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Green Synthesis and Characterization of Anticancer Effected Silver Nanoparticles with Silverberry (*Elaeagnus angustifolia*) Fruit Aqueous Extract

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Abstract

Cancer is the deadliest health problem after cardiovascular system diseases. New strategies have been developed over the years in the fight against cancer. Silver nanoparticles are one of these approaches. In this study, it was aimed to synthesize silver nanoparticles with the green approach using *Elaeagnus angostifolia* aqueous extract and to investigate the cytotoxic effects of these nanoparticles. Silver nanoparticles have been characterized by analytical methods such as UV-Vis, FTIR, SEM, EDX. The peak around 3 keV in the EDX spectrum confirms the synthesis of silver nanoparticles. In vitro cytotoxic activity of silver nanoparticles was tested on human prostate cancer cell line PC3, human cervical cancer cell line HELA and normal mouse fibroblast cell line L929. It has been found that silver nanoparticles synthesized with the aqueous extract of *Elaeagnus angustifolia* showed a dose-dependent cytotoxic effect on HELA and PC3 cells.

Keywords: Anti-cancer, *Elaeagnus angustifolia*, green synthesis, silverberry, silver nanoparticles

Antikanser Etkili Gümüş Nanopartiküllerinin İğde (*Elaeagnus angustifolia*) Meyvesi Sulu Ekstraktı ile Yeşil Sentezi ve Karaktarizasyonu

Öz

Kanser kardiyovasküler sistem hastalıklarından sonra gelen en ölümcül sağlık problemidir. Kanserle mücadelede yıllar içerisinde yeni stratejiler geliştirilmiştir. Gümüş nanopartikülleri bu yaklaşımlardan bir tanesidir. Bu çalışmada *Elaeagnus angostifolia* sulu ekstraktı kullanılarak gümüş nanopartiküllerinin yeşil sentezi ve bu nanopartiküllerin sitotoksik etkilerinin belirlenmesi amaçlanmıştır. Gümüş nanopartikülleri UV-Vis, FTIR, SEM, EDX gibi analitik metotlar ile karakterize edilmiştir. EDX spektrumunda 3 keV civarındaki pik gümüş nanopartiküllerinin sentezini doğrulamaktadır. Gümüş nanopartiküllerinin in vitro sitotoksik aktivitesi insan prostat kanser hücre hattı PC3, insan serviks kanseri hücre hattı HELA ve normal mouse fibroblast hücre hattı L929 üzerinde test edilmiştir. *Elaeagnus angustifolia* sulu ekstraktı ile sentezlenen gümüş nanopartiküllerinin HELA ve PC3 hücreleri üzerinde doza bağımlı sitotoksik etki gösterdiği bulunmuştur.

Anahtar Kelimeler: Anti-kanser, *Elaeagnus angustifolia*, yeşil sentez, iğde, gümüş nanopartikülleri

INTRODUCTION

Cancer is one of the most important health problems threatening human life and ranks second worldwide after cardiovascular system diseases among the deaths whose cause is known (Siegel et al., 2019). Chemotherapy, which is the main strategy used in the fight against cancer, can be used alone or in combination with various treatment approaches (Hassanpour and Deghdani, 2017). Studies on the use of silver nanoparticles in cancer treatment have gained momentum in recent years (Jeyeraj et al., 2013).

Silver nanoparticles have succeeded in attracting the attention of the scientific world due to their superior physical, chemical and biological properties compared to other metal nanoparticles. Studies on the use of silver nanoparticles in medicine as anti-microbial, anti-fungal and anti-cancer agents are continuing intensively (Prabhu and Poulouse, 2012; Öztürk et al., 2020; Mohammed et

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al., 2020). There are three basic approaches in the synthesis of silver nanoparticles: physical, chemical, and biological. Since physical and chemical methods have some disadvantages such as expensive equipment, waste of time and the use of toxic materials, biological methods are more preferred in the synthesis of silver nanoparticles (Erdoğan et al., 2019; Zhang et al., 2021). Biocomponents found in biological materials play a role in synthesis reactions as reducing agents and reduce silver ions to metallic silver nanoparticles. Bacteria, fungi, algae and various plant components are used in biological synthesis (Wei et al., 2015). Since this method is environmentally and nature friendly, it is also called "Green Synthesis" in the literature. Plant extracts are a more ideal material in the green synthesis of nanoparticles since they do not have any contamination risk (Beykaya and Çağlar, 2016).

Elaeagnus angustifolia, known as İğde in our country and known as Russian olive throughout the world, grows especially in Asia and Europe. Especially in Middle Eastern countries, silverberry fruit is frequently used in wound healing, anti-ulcerogenic, anti-inflammatory, anti-emetic treatments and traditional medicine (Natanzi et al., 2012; Gurbuz et al., 2003; Ahmadiani et al., 2000; Rasekhi et al., 1999). *Elaeagnus angustifolia* fruit extract has been reported to contain various metabolites such as phytosterols, flavonoids, phenolic acids and terpenoids (Azez et al., 2018; Tepe and Doyuk, 2020). It is known that this rich metabolite content facilitates the reduction and stabilization of metal ions in nanoparticle synthesis (Baran, 2019).

In this study, it was aimed to synthesize silver nanoparticles with the green approach using *Elaeagnus angostifolia* aqueous extract and to investigate the cytotoxic effects of these nanoparticles. The synthesized nanoparticles were characterized by Ultraviolet-Visible Spectroscopy (UV-Vis), Infrared Spectroscopy (FTIR), Scanning Electron Microscopy (SEM), Energy Dispersive X-Ray (EDX) Spectroscopy. In addition, cytotoxic effects of silver nanoparticles on human cervical cancer cells (HELA), human prostate cancer cells (PC3) and mouse fibroblast cells (L929) were investigated.

MATERIAL AND METHODS

Preparation of *Elaeagnus Angustifolia* Fruit Aqueous Extract

The fruits of *Elaeagnus angustifolia*, which grows in stony soil at Aydin Adnan Menderes University Central Campus (37°51'15"N 27°51'22"E) were freshly picked in October 2020. The seed part of the fruit was discarded, and the pulp part was used for extraction (Figure 1). 100 g of fruit pulp was weighed and transferred to a 500 mL conical flask. 200 mL of distilled water was added on it. This mixture was heated on magnetic stirrer at 100 °C for 2 hours. After this process, the mixture could come to room temperature and filtered with Whatman filter paper (Grade 1). The filtrate was stored in a refrigerator at +4 °C until it was used in nanoparticle synthesis (Rao et al., 2015).

Green Synthesis of Silver Nanoparticles

20 mL of silver nitrate solution (10 mM) was added to the beaker. 20 mL of *Elaeagnus angustifolia* fruit aqueous extract was added drop by drop with the help of a pasteur pipette and kept in an ultrasonic bath for 10 minutes. The reaction mixture was exposed to 360W microwave rays for 5 minutes. The mixture in the beaker was transferred to falcon tubes and centrifuged at 4000 rpm for 10 minutes. Since the supernatant was seen to be clear, it was concluded that the particulate precipitation was complete. The pellet part containing the precipitated particles was washed 3 times with cold ethanol in order to remove organic residues from the extract. After the falkon tube was centrifuged again at 4000 rpm for 10 minutes, the pellet part was collected and left to dry overnight in a 100 °C oven. The obtained silver nanoparticles were stored in eppendorf tubes at room temperature to be used in characterization and cytotoxicity experiments (Joseph and Mathew, 2015; Haris et al., 2017).

Characterization of Silver Nanoparticles

The UV-Vis spectrum of the synthesized silver nanoparticles was taken with an Ultraviolet visible (UV-Vis) spectrophotometer (Thermo Scientific Multiscan Spectrum 1500) in the range of 200-800 nm. Functional group analysis of silver nanoparticles was performed by making measurements in the range of 400-4000 cm^{-1} with a Fourier-transform infrared (FT-IR) spectrophotometer (Shimadzu IR 8000). The structural properties and surface morphological properties of the nanoparticles were determined by examining the micrographs taken from the scanning electron microscope (SEM) (LEO 1430 VP). In addition, elemental composition

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analyzes of silver nanoparticles were analyzed by Energy Dispersion X-Ray (EDX) spectroscopy (LEO 1430 VP). To obtain SEM image and EDX analysis; the sample of silver nanoparticles were coated with gold under $4x10^{-2}$ mbar pressure by sputtering technique to make them better conductor. Then, the SEM images were collected at $1.3x10^{-5}$ pressure. The EDX analysis was recorded by local mapping technique from the best captured image.

Cell Culture Studies

In this study, HELA human cervical cancer, PC3 human prostate cancer and L929 mouse fibroblast cells belonging to the American Type Culture Collection were used to determine the cytotoxic effects of the synthesized silver nanoparticles. DMEM medium containing 10% FBS (Sigma F-2442), 2mM L-glutamine (Sigma G-6392), 100 U/mL penicillin and 100 µg/mL streptomycin was used for the growth of HELA and L929 cells. PC3 cells were cultured in RPMI-1640 medium containing 10% FBS (Sigma F-2442), 2mM L-glutamine (Sigma G-6392), 100 U/mL penicillin and 100 µg/mL streptomycin. Cells extracted from liquid nitrogen were planted in 75 cm^2 flasks and grown in an oven with 5% CO_2 (Core EC-160) at 37°C until the cells became a full layer. When the flask base was filled to 90%, the cells were removed with 0.05% Trypsin-EDTA (Sigma T-4049) and passaged (Cevik et al., 2020).

MTT measurements

The MTT test is widely used as a fast and sensitive method in evaluating the cytotoxicity of anticancer agents (Wan et al., 1994). The working principle of this method is the disintegration of the tetrazolium ring of the MTT dye into formazan by means of the succinate dehydrogenase enzyme in the intact mitochondria of the cells (Baek et al., 1998). To determine the cytotoxic effect of silver nanoparticles, cells were seeded in 96-well cell culture plates at a density of $1x10^4$ per well in 100 µL medium. In order to adhere the cells to the plate base, incubation was carried out in an oven with 5% CO_2 at 37°C. After adding different concentrations of silver nanoparticles (1, 10, 100, 1000 µg/mL) to the cells, the plate was re-incubated for 24 hours. The medium from the wells was discarded and 100 µL of fresh medium was added to each well. 10 µL of the previously prepared MTT dye was added to all wells. After the cells were incubated for 4 hours, the medium was decanted and 100 µL of dimethyl sulfoxide was added to each well to dissolve the formazan dye formed. The intensity of the formed color was measured at 570 nm in a microplate reader (Biotek Co., USA). Cell viability % was calculated with the aid of equation 1 and IC50 values using GraphPad Prism program (Cevik et al., 2018).

% Cell viability= (OD test sample)/(OD control) X 100
(Eq. 1)

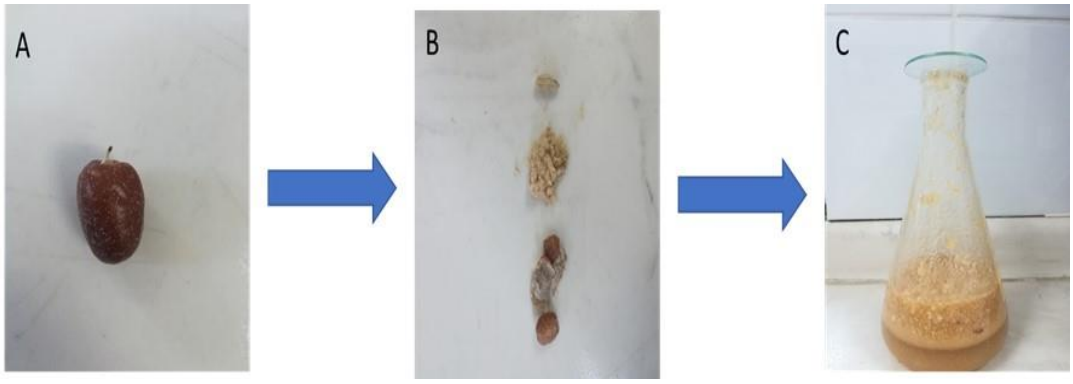

Figure 1: A) *Elaeagnus angustifolia* fruit. **B)** The part of *Elaeagnus angustifolia* fruit. **C)** The preparation of *Elaeagnus angustifolia* fruit aqueos extract

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Statistical analysis

Data from three independent experiments are presented as mean ± SD. Differences between groups were analyzed by student's t test. Statistical analysis was performed using GraphPad Prism version 5.0 software. Statistical significance is defined as follows: *, p≤0.05; **, p≤0.01; ***, p≤0.001.

RESULTS AND DISCUSSION

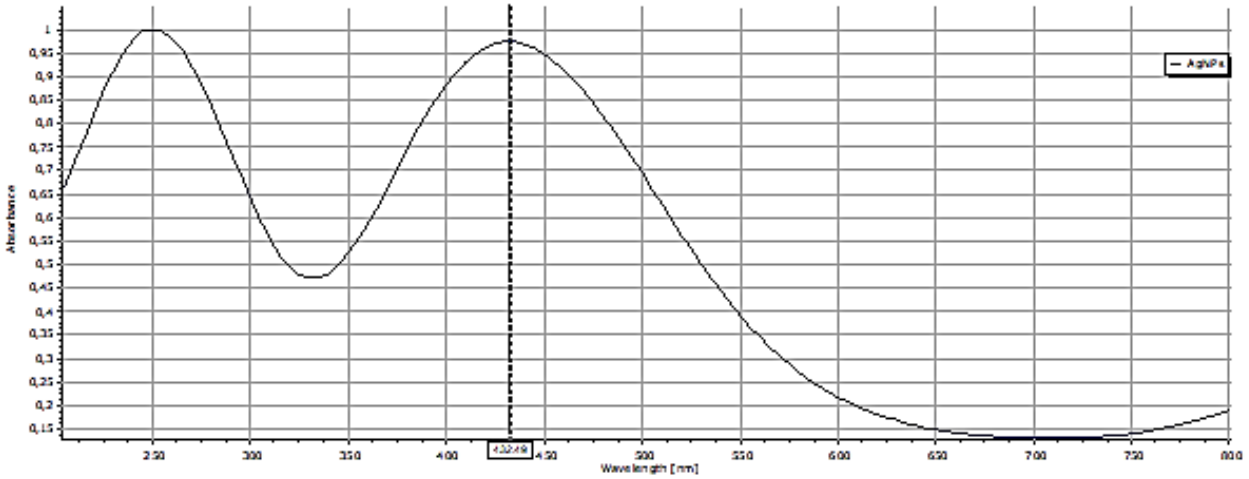
Synthesis and Characterization of Silver Nanoparticles

The use of green synthesis, which is a nature and life-friendly method that does not require the use of toxic chemicals in the synthesis of nanoparticles, has become a popular field of study (Ong et al., 2013).

In this study, silver nanoparticles were synthesized from green synthesis using *Elaeagnus angustifolia* fruit aqueous extract. Thus, a more advantageous method was preferred in terms of cost, time, environment, and health. In the characterization and structural analysis of silver nanoparticles, various analytical methods such as ultraviolet-visible region (UV-Vis) spectroscopy, fourier transform infrared (FTIR) spectroscopy, scanning electron microscopy (SEM), energy dispersion X-ray (EDX) spectroscopy and elemental analysis are used.

Ultraviolet-visible spectroscopy (UV-Vis) is one of the most important methods used in the characterization of silver nanoparticles. The most important indicator confirming the synthesis of silver nanoparticles is the color of the solution that turns brown during the reaction. This color formation is due to the surface plasmon resonance of the silver nanoparticles (Darroidi et al., 2010). The increase in absorbance between 420-470 nm in the UV spectrum is due to the surface plasmon resonance of silver nanoparticles (Bhui et al., 2009). Nahar et al. (2021) stated that the maximum absorbance at 442 nm wavelength was observed in the UV spectrum of silver nanoparticles synthesized with Citrus sinensis extract. When looking at the UV graph of silver nanoparticles synthesized with the aqueous extract of the silverberry fruit, λmax was obtained at 432 nm (Figure 2). On the other hand, the appearance peak at the about 250 nm is probably comes from the presence heteroatoms such as N, O (Njoku et al., 2013).

Figure 2: UV-Vis spectrum of silver nanoparticles synthesized with aqueous extract of *Elaeagnus angustifolia* fruit



In the green synthesis of silver nanoparticles, the bio-reducing agents contained in the extracts are adsorbed on the surface of the nanoparticles. Functional group analysis of these biocomponents on the surface of nanoparticles is determined by FTIR spectroscopy. When the FTIR spectrum of the silver nanoparticles synthesized with the aqueous extract of the silverberry is examined, bands are seen at 3410, 2918, 2850, 2360, 1739, 1622 and 669 cm^{-1} (Figure 3).

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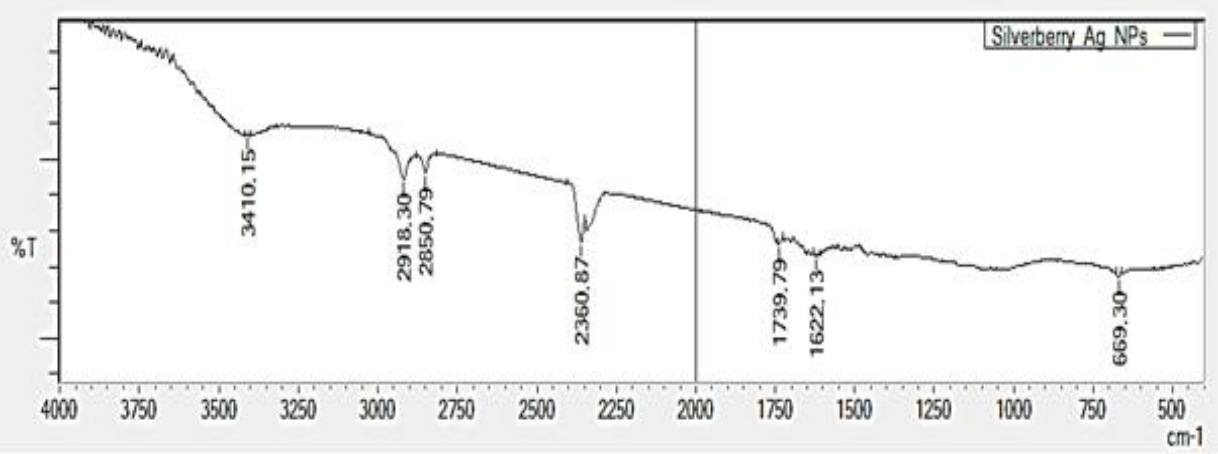

Figure 3: FTIR spectrum of silver nanoparticles synthesized with aqueous extract of *Elaeagnus angustifolia* fruit

The broad band at 3410 cm^{-1} belongs to the O-H stretch. The peak at 2360 cm^{-1} is due to atmospheric carbon dioxide. The peak at 669 cm^{-1} is the vibrations of silver (Banerjee and Nath, 2015; Balashanmugan and Kalaichelvan, 2015).

Morphological properties of silver nanoparticles are examined by scanning electron microscopy. When the SEM micrograph of the silver nanoparticles is examined (Figure 4), nano-sized particles are seen, most of which are spherical and

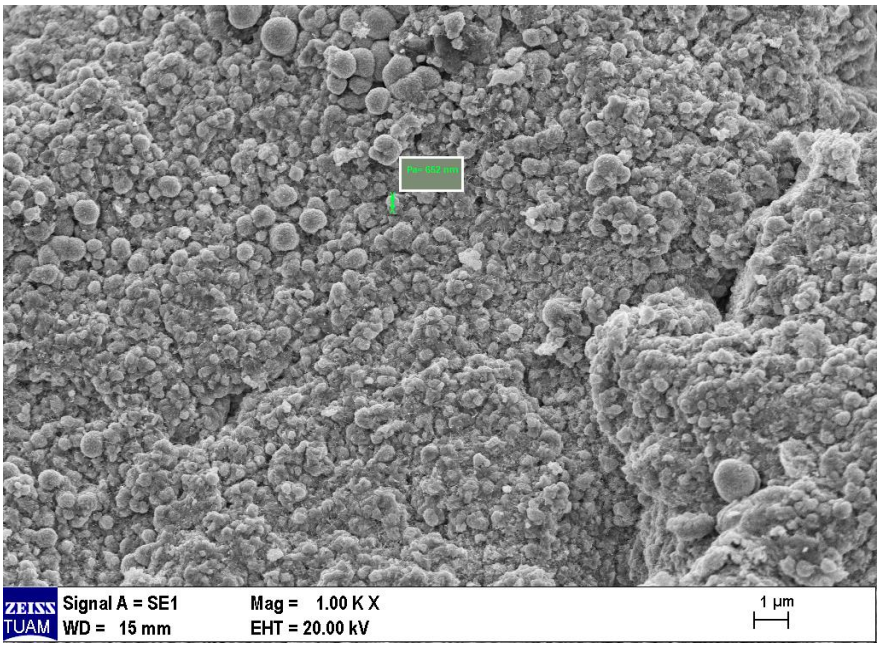

Figure 4: SEM micrograph of silver nanoparticles synthesized with the *Elaeagnus angustifolia* fruit aqueous extract

some of them irregularly shaped. It has also been determined that these nanoparticles form micron-sized aggregates. The approximate sizes of nanoparticles were found to be 652 nm.

Energy dispersion X-Ray crystallography is an analytical method used to determine the elemental composition of silver nanoparticles. In the EDX spectrum, the peak around 3 keV confirms the presence of silver (Govarthanan et al., 2014). When

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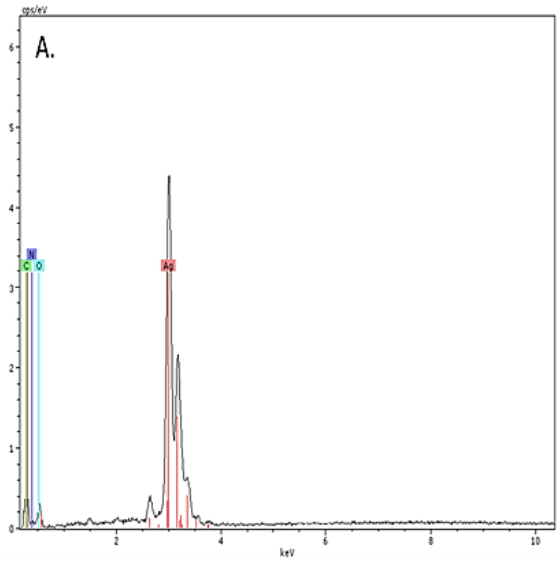
the EDX spectrum of the synthesized nanoparticle is examined (Figure 5A), the peak around 3 keV, supports the synthesis of silver nanoparticles. The abundance of silver atom was found to be 82.32%. Other contaminants such as carbon and nitrogen probably were caused by *Elaeagnus angustifolia* residues (Figure 5B).



B.

Element	Series	Net	unn. C	norm. C	Atom. C	Oxid	Oxid. C
		[wt.-%]	[wt.-%]	[at.-%]		[wt.-%]	
Carbon	K series	2018	3.72	1.69	6.52	CO_2	6.46
Nitrogen	K series	400	15.07	6.84	22.68	N_2O	11.22
Silver	L series	61701	173.72	78.79	33.94	Ag	82.32

Figure 5: A) EDX spectrum of silver nanoparticles synthesized with Elaeagnus Angustifolia fruit aqueous extract. **B)** Elemental analysis results

Cytotoxic Effects of Silver Nanoparticles

Cancer is a health problem that is difficult to treat and has a high mortality compared to other diseases. Current chemotherapeutic drugs such as cisplatin, doxorubicin, taxol and bleomycin bring some adverse conditions such as low specificity, high cost, high toxicity, undesirable side effects and drug resistance. Development of new treatment methods becomes necessary to overcome these disadvantages (Erdoğan, 2018; Wafa and Ghareib, 2018). Scientific research on the synthesis, characterization, stability, formulation and delivery of nanoparticles as cytotoxic agent and drug delivery system in cancer treatment continues intensively.

It has been reported that silver nanoparticles synthesized by green synthesis have better cytotoxic effects than chemically synthesized ones. It is thought that this effect is due to the biocomponents contained in the biological material used in the synthesis (Kummara et al., 2016). For this reason, the cytotoxic effects of silver nanoparticles synthesized with different plant extracts are investigated on various cell lines. Selvan et al. (2018) investigated the cytotoxic effects of silver nanoparticles synthesized with carnelia sinensis extract on MCF7, HELA, HepG2, A549 and NHDF cells. They found the IC50 values of silver nanoparticles on these cells as 19.94, 16.75, 27.63, 13.26 and >100, respectively. In our study, cytotoxic effects of silver nanoparticles synthesized with the aqueous fruit extract of *Elaeagnus angustifolia* were investigated on HELA and PC3 as cancerous cells and on L929 as normal mouse fibroblast cells. IC50 value of a potential chemotherapeutic agent is expected to be low in cancer cells and high in normal cells (Damiani et al., 2019). IC50 values of silver nanoparticles for HELA, PC3 and L929 cells were calculated as 11.8, 18.8 and 13.6 µg/mL, respectively (Figure 6A).

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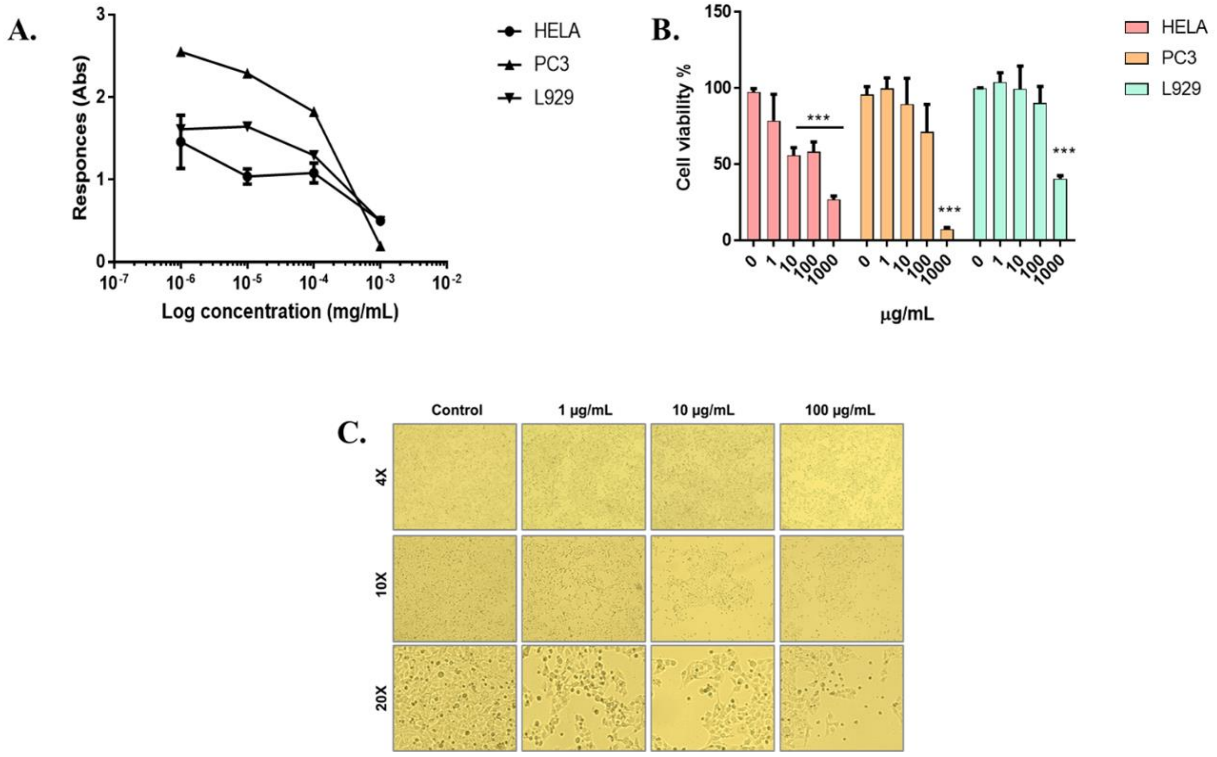

Figure 6: A) IC50 plots of HELA, PC3 and L929 cells treated with silver nanoparticles. **B)** Cell viability graphs of HELA, PC3 and L929 cells treated with silver nanoparticles. **C)** Inverted microscope images of HELA cervical cancer cells treated with silver nanoparticles

These results clearly show that the IC50 value of the silver nanoparticle synthesized with *Elaeagnus angustifolia* is lower compared to other studies. Bioactive compounds from *Elaeagnus angustifolia* may have increased the cytotoxic activity of silver nanoparticles. When the cell viability graph was examined (Figure 6B), it was found that silver nanoparticles decreased the proliferation of PC3 and L929 cells in a dose-dependent manner. Especially, 1000 µg/mL dose reduced the viability of PC3 prostate cancer cells up to 10%. The IC50 value of silver nanoparticles was found to be the lowest in HELA cells. Therefore, the morphological effects of these nanoparticles on HELA cervical cancer cells were examined with images taken at 4X, 10X and 20X magnification (Figure 6C). HELA cells treated with 100 µg/mL silver nanoparticles were found to exhibit apoptotic markers such as cell size reduction and bubbling in the plasma membrane.

CONCLUSION

The use of nanotechnological metal atoms both as cytotoxic agents and as a carrier system in cancer treatment is increasing day by day. With this study, silver nanoparticles were synthesized with green synthesis, which is a time-saving, less costly, environmentally friendly and more easily applicable method. In addition, these biogenic silver nanoparticles have the potential to be used as an anticancer agent in the treatment of cervical and prostate cancer due to their cytotoxic effect on HELA and PC3 cells.

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CONFLICT OF INTEREST

The Author report no conflict of interest relevant to this article

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RESEARCH AND PUBLICATION ETHICS STATEMENT

The author declares that this study complies with research and publication ethics.

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Figure Legends

Figure 1: A) *Elaeagnus angustifolia* fruit. B) The part of *Elaeagnus Angustifolia* fruit. C) The preparation of *Elaeagnus Angustifolia* fruit aqueos extract

Figure 2: UV-Vis spectrum of silver nanoparticles synthesized with aqueous extract of *Elaeagnus angustifolia* fruit

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Figure 3: FTIR spectrum of silver nanoparticles synthesized with aqueous extract of *Elaeagnus angustifolia* fruit

Figure 4: SEM micrograph of silver nanoparticles synthesized with the *Elaeagnus angustifolia* fruit aqueous extract

Figure 5: A) EDX spectrum of silver nanoparticles synthesized with Elaeagnus Angustifolia fruit aqueous extract. B) Elemental analysis results

Figure 6: A) IC50 plots of HELA, PC3 and L929 cells treated with silver nanoparticles. B) Cell viability graphs of HELA, PC3 and L929 cells treated with silver nanoparticles. C) Inverted microscope images of HELA cervical cancer cells treated with silver nanoparticles