

Research Article

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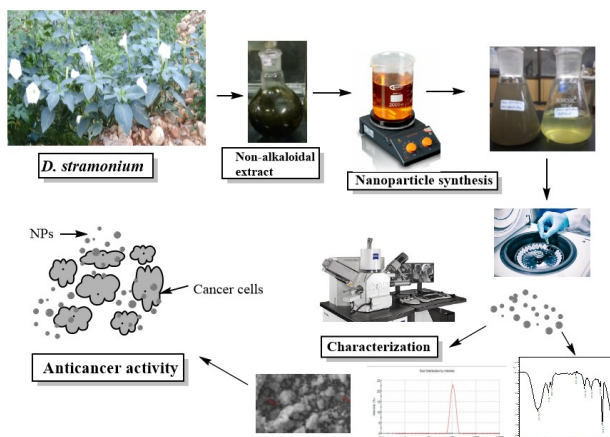
Synthesis, characterization and anticancer activities of silver nanoparticles from the leaves of *Datura stramonium* L.

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Abstract: In recent years, a wide range of studies has pointed out the role of nanoparticles as reservoirs of therapeutics for several diseases, including cancer. Nowadays, cancer research is focused on the development of novel treatment approaches to fight this dreadful disorder. Based on the evidential research and applications of nanoparticles, it is expected that green synthesized nanoparticles may show a prominent role, especially in the biomedical field. The present work is centered on the preparation and characterization of silver nanoparticles (Ag-NPs) from the aqueous (AQ) extract and non-alkaloidal (NA) fraction of *Datura stramonium* leaves and to evaluate their anticancer potential against mammalian cell lines. The biogenic Ag-NPs are characterized by UV-vis spectra, FTIR DLS, UV-Vis, SEM, and TEM. SEM and TEM analysis reveals the spherical morphology of NPs. The Ag-NPs exhibit cytotoxicity against various mammalian cell lines (A549, HCT-116, PANC-1, SH-SY5Y, and U87), which indicate that the AQ and NA based NPs are highly potent to cause cancer cell death. To the best of our knowledge, the present report, for the first time, describes the green synthesis of Ag-NPs from the NA fraction of the *D. stramonium* and provides pieces of evidence for its anticancer potential.

Keywords: *Datura stramonium*, plant extracts, biogenic nanoparticles, anticancer.



Graphical abstract

1 Introduction

Green nanotechnology is one of the leading technologies in metallic nanoparticles (NPs) synthesis using biological materials with an eco-friendly perspective. Varied NPs of size from 1 to 100 nm range make them suitable for their bio-applications and target-based delivery. These nanostructures have diverse applications as a courtesy of their enhanced attributes like their size, distribution, and morphology. These small-sized particles contribute to different

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fields, especially in biomedical sciences as catalysis, for targeted drug delivery, chemical industries such as cosmetics, food, space industries, non-linear optical devices, and electrochemical uses [1, 2]. More recently, nanotechnology has been used to detect the circulating tumor cells (CTC) as well as different biomarkers for cancer [3]. Most of these nanomaterials used in the biomedical field lead us to 'green nanotechnology', which utilizes plant products or metabolites to formulate nanoparticles.

Green nanotechnology entails the usage of green chemistry principles for nanoscale material synthesis, nanomaterial production method development, and the applications of a diverse range of nanomaterials. Using green bottom-up synthesis approach, nanoparticles can be prepared via physical, chemical, microwave-assisted synthesis, ultrasonic-assisted reduction, electrochemical reduction and recently, cryomilling methods [4–6]. Due to the feasibility and low toxicity of processes, the green and biogenic bottom-up method is primarily adopted to produce silver NPs. The chemically synthesized silver colloids form aggregates as the time period of storage increase and therefore, the combination of the green chemistry principles in the synthesis of metallic nanoparticles have been highly recommended as these biogenic NPs coated with biomolecules exhibit higher biocompatibility. Green nanotechnology has already established its root in cancer detection and therapy. It is well studied that metallic NPs synthesized via several methods using extracts of different plant parts showed anticancer activities on a variety of cell lines [7–9]. The green nanoparticles have a potential drug delivery system with the advantage of controlling their specific and time-release property, making them more suitable for medical Science [10]. Among these nanoparticles, gold and silver nanoparticles have been extensively used in the biomedical field because of their high stability, static nature, higher biocompatibility, negligible cytotoxicity [11–13]. The utilization of Ag-NPs in drug delivery, drug discovery, and novel drug treatment had shown prominent results on numerous disorders as these NPs use the body's natural mechanism of uptake of the doses by the cells.

Cancer is a major disorder globally known to cause high mortality. According to recent survey, it was reported that 19.3 million new cancer incidences and mortality of approximately 10.0 million took place in 2020 [14]. Over the years, the world has seen exponential growth of work concerning the approaches to counter cancer, including radiotherapy, chemotherapy using antimetabolites, antimitotic and alkylating agents [15]. Moreover, the problem needs the development of potent chemical and biotechnological drugs with high efficacy and low side effects. Deciphering the role of NPs in cancer treatment, a number of cancer cell

lines and animal models have been used for assessing their anticancer activity. The green synthesis of Ag-NPs by extracts of various plant parts viz. leaves, barks, stems, roots, tubers, fruits, etc. involves utilizing major plant metabolites like terpenoids, flavonoids, saponins sugars, alkaloids, and phenolic acids present in them. These phytochemicals can reduce the metal ions and produce NPs with potent biological abilities [16]. Apart from being economically favorable, the synthesis of Ag-NPs from bio-based materials is also simple and environment friendly with some convenient steps and factors like concentration of AgNO_3 , plant extracts etc. [17]. Reports of Ag-NPs from varied sources have been evaluated to be a potential cancer therapy by presenting anti-proliferative and anti-angiogenic activity [18].

One common plant presenting anticancer activity is *Datura stramonium* (*D. stramonium*). Extracts from *D. stramonium* are traditionally used as a sedative, anaesthetic, anti-asthmatic and anti-tumor due to the presence of various phytochemicals [19, 20]. It belongs to the Solanaceae family, consisting of 98 genera and approximately 3000-4000 species that are widely used due to their *ethnomedicinal* values [21]. Recently, *in vivo* anticancer and immunomodulatory activity of *D. stramonium* was evaluated by various groups of researchers, demonstrating their therapeutic potential in cancer and inflammation [22, 23]. Similarly, antibacterial and antioxidant responses of the leaf extract of *D. stramonium* were assessed to be effective and potent free radical scavenger [24, 25].

Furthermore, Ag-NPs synthesized from *D. stramonium* aqueous extract (leaves and seeds) were evaluated for antibacterial activities [26, 27]. Our work involves the green synthesis of Ag-NPs from the aqueous extract and NA fraction of *D. stramonium* leaves, their structural characterization and comparative *in-vitro* anticancer activity evaluation against various cell lines. This work involving the Ag-NPs synthesis from the NA fraction of *D. stramonium* leaves and their anticancer potential was represented for the first time.

2 Materials and Methods

2.1 Materials

All the analytical grade solvents and reagents including glacial acetic acid (99.7%), hydrochloric acid (37%), organic solvents, viz. Acetonitrile, chloroform, ethanol, ethyl acetate, hexane, and methanol were procured from Merck, Mumbai, India. Type III deionized water with resistivity = $15.0 \text{ M}\Omega\cdot\text{cm}$ was used (ELGA Option R 15, Synergy Medical System). Penicillin-streptomycin antibiotic solu-

tion, Trypsin-EDTA, Silver nitrate (AgNO_3), and dimethyl sulphoxide (DMSO) were purchased from HiMedia Pvt. Labs, Mumbai, India. 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT), Dulbecco's Modified Eagle's Medium (DMEM), and fetal bovine serum (FBS) were procured from Thermo Fisher, USA.

2.2 Plant materials and extraction

The *D. stramonium* leaves were collected from Solan region of Himachal Pradesh, India and was authenticated by the Department of Forest Products, Dr. Y. S. Parmar University of Horticulture and Forestry in Himachal Pradesh, India, with a Voucher No. 072 and Herbarium Field book no. 2916). The dried leaves (~2 kg) powder was extracted with ethanol repeatedly three times (solid to solvent ratio 1:5) using the cold percolation method. The ethanolic extract 4.5% (90 g) was taken out by evaporating the solvent under vacuum on a rota vapor. Following acid/base extraction, the separation of alkaloidal and non-alkaloidal (NA) fractions was carried out [28]. To prepare the silver nanoparticles, the NA fraction were used.

2.3 Synthesis of nanoparticles

The reaction parameters such as extract and metal concentration were optimised to get the highest yield of the nanoparticles. Here, the prepared AQ extract (100 mg/10 mL) and NA fraction (100 mg/ 10 mL) were dissolved in de-ionized water (90 mL) and stirred at 60°C along with 1 mM silver nitrate (AgNO_3) for 30 min for a colloidal solution. After 30 mins, the reduction of Ag^+ ions to Ag^0 can be observed visually by the change to dark brown color) and the solution was kept in the dark for 24 h. Nanoparticles were settled at the bottom of the solution, separated from solution by centrifugation (10000 rpm), dried and washed with milli-Q water (5 times), and taken for characterization. The synthesized NPs were oven-dried (60°C) overnight and then kept at room temperature for their structural characterization and bioactivity.

2.4 Characterization

Firstly, UV-vis was done using a spectrophotometer (UV-2600, Shimadzu, Japan). To analyze the functional groups, FTIR spectrum was carried out by using IRSpirit instrument (Shimadzu, Japan). The particles size and stability was checked by Nano ZS, (Malvern, Worcestershire, UK).

The form and morphology of silver NPs were determined by scanning electron microscopy (SEM, Jeol) and transmission electron microscopy (TEM, Jeol).

2.5 Cell Culture Maintenance

A549 (lung carcinoma), HCT-116 (Human colon carcinoma), PANC-1 (Pancreatic cancer), SHSY-5Y (neuroblastoma), and U87 (microglia) cell lines were acquired from National Centre for Cell Sciences, Pune, India. Cell cultures were maintained in the DMEM growth media with 10% (v/v) FBS and 1% penicillin/streptomycin solution (Incubation at 5% CO_2 and 37°C). The 25 cm^2 flasks or 96 well plates (1×10^4 cells per well) were used to seed the cells for experiments.

2.6 Cell cytotoxicity

To study anticancer properties of NPs, A549, HCT-116, PANC-1, SHSY-5Y and U87 were seeded into 96-well plates (1×10^4 per well) in 200 μL of DMEM media and adhered for 24 h. Then, cells treatment was carried out with different concentrations (25–200 $\mu\text{g}/\text{mL}$) of NPs for 24 h. After 24 h, 20 $\mu\text{L}/\text{well}$ of media having MTT (5 mg /mL) was added for 4 h at incubated at 37°C [29]. At last, the 100 μL of media was discarded and 100 μL of Dimethyl sulfoxide (DMSO) was added to solubilize the purple-colored formazon. The plate was recorded at 570 nm using Spectrophotometer (iD3, Molecular Devices, CA, USA). Using GraphPad Prism 5 software, the IC_{50} values were calculated.

$$\% \text{ Cell death} = (\text{Abs}_{\text{control}} - \text{Abs}_{\text{sample}}) / \text{Abs}_{\text{control}} \times 100$$

2.7 Statistical Analysis

Statistical investigation was done by one-way analysis of variance (ANOVA) and Student's t-test using GraphPad Prism 5.0 software. All p values < 0.05 were taken as statistically significant. All the results were done in three independent experiments and represented as mean \pm SEM.

3 Results and Discussion

The *D. stramonium* leaves AQ extract and NA fraction were subjected the green synthesis of Ag-NPs leading to the reduction of the silver by it's phytoconstituents and agglomeration of NPs. Here, the phytoconstituents in the AQ extract and NA fraction of *D. stramonium* leaves worked as stabilising and capping factors. The silver nanoparticles synthesis

of NA fraction of *D. stramonium* was reported for the first time. Previous literature had shown the synthesis of Ag-NPs from aqueous extract of *D. stramonium* leaves [27]. Also, gold nanoparticles from aqueous seeds extract of this plant were previously prepared, characterized and analyzed for their antibacterial activities [30].

3.1 UV-vis spectroscopy studies

The color change to colloidal dark brown of AgNO_3 and leaf extract mixture is a clear indication of Ag-NPs synthesis (Figure 1). The dark brown color of the suspension after 30 min of incubation under stirring conditions was observed. The reduction of Ag^+ ions to Ag^0 can be strongly suggested by these color changes. UV-vis spectroscopy showed absorption peak (λ_{max}) at 366 nm for AQ NPs and at 374 nm for NA NPs (Figure 2). The effective reducing constituents within the plant highly reduced the AgNO_3 as Ag crystal leading to the formation of spherical Ag-NPs.

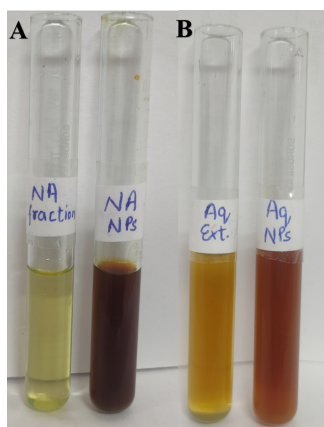


Figure 1: Visual observation of Ag-NPs synthesis from leaves of *D. stramonium* using (a) NA fraction and NA NPs (b) AQ extract and AQ NPs.

3.2 FTIR

FTIR spectrum was analyzed in liquid technique in the varied range ($4000\text{--}400\text{ cm}^{-1}$). The Ag-NPs of *D. stramonium* leaves extract were elucidated by FTIR (Figure 3). The formation of metal NPs and their reduction of metal ions may be due to diverse phytoconstituents present in the leaves extract. FTIR spectrum of Ag-NPs showed up a band spectrum at 3870 cm^{-1} showing O-H stretching, due to N-H stretching at 3340 cm^{-1} , N=C=S stretching at 2051 cm^{-1} , C=O stretching at 1635 cm^{-1} , organo-phosphorous at 1008 cm^{-1} can

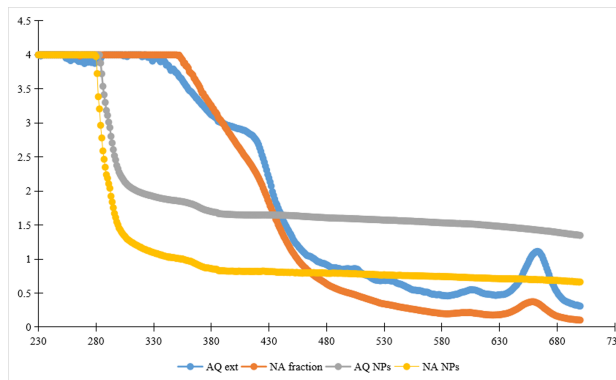


Figure 2: UV-Vis spectra showing absorbance of Ag-NPs synthesized (a) NA fraction and NA NPs (b) AQ extract and AQ NPs.

be due to silver vibrations, showing the formation of Ag-NPs [31].

3.3 Size distribution

The size distribution and surface charge of synthesized nanoparticles were determined by Dynamic light scattering (DLS). From the DLS histogram, (Figure 4), the nanoparticles were in range of 100 nm both for NA and AQ NPs.

3.4 SEM and TEM

SEM and TEM analysis showed the structural morphology of silver nanoparticles prepared from AQ and NA extract of *D. stramonium*. It was found that the SEM images showed aggregates of respective AQ NPs. SEM images (Figure 5) and TEM images (Figure 6) showed the spherical structure of silver nanoparticles. In SEM imaging, clumping and formation of nano-sized structures were visible in the Ag-NPs. For TEM analysis, spherical nanoparticles with a size of less than 30 nm was seen for NPs of NA fraction, while variable size ($< 70\text{ nm}$) were found for the AQ NPs.

3.5 *In vitro* cytotoxicity

The effects of AQ and NA NPs were investigated on A549, HCT-116, Panc1, SHSY-5Y, and U87 cell lines cells by MTT assay. The viability of the cells can be shown as the reduction of MTT exclusively occurs in metabolically active cells. Here, both the extracts and their respective NPs were assessed at $25\text{--}200\text{ }\mu\text{g/mL}$. With increasing concentration ($25\text{--}200\text{ }\mu\text{g}$), the death rate of cancer cells increased as shown in microscopic investigation (Figure 7). The data showed that NPs possess potent anticancer abilities. The IC_{50} values

of extracts and their nanoparticles in various cancer cells were shown in Table 1. It was found that the NA NPs were highly potent against all the cell lines as compared to AQ NPs.

Moreover, both the NPs were better in causing cancer cell death as compared to the extracts (Figure 8). It was observed that the NA NPs were highly potent against A549 cells with an IC_{50} 51.67 ± 1.04 $\mu\text{g/ml}$). Similarly, the NA NPs were effective against SH SY5Y (IC_{50} 56.71 ± 1.05 $\mu\text{g/ml}$) and U87 cells (IC_{50} 60.92 ± 1.05 $\mu\text{g/ml}$). The data indicated that

the NA NPs had increased effects on cancer cells in comparison to NA fraction which could be related to efficacious endocytosis of the NA NPs against cancer cells. Earlier studies also demonstrated that the plant-based NPs displayed better cancer cell death in comparison to their respective extracts. Previous reports on silver nanoparticles of *D. stramonium* (seeds and leaves) revealed anti-microbial activity and showed DNA cleaving as their main mechanism against microbes [26, 27]. Our research group recently showed that the isolated compounds (daturalactone, 12 deoxywithas-

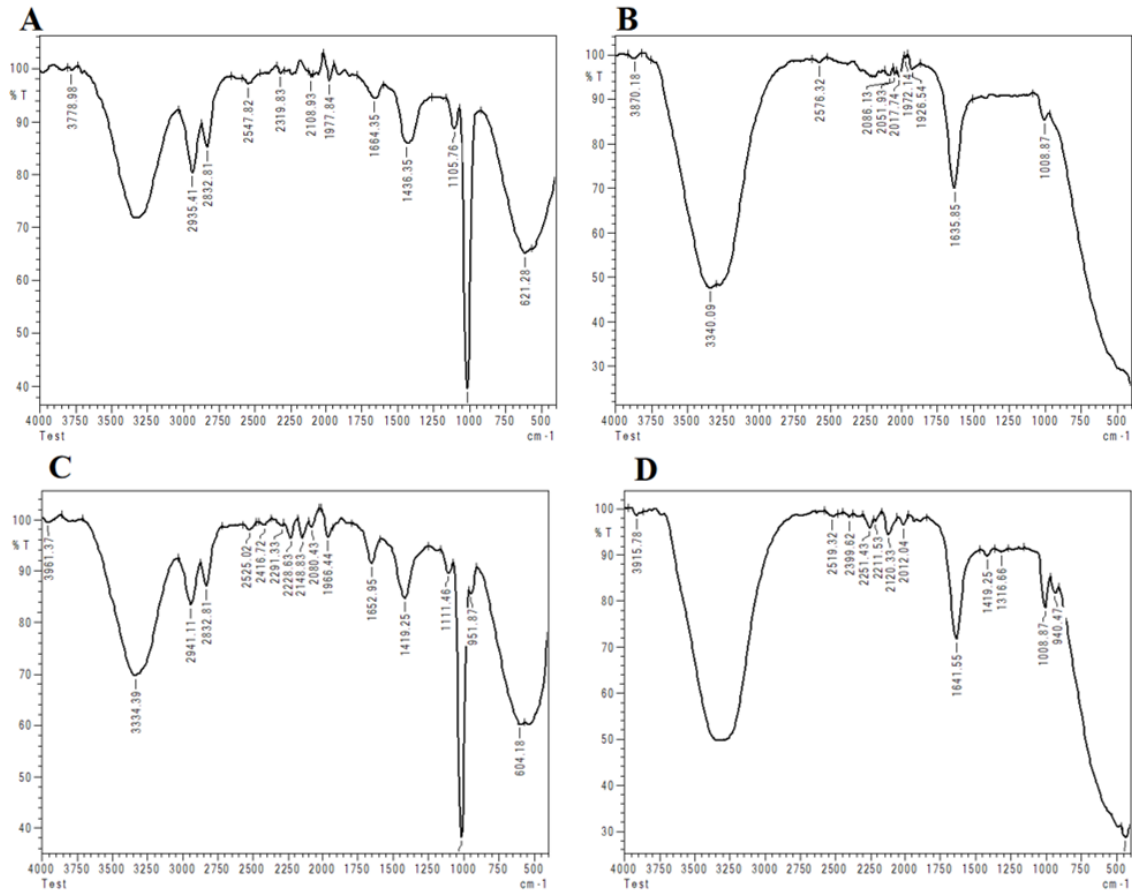


Figure 3: FTIR spectrum of extract and Ag-NPs of *D. stramonium* (a) NA fraction and NA NPs (b) AQ extract and AQ NPs.

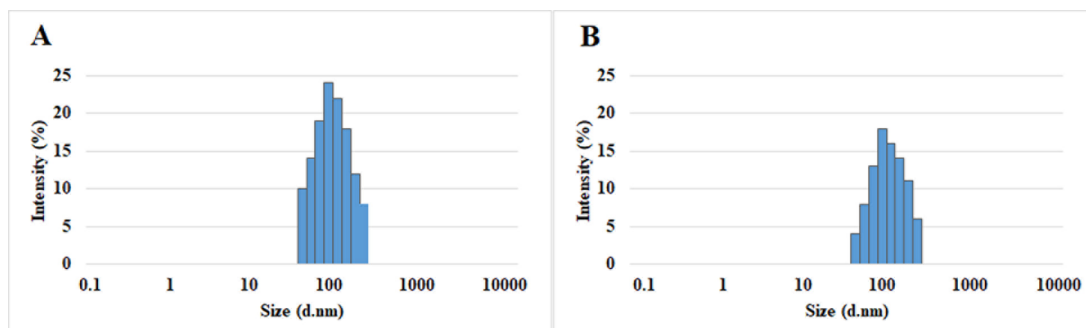


Figure 4: DLS pattern of Ag-NPs, (a) NA NPs (b) AQ NPs.

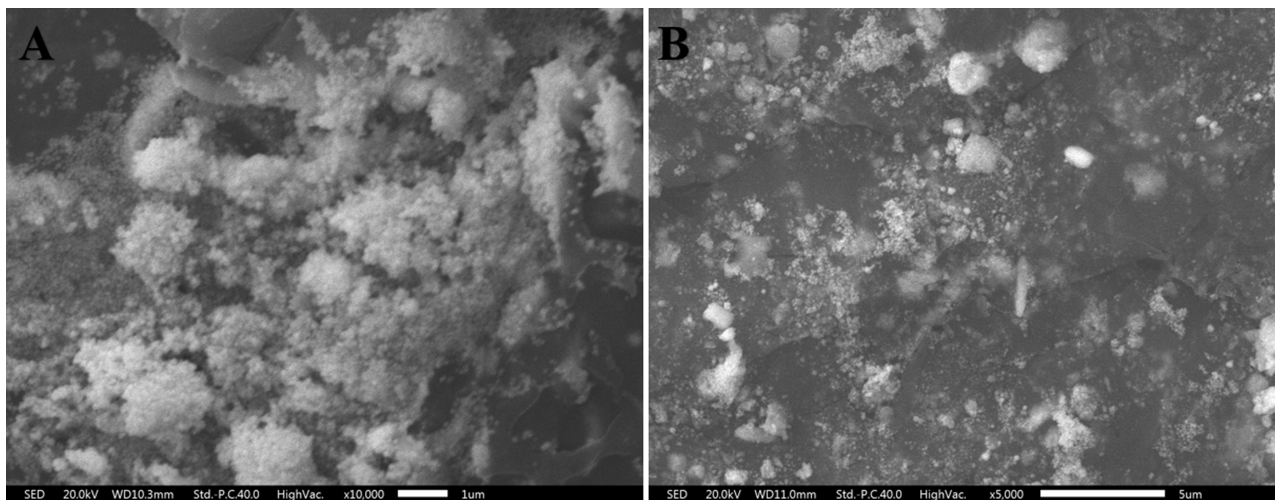


Figure 5: (a) Representative SEM images of synthesized nanoparticles. (a) NA NPs (b) AQ NPs.

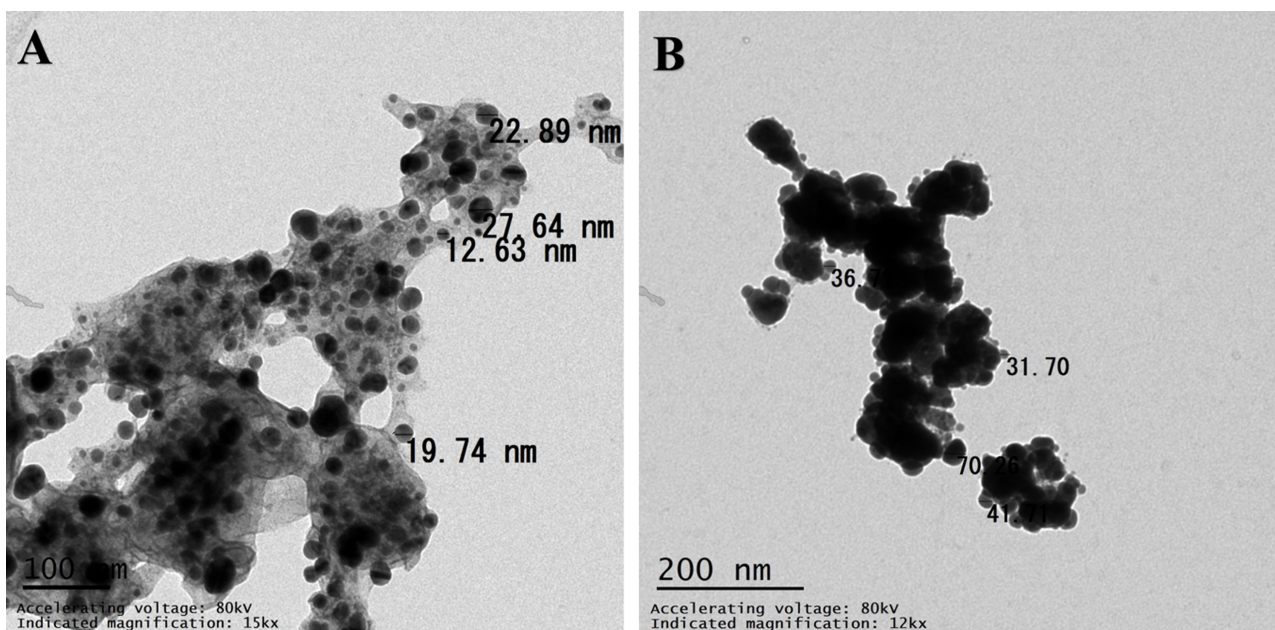


Figure 6: (a) Representative TEM images of synthesized nanoparticles. (a) NA NPs (b) AQ NPs.

Table 1: IC₅₀ values of and nanoparticles AQ extract, NA extract, AQ NPs, and NA NPs against cell lines.

Sample	A549	HCT 116	PANC-1	SH-SY5Y	U87
AQ ext	115.8 ± 1.08	212.3 ± 1.06	178.8 ± 1.05	130.8 ± 1.05	163.3 ± 1.05
NA fraction	98.04 ± 1.06	206.1 ± 1.11	147.7 ± 1.07	113.7 ± 1.05	125.5 ± 1.03
AQ NPs	68.47 ± 1.04	137.7 ± 1.04	120.1 ± 1.04	85.55 ± 1.04	88.93 ± 1.05
NA NPs	51.67 ± 1.04	106.7 ± 1.04	94.33 ± 1.04	56.71 ± 1.05	60.92 ± 1.04

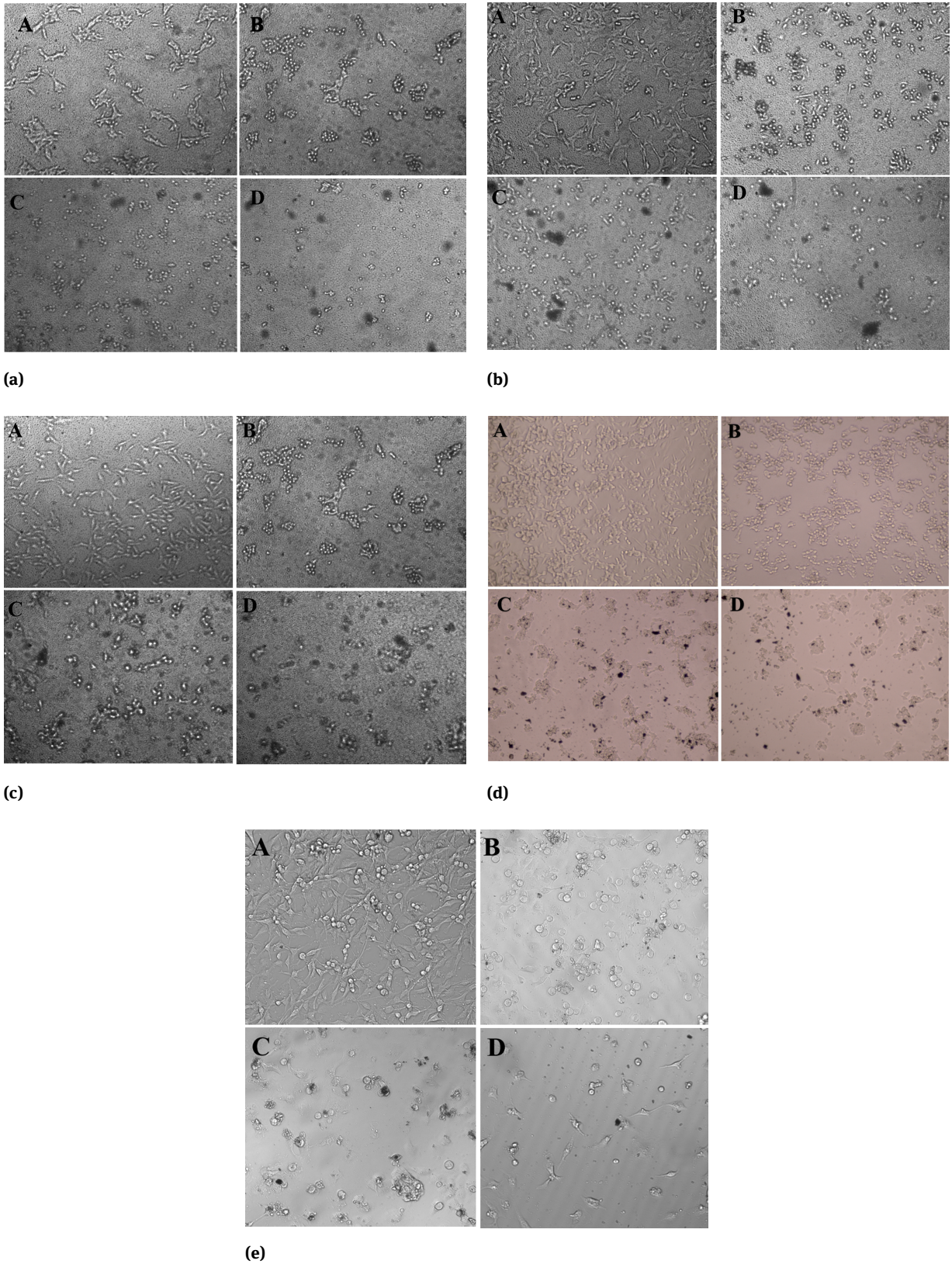


Figure 7: a-e: Microscopic observation of cytotoxic effect of extract and nanoparticles against A549 (a), HCT-116 (b), PANC-1 (c), SH SY5Y (d), and U87 (e) cell line. The figures represents control cells (A), Paclitaxel (B), AQ NPs (C), and NA NPs (D).

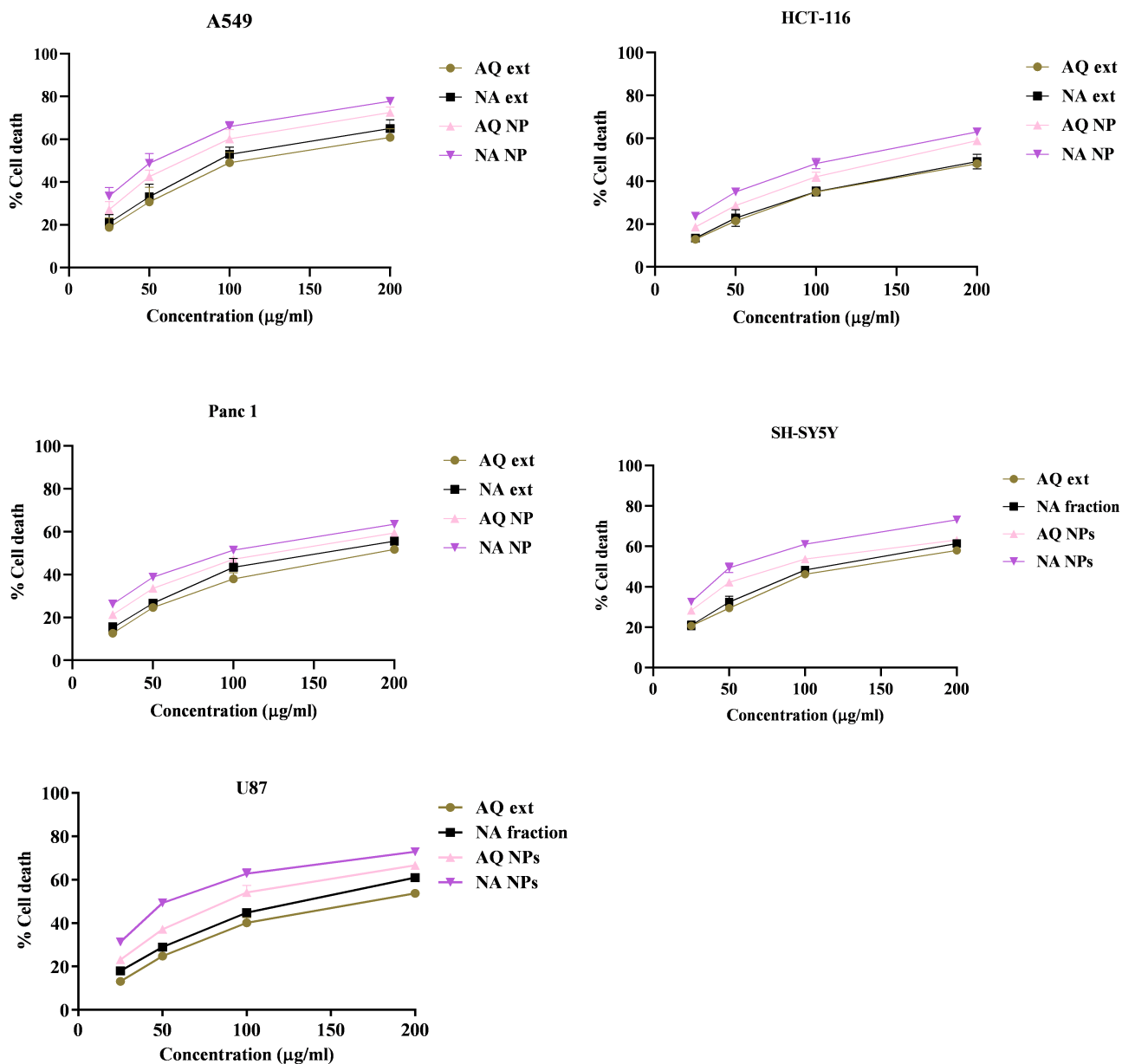


Figure 8: *In-vitro* analysis of the cytotoxicity of AQ extract, NA extract, AQ NPs, and NA NPs against A549, HCT-116, PANC-1, SH-SY5Y, and U87 cell line. Data were shown as mean \pm SEM of three different experiments.

tramonolide, and daturilin) from non-alkloidal fractions of *D. stramonium* leaves showed anti-inflammatory activities using *in vitro*, *in vivo*, and *in silico* models [32]. Additionally, essential oil from leaves of *D. stramonium* showed enhanced immunostimulation of immune cells against gastrointestinal cancers [33]. These studies showed that *D. stramonium* plant parts have diverse phytoconstituents against varied disorders including cancer. A study using ethyl acetate extract of *D. stramonium* on different cancer cell lines (MDA-MB 231, MCF-7 and PC-3) demonstrated potential effects of the extract in causing cancer cell death [22].

Some crucial plants from *Solanaceae* (nightshade family) include *Atropa*, *Capsicum*, *Brugmansia*, *Datura*, *Hyoscyamus*, *Nicotiana*, *Mandragora*, *Physalis*, *Solanum*, *Salpichora*, and *Withania* were traditionally used in herbal practice and for initial research on plant-based therapeutics [34]. The genus *Datura* stands tall for its potent phytochemicals and their medicinal applications for ages. The *D. stramonium* parts, extracts, and preparations have been used as local medicines by humans for millennia by Chinese, African and Ayurvedic medicinal systems. This plant was used as a home remedy for many conditions, includ-

ing pain, bruises, wound infections, swellings and boils, rheumatism, and toothaches, and *Datura* cigarettes were smoked to alleviate asthma and breathing problems [20]. Extracts and compounds (both alkaloids and other components) derived from *Datura* have also been investigated for, among others, anticancer, antibacterial, antiviral, and antifungal activities [35, 36]. Previous studies showed that aqueous extracts of different species of genus *Datura* were used as reducing agents for Ag-NPs synthesis. Ag-NPs from *D. innoxia* extract revealed anti-proliferative effect against breast cancer cells [37]. The Ag-NPs from *D. metel* aqueous extract showed anti-malarial activities [38].

During this century, cancer has been major cause of death and is considered major health cause affecting the quality of life [39]. In addition to a number of therapies, chemotherapy is still most widely used for treating cancer. The mechanism of action of chemotherapy agents is either by effecting the DNA or affecting the factors involved in mitosis by inhibition of its synthesis or uses [40]. However, when compared to other therapies, chemotherapy still remains at high risk with numerous side effects [41, 42]. Although novel advancements in therapeutics against cancer development have been studied in last few decades, yet there is scope for improvements in target-based approaches. Natural products being reservoirs of remedial agents, played a vital role for treatment of innumerable disorders across the globe [43]. Plant-based therapies have gained interest as the potent phytoconstituents not only work effectively against cancer cells without harming the viability of the normal cell [44]. Various plant extracts and isolates are used with more effective cancer-killing with minimal side effects.

New nanotechnology-based drug delivery systems cater an extraordinary approach in respect to target-based therapy. It is well established nowadays that green nanoparticles play a vital role due to their stability and potency to penetrate the target sites of the cancer cells. Green nanoparticle synthesis has made a clear path towards a convenient, eco-friendly, and economically stable utilization of nanoparticle [45]. It has been well discussed and studied that the green nanoparticles specifically deciphering about Ag-NPs emerged as a potential anticancer agent [46]. Moreover, green synthesised NPs have minimum amount of toxicity unlike the chemically synthesised counterparts [47]. The plant extract based Ag-NPs can easily be used in nanomedicines in coming future with an additional advantage of time-mediated release of drugs.

Moreover, due to the presence of huge expense of raw material available in form of plant extract to produce these nanomedicines there will be less fuss about the production charges in high scale production. Green synthesized NPs

provide a way to use the potential phytochemicals present in plants in form of phenols, flavonoids, terpenoids etc [48–50]. These secondary metabolites directly play their multi-action in the therapeutics formed out of green nanoparticles. Assessing the anticancer activity of synthesised Ag-NPs on different cancer cell lines delivers us the practical idea that these Ag-NPs are potential nanomedicines for colon cancer, breast cancer, lung cancer, etc. Silver is the foremost therapeutic metal in medical Science for multiple disorders with high benefits and low risk factors [51]. Plants like *D. stramonium* have the tremendous potentiality to give novel medicines due to rich chemical diversity, especially against cancer. Green synthesized Ag-NPs have unmatched significance covering a wide spectrum of crucial pharmacological activities an alternative to local drugs. Moreover, various studies in the past few decades have proved that the green methods are efficacious to synthesize NPs with minimum experimental failures and ensure easy characterization [52].

4 Conclusion

The current work involved the synthesis of silver nanoparticles from the aqueous and non-alkaloidal fractions of *D. stramonium* leaves. The extract and the nanoparticles displayed anticancer activity against the wide array of cell lines, which might be due to the diversity of potent compounds in the plant. In addition, NA NPs showed the highest anticancer potential compared to AQ NPs, indicating the effects of all the constituents present in this nanoformulation. These results ensure the anticancer abilities of the Ag-NPs; however, the elaborate molecular pathway to determine the effects of these NPs on cancer cells needs to be studied. Also, significant *in vitro* anticancer activity using NPs provide a suitable ground for these nanoparticles as appropriate candidates for subsequent *in vivo* evaluation.

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Conflict of interests: The authors declare that there are no conflicts of interest.

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

Data availability statement: All data generated or analyzed during this study are included in this published article.

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