

Research Article

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Treatment of gastric cancer by green mediated silver nanoparticles using *Pistacia atlantica* bark aqueous extract

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Abstract: We herein demonstrate a novel green mediated silver nanoparticles (AgNPs) using *Pistacia atlantica* bark aqueous extract for the treatment of gastric cancer under *in vitro* conditions. Physicochemical and structural features of the nanocomposite biomaterial were assessed by several techniques like UV-Vis spectrum, transmission electron spectroscopy, field emission scanning electron microscopy, energy-dispersive X-ray spectroscopy, and inductively coupled plasma-optical emission spectroscopy. The Ag NPs showed high antioxidant activities against 2,2-diphenyl-1-picrylhydrazyl (DPPH). The IC_{50} of Ag NPs and Butylated hydroxytoluene against DPPH were 132 and 77 $\mu\text{g/mL}$, respectively. In the oncological part of this research, the status of normal and gastric cancer AGS and KATO III cell lines was determined. The IC_{50} of AgNPs was 193 and 250 $\mu\text{g/mL}$ against AGS and KATO III. It seems that the prepared NP have stopped the growth of gastric cancer cells and the recent cancer cells have been removed with high concentration of NPs.

Keywords: *Pistacia atlantica*, silver NPs, anti-gastric cancer, cytotoxicity

1 Introduction

Pistacia atlantica is a plant used in prescriptions related to cancer treatment. This plant is also known as Bane. This plant belongs to the pistachio family or Anacardiaceae [1,2]. Native people eat the fruits of the *Pistacia atlantica* tree as snacks. In this way, they are roasted and mixed with other nutritious seeds. *Pistacia atlantica* gum is also used to prepare a kind of natural gum [3,4]. The nature of the *Pistacia atlantica* plant and its gum is hot and dry, and doctors have mentioned the therapeutic effects of several parts, such as its fruit, leaves, and gum, to cure a wide range of diseases. So far, the *Pistacia atlantica* plant has been subjected to many studies, a large part of which has been carried out by scientists and students. For example, the antioxidant effects of fruit and peels have been investigated in various *in vitro* studies, and the antioxidant properties of plant extracts have been compared with the standard compounds studied [5–7]. In addition, leaf essential oil and gum have shown significant antibacterial and antifungal effects in different strains [8–12]. A search of reliable sources of traditional medicine shows that *Pistacia atlantica* is used in the treatment of cancer. *Pistacia atlantica* gum is used to treat diseases related to the digestive system and is prescribed to cleanse the brain and nervous system of excess moisture. One of the uses of *Pistacia atlantica* that is widely seen in Iranian medical sources is its use in ointments and poultices that are used to heal swellings, wounds, and injuries that are difficult to treat due to various reasons [13–22]. *Pistacia atlantica* has a special place in the indigenous medicine of different tribes. It is used in the traditional medicine of Algeria, as a compound to strengthen the digestive system and anti-diarrhea [23], in Greece, to freshen the mouth [24], in Turkey, to treat wounds [25], and in Jordan and Morocco, as a medicine

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against respiratory tract infections and painkillers [26,27]. There are ointments related to diseases of cancer, pigs, taalil nails, leprosy, salah, and squirus, one of the components of which is gum *Pistacia atlantica*. Shangarf ointment or Zenjfer is one of the topical medicinal forms for the treatment of cancer and pigs, which is mentioned frequently and with little change in the authentic books of traditional medicine. Syringe ointment is also one of the most frequently used ointment, and one of its components is *Pistacia atlantica*. In addition, sages have prescribed other prescriptions for the treatment of cancer or related diseases, which contain *Pistacia atlantica*. The point that exists in the *Pistacia atlantica* used in traditional medicine texts is that sages use the gum of this plant, and apparently, the rest of the plant's components have not been widely used to treat cancer. Among the other things that can be taken into consideration are the many topical medicinal forms prepared from *Pistacia atlantica* gum and other ingredients for the cure of cancer and other malignancies. The conducted research works show the very high ability of the effective ingredients of the *Pistacia atlantica* to affect cancer cells. The amount of *Pistacia atlantica* constituents are analyzed and determined using methods such as GC and HPLC. According to these research works, the major components of the oil obtained from *Pistacia atlantica* gum are monotrin compounds such as alpha pinene, limonene, and alpha-pineol [28–30]. *Pistacia atlantica* resin also contains various triterpenoid compounds such as morolic acid, masticdienonic acid, and olanolic acid [27–29]. Also, gallic acid, catechin, flavonoids, and anthocyanins have also been identified in *Pistacia atlantica* [29,30]. The effects of polyphenol compounds in cancer prevention have been confirmed in several animal and cell research works [27–30].

Today, several types of cancer treatments including surgery, palliative care, radiation therapy, and chemotherapy are available, and depending on the cancer degree and location, several methods are applied for treatment. Hence, there is a need for modern treatment methods to control cancer [31–33]. In the current age, the term “Nano-biotechnology” has been become quite familiar amongst researchers, which has made a pivotal connection between nanoscience and biotechnology [34,35]. Meanwhile, the science of nanotechnology has contributed greatly to the development and discovery of modern cancer treatment options. For example, we can mention the use of modified nanoparticles (NPs) for the targeted and selective delivery of drugs to carcinoma tissue [36–38]. The use of nanotechnology in the drugs production is one of the promising fields. Because of their excellent physical characteristics, NPs have been applied as an effective candidate for drug treatment, the most important of which is silver NPs [33–36]. Although there are different methods for NP synthesis, biocompatible methods such as synthesis using bacteria, fungi, and plants are very simple and cost-effective alternatives to

chemical and physical methods [39–42]. Meanwhile, plants have received more attention. Various research works have also revealed the anticancer property of plant NPs, so that these plants have been applied for the green synthesis of silver nanoparticles (AgNPs) [43–45]. If the anti-tumor and therapeutic effects of these NPs are approved, this can be a step forward in the advancement of cancer treatment methods [46–49]. Various studies have proven the AgNPs role on Caspase 3 (Casp3) gene and p53 gene in anticancer effects [50–53]. The p53 gene is in the chromosome-17 short arm at position P13.17 and has 11 exons and a length of 20 kb. p53 mutations are found in approximately half of human tumors, and the remaining tumors appear to be caused by defects in p53-related pathways. Casp3 gene is in the chromosome-4 long arm at position q344 and has 8 exons. Cas3 is one of the executive caspases that can be activated by proteolysis and activate other procaspases. Finally, programmed cell death occurs and leads to DNA fragmentation, disintegration of the cell skeleton, and nuclear proteins. Also, AgNPs cause the removal of tumor cells by activating the production path of oxygen free radicals or reactive oxygen species (ROS) [51–55].

The goal of this research is to introduce a method for the green synthesis of AgNPs using *Pistacia atlantica* bark (Figure 1), as novel procedure without using any harmful and toxic agents. The prepared AgNPs were analyzed and their cytotoxicity was determined against gastric carcinoma cells.

2 Experimental methods

2.1 Sources

AgNO₃, NaOH, acetone, and ethanol were procured from Sigma Aldrich. Cancer cells (AGS and KATO III) and normal cell lines were purchased from the Iran Pasteur Institute.



Figure 1: Image of *Pistacia atlantica*.

2.2 Preparation of plant extract

Cleaned and dried *Pistacia atlantica* fruit (1.0 g) was added to 20 mL deionized water and heated at 80°C for 0.5 h. The pale-yellow fruit extract was collected by filtration over Whatman-1paper and used as such.

2.3 Synthesis of AgNPs

10 mL of the prepared fruit extract was added to AgNO₃ (50 mL, 1 mM) aqueous solution and stirred at room temperature for 30 min. The color of the solution turning dark brown confirmed the synthesis of AgNPs (Figure 2). The prepared AgNPs were collected by centrifugation at 1792RCF (G-force) for 10 min, then washed with DI water.

2.4 Characterization of biosynthesized AgNPs

The obtained biosynthesized AgNPs were analyzed by modern characterization methods, as follows: transmission electron spectroscopy (TEM) analysis was performed using a Phillips CM10 microscope. Elements presence in the related composite was assessed by energy-dispersive X-ray spectroscopy (EDX) linked to scanning electron microscopy (SEM). In the spectrophotometric analysis, a double beam UV-Vis instrument (PG, T80+) was used along with quartz cuvettes (10 mm). The spectral data of prepared nanocomposite were recorded in the range of 230–700 nm.

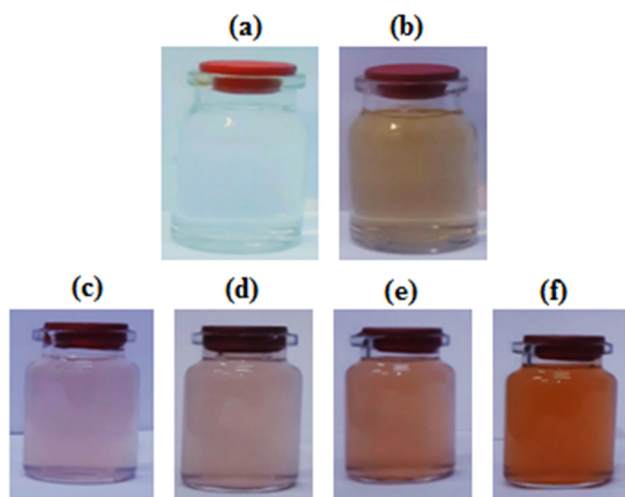


Figure 2: Silver nitrate solution (a), *Pistacia atlantica* extract (b), and color changes in the synthesis of Ag NPs (c–f).

2.5 Measurement of anti-gastric cancer properties

Synthesized Ag NPs' cytotoxic effects on gastric cancer AGS and KATO III cells were assessed by Methy Thiazol Tetrazolium (MTT) test.

DMEM high glucose culture medium enriched with 4 mM L-glutamine and FBS 10% were used for cell culture and the cells were transferred to an incubator. After three successful passages, the cells were cultured to the number of 10⁴ cells in each well. After 24 h of cell culture, they were exposed to several dilutions of NPs for 24, 48, 72, and 96 h. Then, the MTT test was performed to determine the cytotoxicity induced by the above NPs and the percentage of cell survival. After the desired time, a sufficient amount of MTT was added to the wells. After incubating the plates for 3 h, the culture medium was removed and DMSO was added to the wells. After 150 min, optical absorption at 570 nm was read by an ELISA reader (BioTek manufactured by Viragen). The cells' survival percentage was computed using the below formula [54]:

$$\text{Cell viability(\%)} = \frac{\text{Sample } A}{\text{Control } A} \times 100.$$

2.6 Measurement of antioxidant properties

In order to check the antioxidant property, 2,2 diphenyl-1-picrylhydrazil (DPPH) test was conducted. The color change was measured using spectrophotometry. 1 mL of 1 mM DPPH was added to 1 mL of NPs in different dilutions, shaken well, and kept in the dark at 25°C for 0.5 h. Then, the absorbance of the mixture at 517 nm wavelength was measured with blank methanol and DPPH solution and free radical inhibition was calculated using the below formula [54]:

$$\text{DPPH scavenging effect (\%)} = [(A_0 - A_1)/A_0] \times 100.$$

In the above biological tests, IC₅₀ was obtained from a linear graph with a regression coefficient above 0.9.

3 Results and discussion

The AgNP synthesis can be easily detected by visible observations, as shown in Figure 2, where the color of the solution changed to light brown. This result was also confirmed by UV-Vis study, where the AgNPs peak appeared at around 450 nm. Figure 3 shows the reduction sequence in the measured absorbance terms in UV-Vis, at several time intervals.

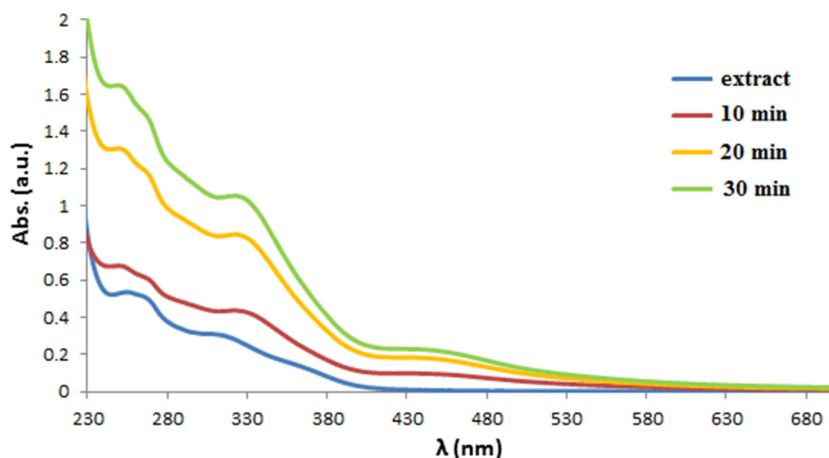


Figure 3: UV-Vis absorption spectra of biosynthesis of AgNPs using *Pistacia atlantica* extract.

The surface size, shape, and morphology of the prepared AgNPs were analyzed using field emission scanning electron microscopy (FESEM) and TEM images (Figures 4 and 5). Subsequently, the inherent structural morphology was dispensed from TEM investigations (Figure 5). As can be seen from TEM images, the materials are well-dispersed with spherical shaped. Nanocomposite particles mean diameter are within 20–30 nm.

EDX investigation of formulated AgNPs was carried out in order to have information on its chemical composition (Figure 6). The appeared strong signal at 2.5–3.2 keV was correspond to Ag species. The O and C small peaks are detected in the lower region corresponding to the phytomolecules from *Pistacia atlantica*.

The findings of the MTT test on gastric cancer cell lines and HUVEC showed that cell viability depended on the concentration of NPs. So, in 48 h after the treatment and

at high doses of this NP, the survival rate of cancer cells decreased drastically (Table 1, Figures 7 and 8). IC_{50} in 48 h for cancer cells was reported to be about 193 and 250 $\mu\text{g/mL}$ on AGS and KATO III, while normal cells revealed a higher percentage of survival than cancer cells. The results indicated that these NPs could inhibit gastric cancer cells more strongly than normal cells.

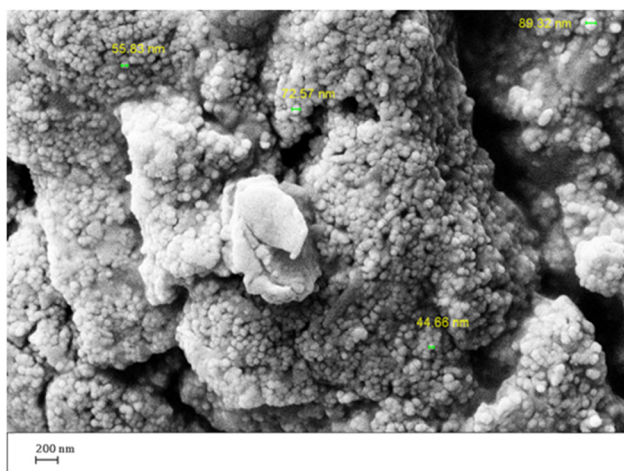


Figure 4: FESEM image of biosynthesized AgNPs.

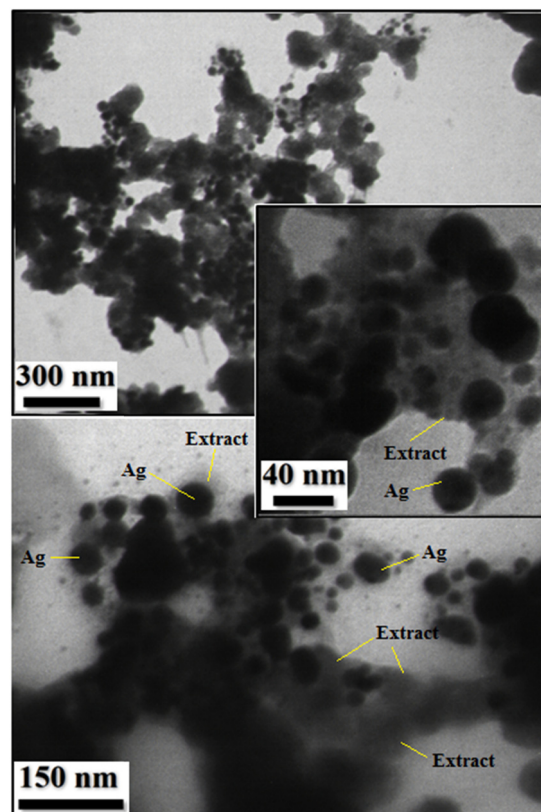


Figure 5: TEM images of formulated NPs.

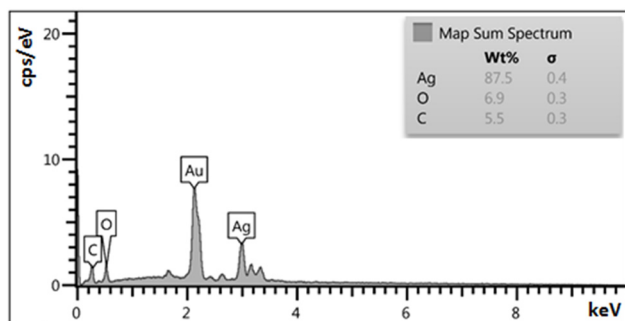


Figure 6: EDX spectrum of biosynthesized AgNPs.

Table 1: AgNPs and *Pistacia atlantica* extract IC₅₀

	AgNPs (μg/mL)	<i>Pistacia atlantica</i> extract
IC ₅₀ against AGS	193 ± 5 ^a	562 ± 5 ^b
IC ₅₀ against KATO III	250 ± 4 ^a	593 ± 7 ^b
IC ₅₀ against HUVEC	–	–

Non-identical words (a, b) show the significant difference.

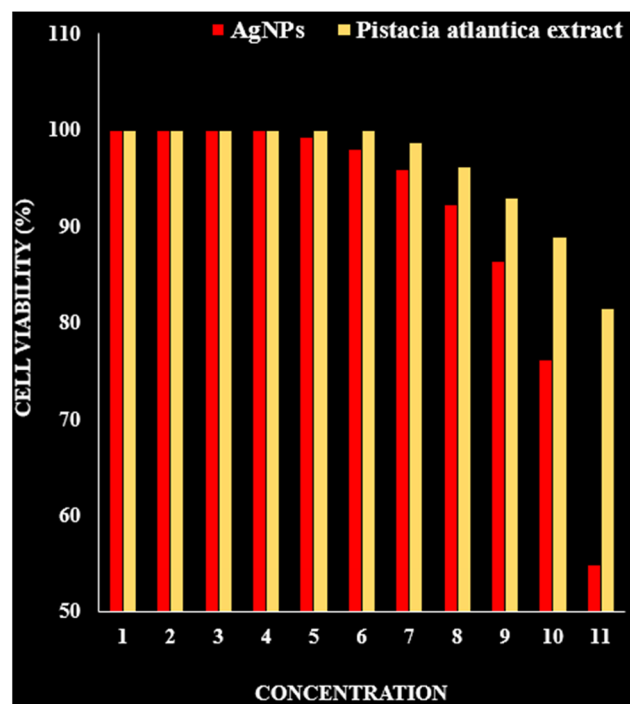


Figure 7: The cytotoxicity effects of *Pistacia atlantica* extract and AgNPs.

Antioxidants prevent the free radicals formation or interrupt the free radicals release from several mechanisms, namely (1) removal of peroxidation initiator species, (2) chelation of metal ions in such a way that they cannot produce ROS or break down lipid peroxide, (3) quenching

O₂ to prevent the peroxide formation, and (4) reducing the O₂ concentration [55–57]. Chain antioxidants, depending on their physical location inside the food and chemical characteristics, are different in terms of antioxidant effect. The antioxidant chemical power and oil solubility affect the access of proxy radicals, especially in the emulsion, micelle, and membrane systems, because for the effectiveness in these systems, the biophilic property is needed [56–59]. The best antioxidants have some properties: (1) Give H to oxidation free radicals and become radicals themselves, (2) have phenolic or aromatic rings, and (3) interrupt free radical chain reactions. The radical intermediates are stabilized based on the electron resonance non-establishment in the aromatic ring and the quinone formation [57–60]. Also, several phenolics lack suitable molecular positions. Propyl gallate, butylated hydroxytoluene (BHT), butylated hydroxyanisole (synthetic antioxidants), and flavonoids (natural plants containing phenolics) work in this way. So, several tissues have developed antioxidant systems to regulate the levels of secondary decomposition products, oxidation mediators, lipid oxidation, and free radicals [59–63]. They are tocopherols, carotenoids, phenolic acids, and flavonoids that act as reducing agents, eliminate free radicals, and inhibit the oxidation. Medicinal plants and herbal NPs have excellent H-donating effects and can have high anticancer properties [64–70].

Colorimetric tests of Ag NPs that were synthesized from plant extracts were done to confirm the presence of antioxidant compounds in NPs and the NPs' toxicity effect on different cancer and normal cell lineages. The activity of antioxidants was tested using DPPH tests and the toxicity effect was tested using the MTT method, and all the findings revealed a raise with the increase in the concentration of NPs. In this research, the maximum antioxidant activity was shown at 1,000 μg/mL and above 100%. The findings of the antioxidant test are shown in Figure 9 and Table 2.

Several research works have been done on the *Pistacia atlantica* fruit, known as Bane, in such a way that the fruit extract has been tested on different types of cancer cells. Based on the studies conducted on the methanolic extract of the pericarp of *Pistacia atlantica* fruit on the breast cancer cell line (T47D), it was found that this extract can induce apoptosis and prevent cell proliferation, and its effect is comparable to that of doxorubicin [71]. In another study by the same group of researchers, to clarify the mechanism of the anti-cancer effect of the skin of Beneh fruit, the effect of the extract on the cell cycle of breast cancer cells (T47D) and the proteins involved in it were analyzed by cytometry and Western blot methods. According to the findings of this research, the anti-cancer activity of Beneh fruit is applied by stopping the cell cycle and greatly decreasing the

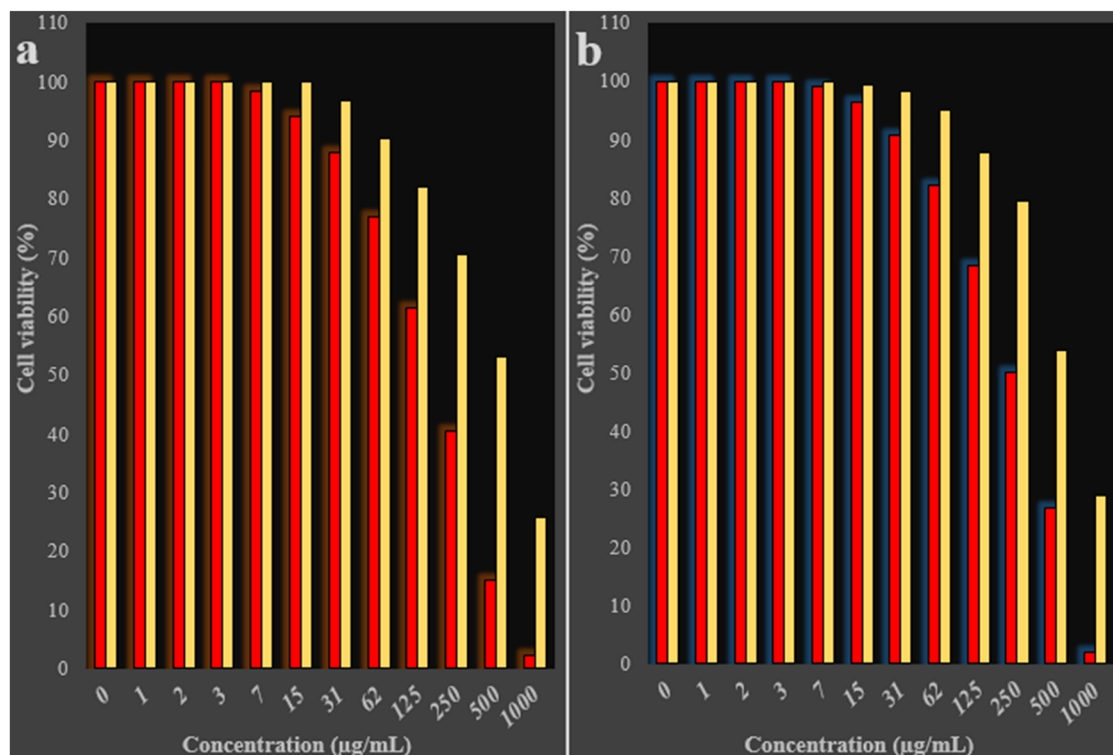


Figure 8: The anti-gastric carcinoma effects of *Pistacia atlantica* extract and AgNPs against AGS (a) and KATO III (b) cells.

expression of the genes related to cdk4 and cyclin D1 proteins, which are the mediator proteins in DNA replication and mitosis division [72]. In another study, the effect of the fruit extract of the tuber on the colon cancer cell line (HT29) was compared with that of doxorubicin. In this study, the extract (0.7 mg/mL) had the same activities as that of doxorubicin

with a concentration of 500 nM. The mechanism of action is the inhibitory effect on gene expression of cyclin A and cyclin B1 proteins [73]. The ethanolic extract of fruit peel of Beneh has been tested on the prostate cancer cell line (PC3) and normal L929 cells. The findings of this research showed that this extract can prevent the PC3 cells proliferation. This inhibitory effect depends on the duration of the test period and the dose of the extract. It was also found that the extract of the skin of Beneh fruit induces apoptosis in PC3 cells and its cytotoxic effects on PC3 cells are more than normal L929 cells [74]. In addition to this, research has been conducted to assess the effect of the fruit extract on the SK-N-MC (neuroblastoma cell line). In this research, dry fruits were powdered and extracted by methanol and water with a ratio of 70–30 using the percolation method. Examining the compounds of the extract with the HPLC method has shown that terpenoids are the key compounds in the said extract. The mentioned

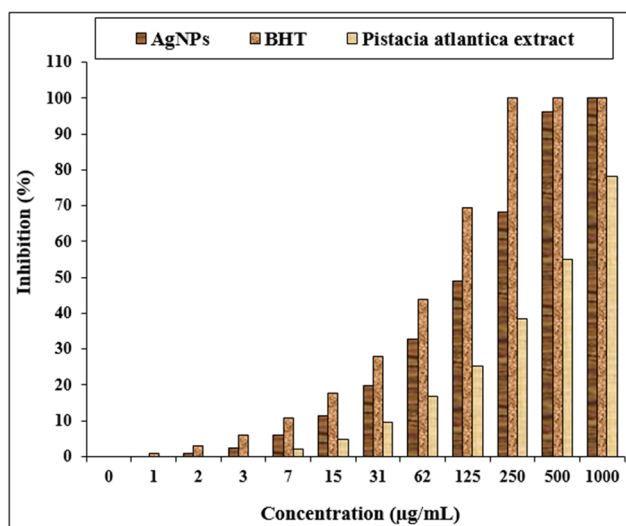


Figure 9: The antioxidant potentials of *Pistacia atlantica* extract, BHT and AgNPs.

Table 2: IC₅₀ of *Pistacia atlantica* extract, BHT, and AgNPs

	AgNPs (µg/mL)	BHT (µg/mL)	<i>Pistacia atlantica</i> extract (µg/mL)
IC ₅₀ against DPPH	132 ± 3	77 ± 3	426 ± 6

extract has confirmed effects on inhibiting the human neuroblastoma cell line. Since continuous cell division is one of the indicators of cancer cells and microtubule proteins play a key role in these cell divisions, the effect of the extract on the polymerization of microtubules has been tested. Based on the results of this study, it has been found that Beneh fruit extract causes structural changes in tubulin proteins and inhibits the polymerization of microtubules. Based on these results, Beneh fruit has been introduced as a source for the preparation of herbal anti-cancer drugs [75]. Ethanol extract of *Pistacia atlantica* leaves has been investigated on gastric cancer cells (AGS), uterine cancer cells (HeLa), and skin fibroblast cells (HDFS). The values of IC_{50} or inhibition of 50% of the growth of cancer cells were determined to be 382 $\mu\text{g}/\text{m}$ for AGS cells, 332 $\mu\text{g}/\text{m}$ for HL cells, and 896 $\mu\text{g}/\text{m}$ for HDF cells. According to the mentioned results, *Pistacia atlantica* leaf extract can inhibit the gastric and uterine cancer cells proliferation [76]. The bark and leaves of the *Pistacia atlantica* grown in Jordan have also been the subject of research on the anti-cancer effects of this plant. The essential oil obtained from leaves and gall have been tested on colon cancer (HCT116 and Caco2) and breast cancer (T47D and MCF7) cell lines. In addition, their effects have been investigated in combination with doxorubicin. Both leaf and gall essential oils have been investigated in terms of chemical compounds, monoterpenes with low molecular weight were the dominant compounds of both essential oils, but sesquiterpenes were present in a higher percentage in the leaf essential oil. The comparison of these two essential oils has shown stronger cytotoxic effects of leaf essential oil than gall essential oil in the tested cell lines. In addition, the effects of the drug doxorubicin increase with leaf essential oil, while this effect is not seen in the case of gall essence [77]. A group of researchers conducted a study on *Pistacia atlantica* resin and investigated its cytotoxic and genotoxic effects on normal and cancer cells. In this study, *Pistacia atlantica* resin was dissolved in a phosphate-saline buffer containing 5% of DMSO and tested on NIH 33 KB and HUVEC cells. According to the findings of this research, *Pistacia atlantica* resin has cytotoxic and genotoxic effects on both normal cells and cancer cells. The researchers of this study have suggested that since *Pistacia atlantica* gum is a natural gum and is also commonly used to treat diseases, *in vivo* studies should be done to investigate its cytotoxic and genotoxic effects [78].

4 Conclusion

In conclusion, we introduced a method for the green synthesis of AgNPs using *Pistacia atlantica* bark, as novel procedure without using any harmful and toxic agents. The IC_{50} of BHT

and AgNPs were 77 and 132 $\mu\text{g}/\text{mL}$, respectively. The silver NPs were checked in anticancer potentials against gastric cancer AGS and KATO III cells. The viability of cancer cells reduced in the presence of Ag NPs.

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Conflict of interest: Authors state no conflict of interest.

Ethical approval: The conducted research is not related to either human or animal use.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

- [1] Amin GH. Popular Medicinal Plants of Iran. Tehran: Tehran University of Medical Sciences; 2005.
- [2] Ghahreman A, Okhovvat R. Matching the old medicinal plant names with scientific terminology. Tehran: Tehran University of Medical Sciences; 2004.
- [3] Bozorgi M, Memariani Z, Mobli M, Salehi Surmaghi MH, Shams-Ardekani MR, Rahimi R. Five *Pistacia* species (*P. vera*, *P. atlantica*, *P. terebinthus*, *P. khinjuk*, and *P. lentiscus*): a review of their traditional uses, phytochemistry, and pharmacology. *Sci World J.* 2013;2013:219815.
- [4] Daneshrad A, Aynehchi Y. Chemical studies of the oil from *Pistacia* nuts growing wild in Iran. *J Am Oil Chem Soc.* 1980 Aug;57(8):248–9.
- [5] Peksel A. Antioxidative properties of decoction of *Pistacia atlantica* Desf. leaves. *Asian J Chem.* 2008 Jan 1;20(1):681.
- [6] Farhoosh R, Khodaparast MH, Sharif A. Bene hull oil as a highly stable and antioxidative vegetable oil. *Eur J Lipid Sci Technol.* 2009 Dec;111(12):1259–65.
- [7] Farhoosh R, Tavassoli-Kafrani MH, Sharif A. Antioxidant activity of the fractions separated from the unsaponifiable matter of bene hull oil. *Food Chem.* 2011 May;126(2):583–9.

- [8] Sharifi MS, Hazell SL. Isolation analysis and antimicrobial activity of the acidic fractions of Mastic, Kurdica, Mutica and Cabolica gums from genus *Pistacia*. *Glob J Health Sci*. 2012 Jan;4(1):217.
- [9] Adams M, Plitzko I, Kaiser M, Brun R, Hamburger M. HPLC-profiling for antiparasitoid compounds – 3-Methoxycarpachromene from *Pistacia atlantica*. *Phytochem Lett*. 2009;2(4):159–62.
- [10] Ghalem BR, Mohamed B. Essential oil from gum of *Pistacia atlantica* Desf.: screening of antimicrobial activity. *African. J Pharm Pharmacol*. 2009 Mar;3(3):087–91.
- [11] Tohidi M, Khayami M, Nejati V, Meftahzade H. Evaluation of antibacterial activity and wound healing of *Pistacia atlantica* and *Pistacia khinjuk*. *J Med Plants Res*. 2011 Sep;5(17):4310–4.
- [12] Yoram G, Inbar M. Distinct antimicrobial activities in aphid galls on *Pistacia atlantica*. *Plant Signal Behav*. 2011 Dec;6(12):2008–12.
- [13] Avicenna. *Al-Qanun fi al-Tibb* (The Canon of Medicine). Translated by Sharafkandi A. Vol. 2. Tehran: Soroush Press; 2016.
- [14] Jorjani SE. *Zakhiyeh Kharazmshahi*. 1st edn. Qom: Ehya'e Tebbe Tabiee; 2012 [in Persian].
- [15] Rhazes. *Al-Havi fi al-Tibb* (Contain Med). Vol. 2. Beirut: Darolahya-e-Serat Alarabiye; 2001. p. 9.
- [16] Aghili Alavi Shirazi MH. *Makhzan al-Advieh*. Tehran: Tehran University of Medical Sciences Press; 2009.
- [17] Aghili Alavi Shirazi MH. *Gharabadin-e Kabir*. Tehran: Tehran University of Medical Sciences Press; 2009.
- [18] Hakim Momen M. *Tohfat al-Momenin*. Tehran: Shahr Publication; 2008.
- [19] Azamkhan M. *Exir Azam*. Tehran: Research Institute for Islamic and Complementary Medicine; 2009.
- [20] Heravi A. *Al –Abnieh an Haghayegh al –Advieh*. Tehran: Tehran University of Medical Sciences Press; 1967.
- [21] Gharshi I. *Al-Shamil fi al-Sina'ah al-Tibbiyah*. Tehran: Tehran University of Medical Sciences Press; 2008.
- [22] Abu Reihane Biruni A. *Al-Saydaneh fi al-Tibb*. Tehran: Tehran University of Medical Sciences Press; 1991.
- [23] Yousfi M, Nedjmi B, Bellal R, Ben Bertal D, Palla G. Fatty acids and sterols of *Pistacia atlantica* fruit oil. *J Am Oil Chem Soc*. 2002 Oct;79(10):1049–50.
- [24] Tzakou O, Bazos I, Yannitsaros A. Volatile metabolites of *Pistacia atlantica* Desf. From Greece. *Flavour Fragr J*. 2007 Sep;22(5):358–62.
- [25] Altundag E, Ozturk M. Ethnomedicinal studies on the plant resources of east Anatolia, Turkey. *Procedia-Soc Behav Sci*. 2011 Jan;19:756–77.
- [26] Hamdan II, Afifi FU. Studies on the in vitro and in vivo hypoglycemic activities of some medicinal plants used in treatment of diabetes in Jordanian traditional medicine. *J Ethnopharmacol*. 2004 Jul;93(1):117–21.
- [27] Barrero AF, Herrador MM, Arteaga JF, Akssira M, Mellouki F, Belgarrabe A, et al. Chemical composition of the essential oils of *Pistacia atlantica* Desf. *J Essent Oil Res*. 2005 Jan;17(1):52–4.
- [28] Graf F, Koehler L, Knies T, Wuest F, Mosch B, Pietzsch J. Cell cycle regulating kinase Cdk4 as a potential target for tumor cell treatment and tumor imaging. *J Oncol*. 2009;2009:106378.
- [29] Mecherara-Idjeri S, Hassani A, Castola V, Casanova J. Composition of leaf, fruit and gall essential oils of Algerian *Pistacia atlantica* Desf. *J Essent Oil Res*. 2008;20(3):215–9.
- [30] Delazar A, Reid RG, Sarker SD. GC-MS analysis of the essential oil from the oleoresin of *Pistacia atlantica* var. *mutica*. *Chem Nat Compd*. 2004 Jan;40(1):24–7.
- [31] Rashid F, Ahmed Z, Hussain S, Huang JY, Ahmad A. *Linum usitatissimum* L. seeds: Flax gum extraction, physicochemical and functional characterization. *Carbohydr Polym*. 2019;215:29–38.
- [32] Ramesh M. Flax (*Linum usitatissimum* L.) fibre reinforced polymer composite materials: A review on preparation, properties and prospects. *Prog Mater Sci*. 2019;102:109–66.
- [33] Saleem MH, Ali S, Hussain S, Kamran M, Chattha MS, Ahmad S, et al. Flax (*Linum usitatissimum* L.): A potential candidate for phytoremediation? Biological and economical points of view. *Plants*. 2020;9(4):496.
- [34] Alkasir M, Samadi N, Sabouri Z, Mardani Z, Khatami M, Darroudi M. Evaluation cytotoxicity effects of biosynthesized zinc oxide nanoparticles using aqueous *Linum Usitatissimum* extract and investigation of their photocatalytic activity. *Inorg Chem Commun*. 2020;119:108066.
- [35] Saleem MH, Kamran M, Zhou Y, Parveen A, Rehman M, Ahmar S, et al. Appraising growth, oxidative stress and copper phytoextraction potential of flax (*Linum usitatissimum* L.) grown in soil differentially spiked with copper. *J Environ Manag*. 2020;257:109994.
- [36] Hoque A, Fiedler JD, Rahman M. Genetic diversity analysis of a flax (*Linum usitatissimum* L.) global collection. *BMC Genom*. 2020;21(1):1–13.
- [37] Goudenhooff C, Bourmaud A, Baley C. Flax (*Linum usitatissimum* L.) fibers for composite reinforcement: exploring the link between plant growth, cell walls development, and fiber properties. *Front Plant Sci*. 2019;10:411.
- [38] Zhou X, Huang N, Chen W, Xiaoling T, Mahdavi B, Raoofi A, et al. HPLC phenolic profile and induction of apoptosis by *Linum usitatissimum* extract in LNCaP cells by caspase3 and Bax pathways. *Amb Express*. 2020;10(1):1–11.
- [39] Chhillar H, Chopra P, Ashfaq MA. Lignans from linseed (*Linum usitatissimum* L.) and its allied species: retrospect, introspect and prospect. *Crit Rev Food Sci Nutr*. 2021;61(16):2719–41.
- [40] Suri K, Singh B, Kaur A, Yadav MP, Singh N. Influence of microwave roasting on chemical composition, oxidative stability and fatty acid composition of flaxseed (*Linum usitatissimum* L.) oil. *Food Chem*. 2020;326:126974.
- [41] Saleem MH, Fahad S, Khan SU, Din M, Ullah A, Sabagh AE, et al. Copper-induced oxidative stress, initiation of antioxidants and phytoremediation potential of flax (*Linum usitatissimum* L.) seedlings grown under the mixing of two different soils of China. *Environ Sci Pollut Res*. 2020;27(5):5211–21.
- [42] De Jong WH, Borm PJ. Drug delivery and nanoparticles: applications and hazards. *Int J Nanomedicine*. 2008;3(2):133–49.
- [43] Shaabani A, Rahmati A, Badri Z. Sulfonated cellulose and starch: New biodegradable and renewable solid acid catalysts for efficient synthesis of quinolines. *Catal Commun*. 2008;9:13–6.
- [44] Budarin VL, Clark JH, Luque R, Macquarrie DJ, White RJ. Palladium nanoparticles on polysaccharide-derived mesoporous materials and their catalytic performance in C–C coupling reactions. *Green Chem*. 2008;10:382–7.
- [45] Dehnoee A, Kalbasi RJ, Zangeneh MM, Delnavazi MR, Zangeneh A. One-step synthesis of silver nanostructures using *Heracleum persicum* fruit extract, their cytotoxic activity, anti-cancer and antioxidant activities. *Micro Nano Lett*. 2023;18(1):e12153.
- [46] Elkhenany H, Elkodous Abd, Ghoneim M, Ahmed NI, Ahmed TA, Mohamed SM, et al. *Int J Biol Macromol*. 2020;143:763–74.
- [47] Borm PJ, Robbins D, Haubold S. The potential risks of nanomaterials: a review carried out for ECETOC. Part Fibre Toxicol. 2006;3(1):11.
- [48] Stapleton PA, Nurkiewicz TR. Vascular distribution of nanomaterials. *Wiley Interdisciplinary reviews. Nanomed Nanobiotechnol*. 2014;6(4):338–48.

- [49] Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MDP, Acosta-Torres LS, et al. Nano based drug delivery systems: Recent developments and future prospects. *J Nanobiotechnol.* 2018;16:71.
- [50] Itani R, Al Faraj SA. siRNA conjugated nanoparticles-a next generation strategy to treat lung cancer. *Int J Mol Sci.* 2019;20(23):6088.
- [51] Trojer MA, Li Y, Wallin M, Holmberg K, Nyden M. Charged microcapsules for controlled release of hydrophobic actives Part II: surface modification by LbL adsorption and lipid bilayer formation on properly anchored dispersant layers. *J Colloid Interface Sci.* 2013;409:8–17.
- [52] Liu D, Chen L, Jiang S. Formulation and characterization of hydrophilic drug diclofenac sodium-loaded solid lipid nanoparticles based on phospholipid complexes technology. *J Liposome Res.* 2014;24(1):17–26.
- [53] Onwudiwe DC, Ravele MP, Elemike EE. Eco-friendly synthesis, structural properties and morphology of cobalt hydroxide and cobalt oxide nanoparticles using extract of *Litchi chinensis*. *Int J Pharmtech Res.* 2020;23:100470.
- [54] Ma L, Ahmeda A, Wang K, Jalalvand AR, Sadrjavadi K, Nowrozi M, et al. Introducing a novel chemotherapeutic drug formulated by iron nanoparticles for the clinical trial studies. *Appl Organomet Chem.* 2022;36(12):e5498.
- [55] Lademann J, Richter H, Teichmann A, Otberg N, Blume-Peytavi U, Luengo J, et al. Nanoparticles—an efficient carrier for drug delivery into the hair follicles. *Eur J Pharm Biopharm.* 2007;66(2):159–64.
- [56] Yu H, Cheng L, Yin J, Yan S, Liu K, Zhang F, et al. Structure and physicochemical properties of starches in lotus (*Nelumbo nucifera* Gaertn.) rhizome. *Food Sci Nutr.* 2013;1(4):273–83.
- [57] Nagajyothi PC, Muthuraman P, Sreekanth TVM, Kim DH, Shim J. Green synthesis: in-vitro anticancer activity of copper oxide nanoparticles against human cervical carcinoma cells. *Arab J Chem.* 2017;10:215–25.
- [58] Namvar F, Rahman HS, Mohamad R. Cytotoxic effect of magnetic iron oxide nanoparticles synthesized via seaweed aqueous extract. *Int J Nanomedicine.* 2014;19:2479–88.
- [59] Sankar R, Maheswari R, Karthik S. Anticancer activity of *Ficus religiosa* engineered copper oxide nanoparticles. *Mater Sci Eng C.* 2014;44:234–9.
- [60] Yang F, Jin C, Jiang Y. Liposome based delivery systems in pancreatic cancer treatment: from bench to bedside. *Cancer Treat Rev.* 2011;37(8):633–42.
- [61] Sangami S, Manu M. Synthesis of green iron nanoparticles using Laterite and their application as a Fenton-like catalyst for the degradation of herbicide Ametryn in water. *Environ Technol Innov.* 2017;8:150–63.
- [62] Katata-Seru L, Moremedi T, Aremu OS. Green synthesis of iron nanoparticles using *Moringa oleifera* extracts and their applications: Removal of nitrate from water and antibacterial activity against *Escherichia coli*. *J Mol Liq.* 2018;256:296–304.
- [63] Radini IA, Hasan N, Malik MA. Biosynthesis of iron nanoparticles using *Trigonella foenum-graecum* seed extract for photocatalytic methyl orange dye degradation and antibacterial applications. *J Photochem Photobiol B: Biol.* 2018;183:154–63.
- [64] Beheshtkhoo N, Kouhbanani MAJ, Savardashtaki A. Green synthesis of iron oxide nanoparticles by aqueous leaf extract of *Daphne mezereum* as a novel dye removing material. *Appl Phys A.* 2018;124:363–9.
- [65] Xinli DHZS. Applications of nanocarriers with tumor molecular targeted in chemotherapy. *Chemistry.* 2021;75(7):621–7.
- [66] Li YN. Recent progress in doxorubicin nano-drug delivery systems for reserving multidrug resistance. *Drug Deliv.* 2014;11(3):177–81.
- [67] Mohammed MI, Makky AM, Teaima MH, Abdellatif MM, Hamzawy MA, Khalil MA. Transdermal delivery of vancomycin hydrochloride using combination of nano-ethosomes and iontophoresis: in vitro and in vivo study. *Drug Deliv.* 2016;23(5):1558–64.
- [68] Gao J, Wang Z, Liu H, Wang L, Huang G. Liposome encapsulated of temozolomide for the treatment of glioma tumor: preparation, characterization and evaluation. *Drug Discov Therapeut.* 2015;9(3):205–12.
- [69] Byrne JD, Betancourt T, Brannon-Peppas L. Active targeting schemes for nanoparticle systems in cancer therapeutics. *Adv Drug Deliv Rev.* 2008;60(15):1615–26.
- [70] Allen TM. Ligand-targeted therapeutics in anticancer therapy. *Nat Rev Cancer.* 2002;2(10):750–63.
- [71] Rezaei PF, Fouladdel S, Cristofanon S, Ghaffari SM, Amin GR, Azizi E. Comparative cellular and molecular analysis of cytotoxicity and apoptosis induction by doxorubicin and Baneh in human breast cancer T47D cells. *Cytotechnology.* 2011;63:503–12.
- [72] Rezaei PF, Fouladdel S, Ghaffari SM, Amin G, Azizi E. Induction of G1 cell cycle arrest and cyclin D1 down-regulation in response to pericarp extract of Baneh in human breast cancer T47D cells. *DARU J Pharm Sci.* 2012 Dec;20(1):101.
- [73] Rezaei PF, Fouladdel S, Hassani S, Yousefbeyk F, Ghaffari SM, Amin G, et al. Induction of apoptosis and cell cycle arrest by pericarp polyphenol-rich extract of Baneh in human colon carcinoma HT29 cells. *Food Chem Toxicol.* 2012 Mar;50(3–4):1054–9.
- [74] Amiri M, Kazerouni F, Namaki S, Tamijani HD, Rahimpour H, Boroumand N, et al. Cytotoxic effects of the ethanol bane skin extract in human prostate cancer Pc3 cells. *Iran J Cancer Prev.* 2016 Apr;9(2):e4755.
- [75] Shafiei BH, Shasaltaneh MD, Ghaffari SM, Ahmadian S, Kamarehei M, Raizi GH. An in vitro study on the effect of *Pistacia atlantica* sub kurdica extract on microtubule proteins: A potential anti-cancer compound. *Int J Pharm Sci Res.* 2015 Dec;6(12):5029.
- [76] Hashemi L, Asadi-Samani M, Moradi MT, Alidadi S. Anticancer activity and phenolic compounds of *Pistacia atlantica* extract. *Int J Pharm Phytopharmacol Res.* 2017;7(2):26–31.
- [77] Awwad O, Abu-Dahab R, Abaza IF, Alabbassi R, Majdalawi L, Afifi FU. Effect of the Gallling Aphid of *Baizongia pistaciae* L. on composition and biological activities of essential oils of *pistacia atlantica* Desf. growing wild in Jordan. *J Essent Oil Bear Plants.* 2017 May;20(3):791–800.
- [78] Rahbar Saadat Y, Barzegari A, Zununi Vahed S, Saeedi N, Eskandani M, Omid Y, et al. Cyto/genotoxic effects of *Pistacia atlantica* resin, a traditional gum. *DNA Cell Biol.* 2016 Jun;35(6):261–6.