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Green Synthesis of platinum nanoparticle-based drugs for cancer therapy and drug delivery

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Abstract

Platinum-based chemotherapy agents, including cisplatin, carboplatin, and oxaliplatin, are extensively employed for the eradication of cancer. Nevertheless, the therapeutic use of platinum medicines is significantly restricted due to their adverse effects, including poor selectivity, elevated systemic toxicity, and the emergence of drug resistance. In recent years, significant breakthroughs in the fields of nanotechnology and chemical synthesis have led to notable success in the development of platinum-based anti-cancer medicines for cancer therapy. The utilization of botanical extracts in the production of diverse metal nanoparticles has garnered significant attention in recent times due to its straightforward, low-risk, sustainable, and economical approach. This study presents a straightforward and environmentally sustainable approach for the production of platinum nanoparticles (Pt-NPs) through the utilization of Nigella sativa (black cumin) seed extract as a reducing agent. The anticancer activities of the green Pt-NPs have been assessed through in vitro investigations. Following this, molecular modeling studies have been carried out in order to clarify the mechanistic actions of these nanoparticles (NPs) as potential agents for treating cancer. The biogenic Pt-NPs, which were produced using black cumin seed extract, were subjected to a comprehensive characterization process involving Transmission Electron Microscopy (TEM) and X-ray diffraction (XRD). Based on the findings of TEM examination, it has been observed that Pt-NPs exhibited a spherical morphology and possessed a mean particle dimension of 3.51 ± 1.42 nm. In addition, it was observed that the Pt-NPs displayed notable cytotoxic effects on lung cancer (A549) and breast adenocarcinoma (MCF-7) cells, with IC50 values of 9.1±0.24 and 4.7±0.37 µg/mL, respectively.

Key Words: green synthesis, nigella sativa, anti-cancer, platinum nanoparticles, transmission electron microscopy, molecular docking

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INTRODUCTION

The popularity of metal NPs has witnessed a steady increase since the conclusion of the 20th century. This phenomenon is not unexpected, as they are extensively employed throughout many domains of human endeavor due to their numerous advantageous characteristics. Green technologies, also known as eco-friendly technologies, have significant significance due to their simplicity, cost-effectiveness, little waste generation, and capacity to regulate the properties of producing NPs (such as shape, dimension, and resilience) [1]. Consequently, they have gained considerable attention as a subject of research in recent times. This assertion is supported by the notable growth in the quantity of scholarly papers pertaining to this subject during the past two decades. The user's text does not contain any information. Various types of NPs, nanocomposites, and nanostructures that exhibit biological compatibility have garnered significant attention across a range of human activity domains. These include applications in the food industry, such as food packaging and the growth of functional food products aimed at enhancing food safety, detecting food pathogens, and prolonging the shelf life of food items [2]. Additionally, these nanomaterials have found utility as catalysts for biofuels, exemplified by the utilization of Cs2O−MgO/MPC nanocomposite as a primary nanocatalyst for biodiesel fabrication from olive oil. Furthermore, they have been employed in the realms of cosmetics and skincare, and in the fields of examination, healthcare, theranostics, and tissue engineering. Notably, these applications encompass not only metal NPs but also nanostructured calcium phosphates (CaPs) exhibiting surface-rich hydroxyl (OH) groups and calcium ions (Ca2+), which exhibit effective adsorption of therapeutic agents [3]. Biosynthesis solutions encompass the utilization of living creatures, such as bacteria, fungus, or plants, as biologically-

driven manufacturing systems for the creation of metal NPs [4]. The medicinal compounds developed exhibit significant potential for use in the biomedical sector, particularly in the areas of pathogen fight for different diseases, early detection and treatment of cancer, medication delivery, and detection systems, among others.

While silver and gold NPs are widely recognized, there is now a growing interest in the production and characterization of nanoparticles composed of other metals [5]. One of the aforementioned metallic elements is platinum. The Incas were early adopters of mining and utilization techniques for platinum, although in the Old World, platinum remained unfamiliar until the 16th century. The conquistadors from South America were the first to see it, and it was subsequently named platina, derived from the Spanish term "little silver," due to its resemblance to actual silver [6]. Platinum, because to its high refractory properties, was historically not regarded as a valuable resource for an extended period. It was consistently assigned a lesser value compared to silver and gold. From 1889 to 1960, the worldwide standard for defining one meter consisted of a platinum alloy, which accounted for 90% of the composition. in now, South Africa and Russia are the primary nations in the forefront of platinum extraction. Platinum is classified as an inert metal and does not appear to possess significant biological relevance in the critical processes of living beings. Furthermore, it should be noted that this particular metal exhibits non-toxic properties while in its metallic state.

Platinum is utilized in the process of electroplating. It serves as a catalyst in many sectors, encompassing the use of coating microwave technology components and the production of jewelry. Platinum compounds, specifically cytostatics like cisplatin, are utilized in dentistry for medicinal purposes [7]. Additionally, these compounds are employed in the treatment of oncological diseases. Nevertheless, it is worth noting that medicines like as cisplatin and carboplatin have nephrotoxic, neurotoxic, and cytotoxic properties. The aforementioned impacts can be mitigated by the utilization of green production techniques for Pt-NPs, hence presenting a promising avenue for addressing several medical challenges. Bio-factories, which encompass bacteria, fungi, and plants, contain a diverse array of biological chemicals, including proteins, enzymes, acids, and other substances. These compounds play a crucial role in the synthesis of Pt-NPs, which are generated within various organisms and exhibit distinct distinctive properties. The significance of bio-compounds lies not only in their involvement in the synthesis of NPs, but also in the subsequent assembly processes. With their distinctive characteristics, these NPs possess the capability to enhance the beneficial impact of Pt-NPs utilization. Furthermore, the significance of "green" technology, the lack of harmful side effects, and the specific impact on the human body remain pertinent. The current existing data on the antibacterial activities, anticancer effects, and other potentially advantageous characteristics of Pt-NPs provide them a compelling subject for thorough investigation [8]. This work focuses on the biological creation of Pt-NPs, elucidating the underlying mechanism of this process and examining its impact on cellular structures inside live organisms. Additionally, prospective biomedical applications of these nanoparticles are explored.

RELATED WORKS

Medical science has focused on developing cancer treatments. Nanotechnology, particularly nanoparticles, has emerged as a promising cancer treatment method in recent years. Due to their unique properties, Pt-NPs have garnered scientific attention. This literature review examines new research on environmentally friendly Pt-NP-based pharmaceutical production for cancer treatment and transportation. The compelling synthesis techniques, therapeutic efficacy, and many uses of nanodrugs demonstrate the importance and promise of this new field. This study provides an academic overview of green-synthesized Pt-NP research for cancer and DD. It aims to illuminate this field's advances and researchers' challenges.

In their study, Xie et al. introduced novel DD methods utilizing nanoparticles and platinum pharmaceuticals to address the challenge of drug resistance in cancer treatment [9]. The authors' methodology unveiled a heightened IC50 value, which represents the concentration of resistance,

for NPs loaded with platinum pharmaceuticals in comparison to free platinum medications. This finding underscores the efficacy of these NPs in combating drug resistance. One of the advantages of this approach is its ability to overcome resistance mechanisms. However, it is important to note that there may be possible downsides connected with platinum drug toxicity.

The authors Abed et al. conducted a study on the synthesis and biomedical application of Pt-NPs, focusing on their production and anti-cancer properties [10]. The study presented encouraging findings regarding the anti-cancer properties, showcasing a drop in IC50 and so indicating improved effectiveness of the medicine. One of the primary benefits associated with this phenomenon is its potential to combat cancer. However, it is important to acknowledge that there are certain drawbacks to consider, such as concerns over the toxicity of nanoparticles and their bioavailability.

Mukherjee et al. underscored the significance of employing a green synthesis approach for the production of monodispersed gold NPs. The researchers' investigation demonstrated a decrease in the toxicity of the NPs and successful administration of Doxorubicin (DOX) [11]. The findings of the study revealed a decrease in IC50, highlighting the significant therapeutic prospects associated with the observed outcomes. One of the notable benefits is the environmentally sustainable synthesis and decreased toxicity, whereas potential drawbacks may encompass challenges pertaining to the manufacturing on a big scale and the stability of the synthesized product.

The authors Zheng et al. established a multistage DD method for anticancer treatment utilizing gold nanoparticles [12]. The authors' approach presented a complete framework for augmenting the delivery of drugs and optimizing their therapeutic efficacy. One of the advantages of this approach is the possibility of achieving targeted medication administration. However, it is important to consider potential downsides that may arise from the intricate synthesis techniques involved.

Al-Radadi utilized a green synthesis technique to fabricate Pt-NPs by employing an extract derived from Saudi Dates. The resulting nanoparticles were subsequently investigated for their potential uses in the therapy of cancer cells. The study emphasized the therapeutic capacity of the subject matter [13]. The primary benefit is derived from the environmentally sustainable synthesis approach, whilst some drawbacks may pertain to issues regarding stability.

The study conducted by Manzoor et al. (14) examined the application of bio-fabricated Pt-NPs as possible nanodrugs for combating breast cancer cells and drug-resistant bacteria. The findings of their study exhibited the ability to induce cytotoxicity in cancer cells and drug-resistant bacteria, hence emphasizing their multifunctional nature. One notable benefit of these NPs is in their remarkable adaptability, allowing for a wide range of applications. However, it is important to acknowledge that there may be certain drawbacks associated with their use, such as potential regulatory hurdles and safety considerations.

Fahmy et al. conducted a study on the green production of platinum and palladium nanoparticles utilizing the alkaloids found in the seeds of Peganum harmala L. [15]. The work provided valuable insights into the physiological and computational characteristics of these NPs, therefore suggesting new uses. One of the notable benefits of this approach lies in its ecologically conscious synthesis process. However, it is important to acknowledge that there are possible drawbacks associated with this method, such as its restricted scalability and usefulness in certain applications.

Green production methods combined with Pt-NPs' therapeutic properties offer a promising path for cancer treatment and drug delivery. Many studies show the progress made in developing environmentally friendly Pt-NP-based medications. These studies show these treatments can fight cancer resistance and perform multiple functions. To fully utilize nanodrugs, toxicity, scalability, and regulatory issues must be addressed. As scientists continue to study Pt-NPs made by green methods, they anticipate the potential revolution they may bring to cancer treatment and DD.

GREEN SYNTHESIS OF PLATINUM NANOPARTICLE-BASED DRUGS

FOR CANCER THERAPY AND DRUG DELIVERY

The utilization of green synthesis techniques in the production of Pt-NP-based pharmaceuticals represents a cutting-edge strategy in the fight against cancer and the advancement of drug administration methodologies. These minuscule yet highly effective particles are produced using environmentally sustainable techniques, frequently employing plant extracts, microorganisms, or other biocompatible resources. The precise targeting and controlled release of drugs are facilitated by their distinctive physicochemical characteristics, including but not limited to their size, shape, and surface charge

Green Synthesis of platinum nanoparticle

The experiment utilized seed samples of Nigella sativa L. sourced from Turkey. The cell lines utilized in this study, namely HeLa and MDA-MB-23, were procured from the Department of Molecular Biology and Genetics at Bogazici University. The chemicals utilized in the experiments were sourced from Sigma-Aldrich (USA), while the cell culture products were obtained from Gibco. Plastic laboratory products were procured from Corning (USA), CAPP (Denmark), and TPP (Switzerland). Furthermore, all materials requiring sterilization underwent autoclaving at a temperature of 121°C for a duration of 20 minutes.

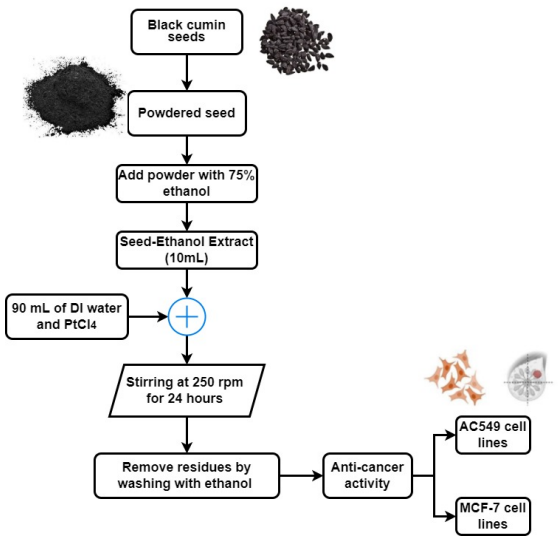


Fig.1. Green synthesis procedure of Pt-NP using black cumin seeds.

The green synthesis procedure of Pt-NP has been shown in Fig. 1. The process of extract preparation involved the crushing of black cumin seeds. Seeds with a weight ranging from 7 to 10 grams were introduced into a solution consisting of 110 milliliters of ethanol with a concentration of 75%. The seed-ethanol combination has been allowed to undergo a period of standing within the microwave, resulting in the acquisition of the extract.

The synthesis of Pt-NPs is a process that involves the creation of nanoscale particles composed of platinum. To initiate the nanoparticle synthesis, a 10 mL extract of Nigella sativa L. was combined with 90 mL of Deionized (DI) water. Subsequently, $PtCl_4$ was introduced into the resulting mixture. The resultant mixture was subjected to stirring at a rate of 250 revolutions per minute and a temperature of 80 degrees Celsius for a duration of 48 hours. The change in color from colorless to black in the solution signifies the reduction of $PtCl_4$ to nanoscale dimensions, resulting in the formation of Pt-NPs. In order to eliminate any unreacted residues present in the solution, a series of ethanol washes were performed using a centrifuge operating at a speed of 4500 revolutions per minute (rpm). This washing process was repeated a minimum of three times. The Pt nanoparticles obtained were left undisturbed at ambient temperature for a duration of 48 hours. Subsequently, their properties were analyzed using TEM, X-ray Diffraction (XRD), and X-ray Photoelectron Spectroscopy (XPS).

Pt-NP-based drugs for cancer therapy and drug delivery

A series of ten dilutions were performed using a Trolox stock solution (positive control) with concentrations of 4500, 3500, 2500, 1500, 850, 650, 450, 250, 150, and 50 µM. The Trolox stock solution had an initial concentration of 5 mM in methanol. Pt-NPs were synthesized in methanol solvent at a dosage level of 0.7 mg/mL.

In Vitro Cell Viability Assay Cell Culture

The breast cancer cells (MCF-7) and lung cancer cells (A-549) were procured from the American Type Culture Collection, located at University Boulevard, Manassas, VA, USA. These cells were cultured in DMEM

medium, which was augmented with streptomycin (150 mg/mL), penicillin (150 units/mL), and 15% heat-inactivated embryonic bovine serum, to ensure their maintenance. The cells were subjected to incubation in an environment containing 7% (v/v) carbon dioxide at a temperature of 36 ◦C.

Sulforhodamine B (SRB) Colorimetric Assay

Various concentrations of platinum (IV) ions, and Pt-NPs were introduced to MCF-7 and A-549. The effectiveness of these substances in inhibiting cancer growth was evaluated using the Sulforhodamine B (SRB) assay. Aliquots of MCF-7 and A-549 cell suspensions, each containing 5 × 103 cells, were evenly distributed into separate wells of 96-well plates. The cells were subjected to incubation for a duration of 24 hours at a temperature of 36 ◦C and an atmospheric concentration of 8% carbon dioxide in Dulbecco's Modified Eagle Medium (DMEM). The cells were subjected to aliquots of 100 µL of DMEM solution containing varying concentrations of Pt (IV) ions and Pt-NPs. Following a period of three days, the media was discarded, and a solution of 10% trichloroacetic acid (150 µL) was introduced into each well. The samples were then incubated for a duration of 1.5 hours at a temperature of 5 ◦C, after which they were subjected to multiple washes using DI water. The cells were treated with a solution of SRB (75 µL; 0.5% w/v) and cultured for a duration of 15 minutes in a dark environment at room temperature. Subsequently, the plates were subjected to a triple washing procedure using a solution of 1.5% acetic acid, followed by an overnight drying period. A solution of TRIS (12 mM, 175 µL) was introduced to facilitate the dissolution of the protein-bound SRB stain. Subsequently, the reactivity of the solution was determined at a wavelength of 550 nm using the FLUOstar Omega instrument located in Ortenberg, Germany. The IC50 value, expressed in µg/mL, was determined by employing concentration-response curves through the utilization of Sigma Plot software, version 10.0, and employing an E-max model equation. The investigations were performed in triplicate, and the data are presented as the mean value plus or minus the standard deviation.

Computational Studies

The green Pt-NPs were evaluated for their anticancer activities through in vitro studies. Subsequently, molecular modeling investigations were conducted to elucidate the mechanistic activities of these NPs as potential anticancer agents. Numerous studies have extensively documented the inhibitory effects of active metals and metallic complexes on various crucial enzymes, such as thioredoxin reductase (TrxR), cysteine proteinases, kinases, and glutathione transferase. Consequently, these findings have established their potential utility in the field of cancer treatment. The upregulation of proteinases is notably pronounced across various cancer types. Therefore, they serve as crucial objectives for cancer treatment. Therefore, the cysteine proteinase was chosen as the subject of investigation for the molecular docking studies involving biogenic Pt-NPs. The crystal structure of the cysteine proteinase was obtained by downloading it from the Protein Data Bank (PDB) with the code 1CV8. The molecular modeling technique was employed to further explore the relatively low antioxidant properties of the metal NPs. The crystallographic structure of the superoxide dismutase enzyme bound to manganese ions (Mn+2) was obtained by retrieving the corresponding data file from the Protein Data Bank (PDB) using the code 6DQY. The reduction and docking methods have been performed using MOE v.2010, in conjunction with dynamic simulations. The resulting interactions were visualized in both 2D and 3D formats. Hydrogen atoms were introduced to the proteins obtained through downloading, and an automated procedure was employed to establish connectivity and assign atom types for all atoms and bonds. The receptor was chosen and subsequent efforts were made to address potential issues. Subsequently, the extraneous chains and ligands were removed in a sequential manner, while concurrently identifying the pocket and ligands that were bound to the complex.

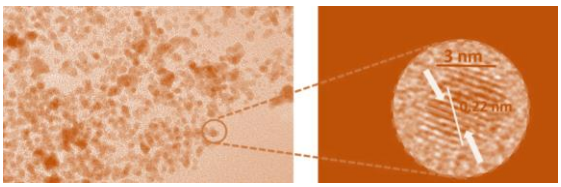
Despite the absence of a comprehensive forcefield capable of accurately capturing the binding between NPs and enzymatic proteins, we attempted to construct a basic model of biogenic Pt-NPs using procedures outlined in existing literature. The metallic structures were depicted utilizing the software tool known as the program builder,

which facilitated the automatic connection of atoms. Additionally, the appropriate type of bonding was assigned to the respective atoms. The dynamic simulation was constructed by implementing a range of 250 checkpoints, starting from zero, with a velocity applied and a time interval of 0.5. A single time duration of 0.75 seconds was selected for the simulations, as it was deemed a suitable and moderate option for the simplistic model. Subsequently, the forcefield employed was designated as the Rule; Empirical forcefield category, with charges being held constant, and the solvent was specified as a water droplet to replicate the DI water utilized in prior laboratory experiments. The calculation of solvent molecules was performed automatically for Pt-NP.

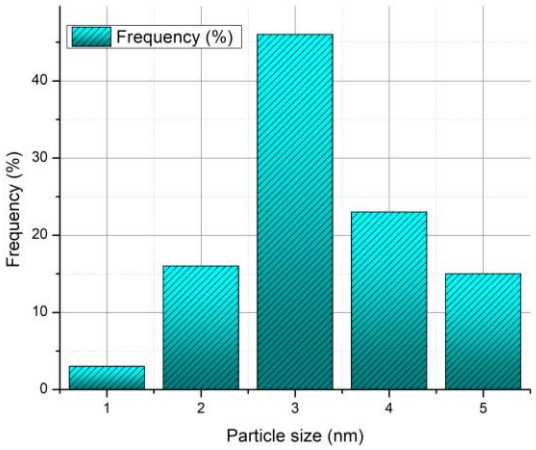
The experimental protocol employed in this study was the Nose–Poincare–Andersen–(NPA) Hamiltonian equations governing motion. For the Pt-NPs, the equilibrium radius was established at 10.2 nm. For the purpose of enhancing the visualization of potential ligand-enzyme interactions in the most stable and energetically favorable state, only the equilibrium state was chosen from the 225 dynamic conformations generated. Dynamic simulations were not performed on enzyme proteins in this study, as the focus was on metal-biomolecule interactions rather than large ligands or protein-protein interactions. As a result, the enzymes were kept under fixed constraints throughout the study. The docking process was performed using the Alpha Triangle placement method, followed by rescoring using the London dG scoring function with no refinement. Additionally, no rescoring was performed in the second step, and a total of 10 scores were retained.

RESULTS AND DISCUSSION

The Pt-NPs were subjected to characterization using various techniques, including TEM and XRD. A solution comprising of Pt-NPs has been created and subsequently deposited onto a carbon-coated copper grid in order to acquire the TEM micrograph. The JEOL 200 kV instrument was employed for TEM analysis. XRD analysis has been conducted to investigate the crystal arrangement and mean crystalline dimensions of the NPs. The examination had been carried out using a high-resolution XRD diffractometer (Panalytical Emperian, Turkey) equipped with a CuK radiation X-ray generator.



(a) Green synthesis procedure of Pt-NP using black cumin seeds.



(b) Histogram of particle size

Fig.2. TEM Characterization of biogenic Pt-NPs

XRD, and TEM techniques have been used to ascertain the crystal structure, particle shape, and size of platinum nanoparticles (Pt-NPs). Fig. 2a displays the TEM image of the synthesized Pt-NPs. The image reveals that the biogenic Pt-NPs exhibited a spherical morphology and possessed a mean particle dimension of 3.51 ± 1.42 nm, as depicted in Fig. 2b in particle size histogram

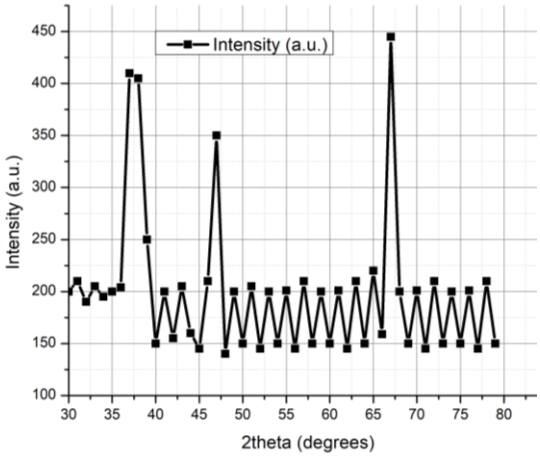


Fig.3. XRD results of the green synthesized Pt-NPs.

Fig. 3 depicts the XRD results of the green synthesized Pt-NPs. The X-ray diffraction

(XRD) analysis of the Pt-NPs synthesized using a green synthesis demonstrates the presence of well-defined peaks at different 2θ (degrees) values, which suggests that the nanoparticles possess a crystalline structure. Significantly, the intensity (in arbitrary units) of these peaks indicates the relative abundance of Pt-NPs at distinct crystallographic planes. The peaks of interest are observed at angles of 37°, 67°, and 73°, exhibiting intensities of 410, 445, and 150 arbitrary units (a.u.) correspondingly. These findings indicate the presence of Pt-NPs with a significant degree of crystallinity at these specific angles. Furthermore, the occurrence of peaks at angles of 30°, 46°, and 78°, accompanied by intensities of 200, 210, and 210 arbitrary units (a.u.), respectively, serves as evidence for the existence of platinum nanoparticles (Pt-NPs) on distinct crystallographic planes. The findings of this study demonstrate the effective utilization of environmentally friendly methods for the synthesis of Pt-NPs, resulting in the production of nanoparticles with well-defined crystalline structures. These results provide significant contributions to the understanding of the material properties of these nanoparticles.

Tab.1. Cytotoxic effects of the alkaloid fraction of Nigella sativa seeds, mediated by platinum nanoparticles (Pt NPs), in comparison to the specific metal ions, on A549 lung cancer cells and breast adenocarcinoma cells (MCF-7) in an in vitro setting.

Cells	Cytotoxic effects in an in vitro setting (IC50 in µg/mL)	
	Pt (IV) ions	Green synthesized Pt-NPs
A549	91.4±0.48	9.1±0.24
MCF-7	30.2±0.42	4.7±0.37

Table 1 aimed to evaluate the cytotoxic properties of the alkaloid fraction derived from Nigella sativa seeds in an in vitro environment. Specifically, the effects of platinum nanoparticles (Pt NPs) were compared to those of platinum (IV) ions on two different cancer cell lines, namely A549 (lung cancer cells) and MCF-7 (breast adenocarcinoma cells). Significantly, the findings demonstrate a pronounced disparity in cytotoxicity. The Pt (IV) ions demonstrated a significantly higher IC50 value of 91.4 µg/mL for A549 cells and 30.2 µg/mL for MCF-7 cells, indicating their comparatively reduced effectiveness in suppressing cell proliferation. In contrast, the Pt-NPs synthesized using green methods exhibited a significantly lower IC50 value of 9.1 µg/mL for A549 cells and 4.7 µg/mL for MCF-7 cells. This finding underscores the considerably enhanced cytotoxic effects of these nanoparticles on both cancer cell lines. The results of this study indicate that the platinum nanoparticles obtained from Nigella sativa seeds exhibit significant anti-cancer characteristics, thereby indicating their potential as a viable option for cancer treatment.

CONCLUSION

This paper introduces a method that is both simple and environmentally sustainable for synthesizing platinum nanoparticles (Pt-NPs). The method involves employing Nigella sativa (black cumin) seed extract as a reducing agent. The in vitro investigations were conducted to evaluate the anticancer activities of the green Pt-NPs. Subsequently, molecular modeling investigations have been conducted to elucidate the mechanistic mechanisms underlying the potential therapeutic efficacy of these NPs in the treatment of cancer. The biogenic platinum nanoparticles (Pt-NPs), synthesized utilizing an extract derived from black cumin seeds, underwent a thorough characterization procedure that encompassed the utilization of TEM and XRD. The results of the TEM analysis indicate that the Pt-NPs displayed a spherical shape and had an average particle size of 3.51 ± 1.42 nm. Furthermore, it was observed that the Pt-NPs exhibited significant cytotoxicity against lung cancer (A549) and breast adenocarcinoma (MCF-7) cells, as evidenced by IC50 values of 9.1±0.24 and 4.7±0.37 µg/mL, respectively.

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