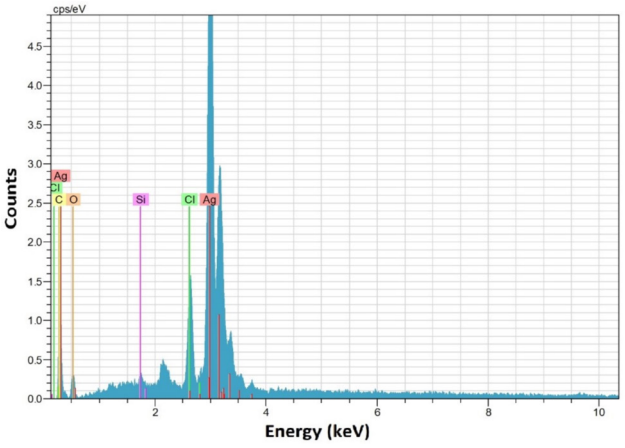

Figure 2. EDX spectrum of AD-AgNPs

FE-SEM and TEM analysis

FE-SEM (Figure 3), and TEM (Figure 4) were used to examine the shapes and sizes of biogenic AgNPs. The nanomaterial is found to be in spherical-shaped clusters that are not in direct touch with each other, especially in the TEM images. This shows that AD-AgNPs have stabilized. The results accord with those of almond (Aktepe and Baran, 2021), *Campsis radicans* and *Cascabela thevetia* (Tufail et al., 2022), *Cicer arietinum* (Baran et al., 2022), *Mimusops coriacea*, (Lopes and Courrol, 2020), *Prunus cerasifera pissardii nigra*, (Hatipoğlu, 2022a), and

Sida cordifolia (Pallela et al., 2018) plants.

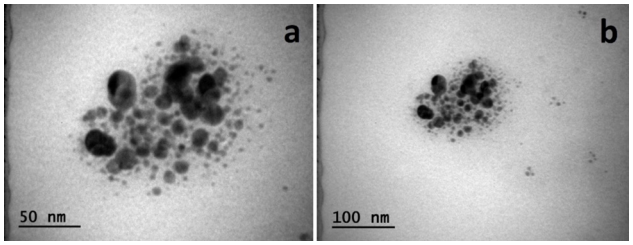

Figure 3. FE-SEM micrograph of AD-AgNPs at 1 µm scale

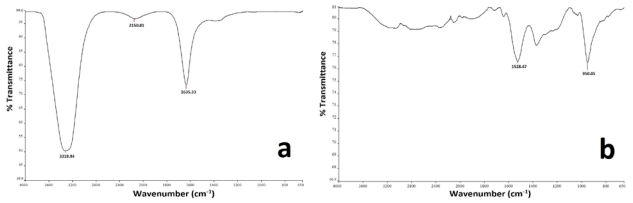

Figure 4. TEM micrographs of AD-AgNPs at 50 nm (a) and 100 nm (b) scale

FT-IR analysis

To determine possible biomolecules contained in *A. dioscoridis* leaf extract that was in charge of the decrease and stability of AgNPs, FT-IR analyses of biosynthesized AgNPs were performed. Absorption bands were observed at 1528.47 and 950.05 cm^{-1}, as seen in the FT-IR spectra (Figure 5). According to the FT-IR data, the peak at 950.05 cm^{-1} reveals the existence of metallic bonding. In addition, it can be said that the peak at 1528 cm^{-1} attached to the aromatic ring belongs to the functional units C=C, N=N, C=N. These outcomes revealed the existence of protein in the extract along with covering agents for the stability of AD-AgNPs (Debnath et al., 2019).

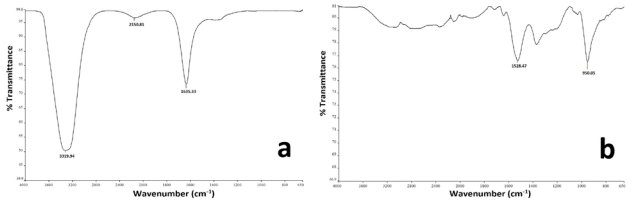

Figure 5. FT-IR spectra of AD leaf extract (a), and manufactured AD-AgNPs (b)

XRD analysis

Regarding the XRD spectrum model for the biogenic AgNPs, 111^0, 200^0, 220^0, and 311^0 diffraction peaks coinciding with 38.37, 44.28, 64.23, and 77.49 at 2θ represent the spherical crystal construction of silver (Figure 6).

Metallic silver ions are face-centered cubic, as seen by the peaks. Several investigations indicated that these diffraction peaks corresponded to the silver ion (Yusof et al., 2018; Hatipoğlu, 2021a; Khan et al., 2021; Naghmachi et al., 2022). The top angle was assessed to be 44.28 and the mean dimension of the nanomaterial was computed as 31.48 nm.

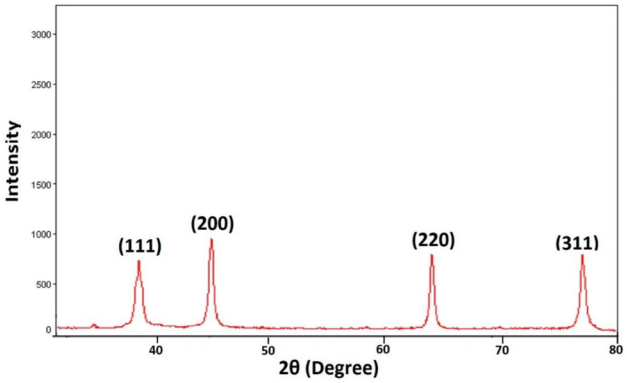

Figure 6. XRD pattern of AD-AgNPs

AFM analysis

Three-dimensional morphology and dimensions of biogenic AgNPs were obtained with the help of AFM (Figure 7). AFM analysis indicated that most of the produced AgNPs were monodisperse and spherical in form. The agglomeration and dissolution model of biogenic AgNPs in this study by AFM analysis was also well supported in the research of Nayak et al. (2020), Atalar et al. (2021), and Basavarajappa et al. (2022).

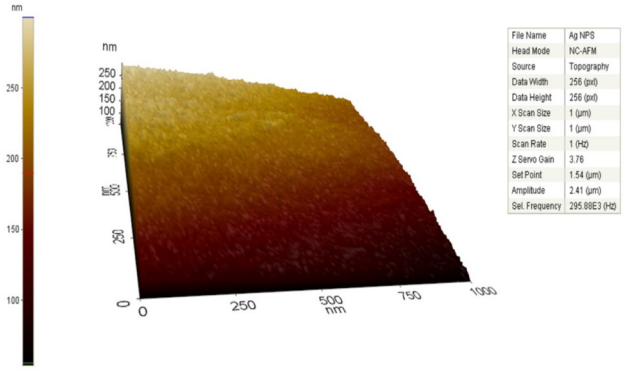

Figure 7. AFM results of AD-AgNPs

Zeta analysis

It is seen in Figure 8 that the mean particle dimension of the manufactured AgNPs ranges between 10-150 nm. The nanomaterial's zeta potential was determined to be -9.76 mV. (Figure 9). As it is known, the upper negative value of the zeta potential reveals the steadiness of AgNPs and their good distribution without clustering (Baran et al., 2022). This conclusion is consistent with the activity of AgNPs generated from other plant leaves by other investigators (Paosen et al., 2017; Aryan et al., 2021).

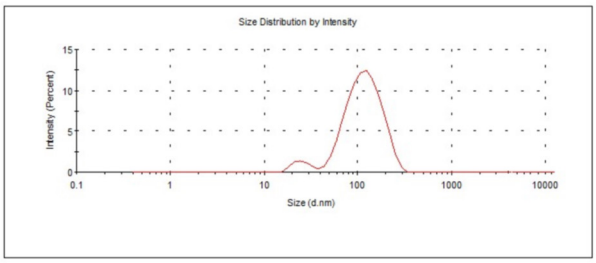

Figure 8. Particle size distribution of AD-AgNPs by density

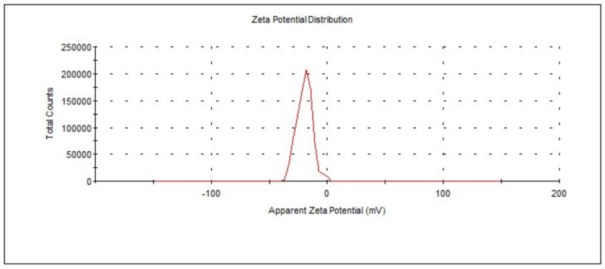

Figure 9. Zeta potential of AD-AgNPs

Antipathogenic activity

Antibiotic resistance has begun to spread around the world in recent years. For this reason, the interest in AgNPs as a substitute for antibiotics is increasing day by day. In the research, the AgNPs were found to decrease yeast and bacterial growth even at extremely low concentrations when compared to traditional antibiotics (Table 1). As compared to other species, AD-AgNPs were discovered to be far more effective towards *S. aureus* and *B. subtilis*. Because Gram-positive bacteria have a tougher polysaccharide coating than Gram-negative ones, their inhibitory effects on AgNPs are greater (Tamboli and Lee, 2013). Various research were revealed that AgNPs had inhibitory effects on pathogenic microorganisms (Hatipoğlu, 2021b; Vanlalveni et al., 2021; Basavarajappa et al., 2022; Younas et al., 2023).

Table 1. Minimum inhibitory concentration results (mg/L) of AD-AgNPs, $AgNO_3$, and standard antibiotics

Microorganisms	AgNPs	$AgNO_3$	Antibiotics
S. aureus	0.250	2.650	2.000
B. subtilis	0.125	1.320	1.000
E. coli	2.000	0.660	2.000
P. aeruginosa	4.000	0.660	2.000
C. albicans	1.000	0.660	2.000

Cytotoxic effects

The MTT assay results showing the effects of AD-AgNPs on HUVEC, CACO-2, MCF-7, and T98-G cell lines utilized in the study are presented in Figures 10, and 11. It was determined that the AD-AgNP had an antiproliferative impact on HUVEC, CACO-2, MCF-7, and T98-G cells. 24 hours after the application, IC_{50} values (µg/mL) in HUVEC, CACO-2, MCF-7, and T98-G cells were found as 2.977, 2.801, 5.694, and 4.392, respectively. As a result of the 48-hour application, these values were ascertained as 2.115, 2.300, 2.612, and 4.091, respectively.

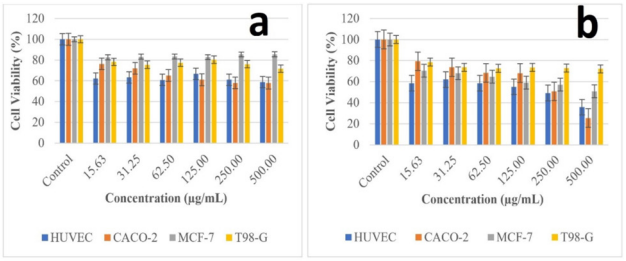

Figure 10. The cell viability percentages of AD-AgNPs at 24 (a), and 48 (b) hours

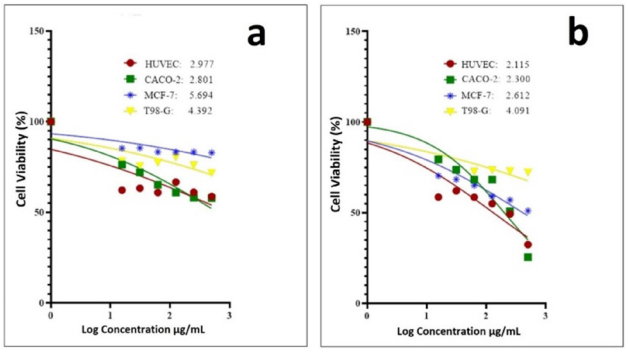

Figure 11. IC_{50} values of AD-AgNPs at 24 (a), and 48 (b) hours

Many researchers tested the silver nanomaterials they synthesized from different biomaterials on cancer cell lines. In these studies, it was reported that the antiproliferative effect levels of biogenic AgNPs (µg/mL) were 5.12-58.00 for MCF-7 (Hamouda et al., 2019; Mariadoss et al., 2019; Hamida et al., 2020), 5.37-6.20 for HCT-116 (human colon cancer cell) (Hamouda et al., 2019; Abu-Dief et al., 2020), and 5.00-90.00 for CACO-2 (Buttacavoli et al., 2018; Hamida et al., 2020; Zein et al., 2020). The IC_{50} values of the cancer cell lines used in this investigation seem to be less than the values reported by the other researchers. In addition, various researchers reported that AgNPs had high cytotoxic effects against lung adenocarcinoma cells (A549), skin cancer cells (A431), and HepG2 cell lines (Nayak et al., 2015; Wang et al., 2016; Donga and Chanda, 2021; Farshori et al., 2022; Naveed et al., 2022). Different cytotoxic effects and concentrations in the studies can be attributed to AgNPs being synthesized from different plants or having different sizes and morphological features.

CONCLUSION

This research proved the ecologically friendly, simple, and low-cost production of AgNPs from *A. dioscoridis* aqueous leaf extract. The sizes, morphological structures, and surface distributions of the manufactured AgNPs were ascertained. The impacts of the phytochemicals in the plant extract in decrease and closure (stabilization)

were proven. The biogenic AgNPs were found to have strong inhibitory impacts on *S. aureus, P. aeruginosa, C. albicans*, *E. coli*, and *B. subtilis*. In other words, it was understood that the synthesized nanomaterial had the potential to be used instead of antibiotics. The antipathogenic activity of AgNPs may be considerably enhanced through their synergistic interactions with antibiotics. AD-AgNPs were shown to decrease the growth of CACO-2, MCF-7, and T98-G cells while causing toxicity in healthy HUVEC cells.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

The authors declared that for this research article, they have no actual, potential or perceived conflict of interest.

Author contribution

The contribution of the authors to the present study is equal. All the authors read and approved the final manuscript. All the authors verify that the Text, Figures, and Tables are original and that they have not been published before.

Ethical approval

Ethics committee approval is not required.

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Data availability

Not applicable.

Consent for publication

Not applicable.

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