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Biocompatible and anti-cancer drug delivery system using gold nanoparticles stabilized with hydrophilic polymer-coated hesperidin

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Abstract

Hesperidin (HP), classified as a flavonone, is well acknowledged for its potential as a therapeutic agent with anti-inflammatory, anti-oxidative, and anti-cancer properties. Nevertheless, the compound's limited breakdown and bioavailability result in little absorption, necessitating the utilization of a delivery mechanism to reach its intended therapeutic site effectively. The utilization of Polymer-Coated (PC) Gold Nanoparticles (GNP) in current pharmacological research as a Drug Delivery System (DDS) has demonstrated efficacy for cancer therapy within the realm of biological applications. In creating pharmacological anti-cancer medications, many aspects, such as dissolution, bioavailability, biological compatibility, and restricted chemical potency, play a crucial role. These characteristics need the use of specialized formulating techniques to ensure optimal DD. The primary objective of this paper was to enhance the dissolution of the medication and mitigate the adverse effects associated with chemotherapy. A straightforward and effective approach for synthesizing Biocompatible GNP stabilized with a Hydrophilic Polymer-Coated Hesperidin (GNP-HPCH) has been presented. These nanoparticles hold promise for use in DDS. The medium, namely the polymer-enriched GNP (Au-mPEG(5000)-SH), has been produced by combining tetrachloroauric acid (HAuCl4) with the polymer. The synthesis of GNP-HPCH has been confirmed by utilizing many characterization methods, including UV-VIS spectroscopy and Transmission Electron Microscopy (TEM). The cytotoxic impact of GNP-HPCH on the female breast cancer cell line has been examined using MTT tests. GNP-HPCH, at a concentration of 100 µg/mL, demonstrates a noteworthy inhibition rate of 84% for treating breast cancer MDA-MB-231, indicating its heightened potential as an anti-cancer agent. The findings demonstrated a notable reduction in cell division and growth retardation in the treated cells when compared to the normal breast epithelial cell line.

Key Words: gold nanoparticles, polymer coating, hesperidin, drug delivery system, anti-cancer, biocompatible

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INTRODUCTION

Cancer continues to pose a huge worldwide health concern, characterized by a rising prevalence and substantial implications for the well-being and longevity of those affected [1]. The advancement of novel DDS has played a crucial role in improving the effectiveness of anti-cancer drugs while simultaneously reducing their adverse effects. GNPs have received significant interest in this context because of their distinctive physicochemical qualities. These properties include the ability to adjust their size, shape, and surface chemistry, making them well-suited for therapeutic payloads. In conjunction with the naturally occurring substance hesperidin and a hydrophilic polymer covering, these GNPs present a potentially advantageous framework for developing a biodegradable and tailored DDS to combat cancer [2]. The present introduction offers a comprehensive outline of the existing obstacles encountered in cancer treatment, the characteristics and prospects of GNPs, the importance of hesperidin, and the involvement of hydrophilic polymers in augmenting the biological compatibility and effectiveness of DDS of this nature.

The existence of cancer presents a significant and severe obstacle to contemporary medical practices, as its wide-ranging and frequently aggressive characteristics distinguish it. The standard treatment techniques, such as radiation treatment, chemotherapy, and surgical procedures, have demonstrated efficacy; nevertheless, they frequently entail significant adverse effects and exhibit limits in their capacity to target cancer cells selectively. Chemotherapy, specifically, depends on the distribution of drugs throughout the body, resulting in unintended harm to healthy tissues and an elevated likelihood of drug resistance, hence constraining its efficacy [3]. Therefore,

developing novel DDS that can enhance the specificity and effectiveness of anti-cancer drugs while mitigating their adverse effects on normal tissues is imperative.

GNPs have been recognized as a flexible and potential framework for delivering pharmaceutical agents. Nanoparticles possess distinctive physicochemical characteristics, including their diminutive size, notable surface area-to-volume ratio, facile customization, and exceptional biological compatibility, rendering them very suitable for transporting therapeutic drugs. GNPs have the potential to be engineered in a manner that enables controlled dispensing of pharmaceuticals in response to certain stimuli, such as alterations in pH or temperature. This capability further enhances their accuracy and regulated drug release capacities [4]. Moreover, functionalizing GNPs with ligands can enhance their ability to target cancer cells selectively, hence improving DD's efficiency to the desired location.

HP, an inherent flavonoid mostly present in citrus fruits, has garnered acknowledgment for its multifaceted pharmacological attributes, encompassing anti-inflammatory, anti-oxidative, and anti-cancer capabilities [5]. The compound in question has gained recognition for its capacity to trigger cellular death and impede angiogenesis, positioning it as a viable contender for anti-cancer treatment. When integrated into a DDS, hesperidin exhibits dual functionality as both an anti-cancer agent and a powerful adjuvant, augmenting other medications' therapeutic effectiveness [6].

The selection of an appropriate polymer is of utmost importance in DDS as it significantly influences nanoparticles' reliability, biological compatibility, and drug release characteristics. Hydrophilic polymers, such as Polyethylene glycol (PEG), have been widely utilized in nanoparticle research to establish a shielding and biocompatible layer. This layer serves the purpose of impeding the accumulation, opsonization, and removal of nanoparticles by the endothelial cells in the retina [7]. The use of this coating extends the duration of nanoparticle circulation inside the blood vessels, hence enhancing the efficacy of DD to the intended destination. In addition, the application of an HPC has been found to improve the durability of the nanoparticle system and regulate the pace at which the medication is released. This, in turn, promotes a prolonged therapeutic impact [8]. This manuscript explores the novel methodology of developing a DDS that integrates the distinctive characteristics of GNP, the anti-cancer efficacy of hesperidin, and the benefits of a hydrophilic polymer coating to establish a biocompatible and site-specific therapeutic platform. By examining the present state of scholarly inquiry in this domain, our objective is to elucidate the prospective impact of this innovative system on the transformation of cancer therapy. This system has promise for offering a treatment strategy that is more productive, targeted, and less harmful, therefore addressing the profound challenges posed by this affliction.

RELATED WORKS

Nanotechnology and novel drug administration methods are changing oncology, offering new opportunities for precision medicine and targeted cancer treatment. A biocompatible, cancer-fighting DDS is one of these revolutionary methods. GNP's unique physicochemical properties make them ideal multifunctional drug carriers for precise drug administration and improved therapeutic effects. These GNPs can improve drug solubility, bioavailability, and targeted DD when co-administered with hesperidin, a naturally occurring flavonoid with anti-cancer properties, and enhanced with HPC. The research in this emerging field is thoroughly reviewed in this literature review. Methodologies, execution, results, and biocompatible and anti-cancer DDS benefits and drawbacks are the main focus of this review.

Alam et al. (2022) studied Xanthan Gum-stabilized colloidal gold nanogel solubility and formulation. The goal was to test this nanogel's hesperidin delivery against Proteus vulgaris [9]. The study included nanogel synthesis, characterization, and antibacterial testing. The nanogel with hesperidin had improved solubility and antibacterial efficacy, as shown by a zone of inhibition. The subsequent analysis will provide numerical values. This method improves drug solubility and antibacterial properties. Be aware of potential drawbacks like long-term stability and systemic safety.

The study [10] used green GNPs for cancer treatment and diagnosis. The proposed method should synthesize and functionalize

environmentally friendly GNPs—implementation involved in vitro and possibly in vivo research to assess cancer treatment and diagnostic uses. The findings showed that green GNPs can be used in therapeutic and diagnostic applications, highlighting their potential for cancer treatment. Scaling up and getting regulatory approval may have drawbacks.

The simple production of sonosensitizing alginate-stabilized gold nanoparticles below 5 nm was described in [11]. This study likely involved nanoparticle synthesis and characterization. Results showed biocompatibility and sonosensitizing properties of materials. Sonodynamic treatment may benefit from these nanoparticles. However, clinical implementation and toxicity concerns may cause issues.

Yap et al. (2021) reviewed the literature on using nanocarriers to transport natural products to improve breast cancer treatment. The method involved a thorough literature review. The results summarized current research in this area and highlighted the benefits of nanocarriers in breast cancer treatment. These benefits include improved DD and fewer side effects. Translation of research findings into clinical practice and safety concerns may be drawbacks.

In reference [13], l-asparaginase was immobilized on gold nanoparticles. This novel drug delivery method targeted human breast carcinoma cells as an anti-cancer agent. The implementation phase likely included GNP synthesis, functionalization, and in vitro testing. The quantitative results in this study suggest that the proposed strategy may treat cancer. Targeted DD can deliver drugs to their target site. However, scaling up production and ensuring drug stability may have drawbacks.

The work in [14] focused on the potential of hesperidin and its aglycone hesperetin's breast cancer treatment. The suggested approach examined modern advances. It summarizes the progress made in using hesperidin and hesperetin as breast cancer treatments and highlights their potential benefits. Potential drawbacks include bioavailability and clinical translation issues.

Gokuladhas et al. (2014) synthesized and characterized biocompatible gold nanoparticles. An HPC medication stabilized these nanoparticles for sustained drug administration to treat hepatocellular carcinoma cells [15]. In addition to in vitro studies, the technique likely involved nanoparticle creation and characterization. The results of this study suggest that sustained drug administration may treat hepatocellular carcinoma-derived cancer cells. The research results are quantified in this report. Controlled medication release has benefits, but large-scale manufacturing may have drawbacks.

GNPs were used to deliver hesperidin in reference [16]. This approach sought biocompatibility, anti-cancer, anti-inflammatory, and phagocytosis stimulation. The suggested method involves nanoparticle production and functionalization, followed by in vitro testing. According to this study, the system under study is biocompatible and therapeutically effective. The experiments quantitatively demonstrate the system's anti-cancer, anti-inflammatory, and phagocytosis effects. This technology's advantage is multifunctionality, but clinical translation and safety are drawbacks.

GNPs stabilized by HPC-hesperidin could treat cancer. The multimodal administration of anti-cancer drugs uses adaptable GNPs, hesperidin's medicinal properties, and hydrophilic polymer coatings' protection. According to research, these systems improve drug solubility, targeted drug administration, and therapeutic benefits. The findings are promising, but other challenges remain. Manufacturing scalability, long-term stability, and clinical safety are among these challenges. However, integrating GNPs with hesperidin and hydrophilic polymers offers a promising opportunity to develop biocompatible and effective cancer DDS.

GNP-HPCH FOR DDS

Materials and methods

HAuCl4, mPEG (5000)-SH, and hesperetin were procured from Sigma-Aldrich. The medium for growth utilized in this study was Minimum Essential Medium (MEM) supplemented with L-Glutamine, NaHCO3, and C3H3NaO3. Antibiotics and bovine plasma were acquired from Invitrogen. All the additional compounds utilized were of statistical solution quality.

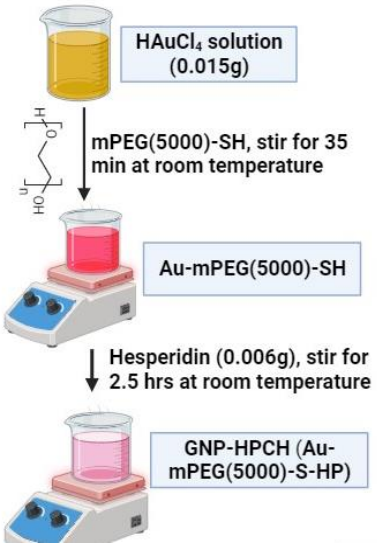

Fig.1. Synthesis of biocompatible GNP-HPCH.

Fig. 1 depicts the synthesis of biocompatible GNP-HPCH. The synthesis of GNPs has been conducted by utilizing a modified Turkevich approach. HAuCl4 was employed as a primer, while mPEG (5000)-SH served the dual purpose of reducing agents and stabilizing substances in our study. The experiment has been conducted under ambient temperature conditions in a light-restricted environment. In a 55 mL beaker, a solution containing 0.015 g of GNP (HAuCl4, 1x10-3 M) was prepared by dissolving it in 10 mL of DI water using a magnetic stirrer. In this experimental procedure, a solution was prepared by dissolving 0.125g of the polymer PEG-SH, which had a concentration of 1x10-3M, in 20 ml of DI water. The resultant solution was subjected to stirring for approximately 35 minutes until a noticeable color transition occurred, shifting from yellow to pink. The sample designated as control was treated with Au-mPEG (5000)-SH. In addition, as a component of this methodology, 0.006 grams of the drug hesperidin (1x10-3M) were incrementally introduced and subjected to agitation for approximately 2.5 hours. The presence of a pale pink hue serves as visual evidence that the drug has been successfully incorporated onto the exterior of the GNP-HPCH (Au-mPEG (5000)-S-HP), as depicted in Fig. 1. Ultimately, the solution underwent filtration using a 0.45 μm filtering cloth.

GNP-HPCH for anti-cancer DDS

Using HPCH to stabilize GNPs presents an innovative and promising strategy for advancing DDS targeting cancer. The amalgamation of GNPs, HP, and hydrophilic polymers results in a versatile framework that effectively tackles various crucial obstacles in cancer therapy, encompassing drug solubility, precise drug administration, and amplified therapeutic effectiveness.

GNPs have become widely recognized as versatile carriers for therapeutic agents due to their distinctive physicochemical properties. Nanoparticles are advantageous for drug delivery applications due to their elevated surface area-to-volume ratio, facile functionalization capabilities, and exceptional biocompatibility. The nanoparticles can be deliberately designed to effectively encapsulate and transport diverse anti-cancer medications, thereby providing a highly accurate and regulated release of drugs specifically at the tumor's location. Moreover, the diminutive dimensions of these particles facilitate heightened cellular absorption, a pivotal element in augmenting the transportation of therapeutic agents to malignant cells.

HP, an inherent flavonoid in citrus fruits, exhibits significant anti-cancer properties. It can trigger cellular apoptosis, hinder the formation of new blood vessels, and regulate multiple signaling pathways crucial for cancer cells' proliferation and viability. When incorporated into DDS, hesperidin exhibits dual functionality as an anti-cancer agent and a facilitator of enhanced therapeutic effectiveness in conjunction with other drugs. HP in anti-cancer DDS is highly appealing due to its ability to enhance cancer cells' sensitivity to treatment, mitigate drug resistance, and decrease the likelihood of adverse effects.

The presence of HPC further enhances the biocompatibility and DD capabilities of GNPs. Polymers, such as PEG, serve as a protective barrier that effectively inhibits nanoparticle aggregation, opsonization, and immune system clearance. Applying this coating enhances the duration of nanoparticle circulation within the bloodstream, thereby facilitating enhanced drug delivery to the specific tumor location while minimizing adverse effects on the overall systemic physiology. In addition, hydrophilic polymers can regulate the drug release rate, thereby facilitating the maintenance of sustained therapeutic effects and enhancing the overall efficacy of treatment.

From a practical standpoint, the synthesis of these DDS entails the initial preparation of GNPs, which are subsequently encapsulated with HP and coated with a hydrophilic polymer. The nanoparticles produced have been specifically designed to effectively encapsulate anti-cancer medications, facilitate their precise transportation to tumor tissues, and improve the release patterns of these drugs.

The potential of utilizing HPCH to stabilize GNPs holds significant implications for advancing cancer therapy. This platform presents a promising opportunity to enhance the efficacy of anti-cancer drugs and reduce adverse effects by tackling significant obstacles such as drug solubility, bioavailability, and site-specific drug release. Nevertheless, it is crucial to take into account potential constraints, such as those about the production on a large scale, the long-term durability, and the safety implications in clinical settings. Additional investigation and advancement in this particular domain are crucial for unleashing the complete capabilities of this anti-cancer DDS and facilitating the provision of more efficient and focused therapies to individuals who have cancer.

In vitro release of HP

The in vitro release of HP from the GNPs on which it has been embedded and from the free HP was conducted with slight modifications. The mixture of NPs and drug underwent centrifugation at 13,500 revolutions per minute for 30 minutes at a temperature of 20 °C. Subsequently, the resulting loose red pellet was collected and divided into multiple aliquots, each containing 250 µL. The sample was diluted with 850µL of either a homeostatic solution at pH 7.5 or an acidic solution at pH 5.1. The combinations were incubated at 38 °C for varying durations, including 10, 20, 30, 45, 115, 160, and 240 minutes. Following every interval, the absorbance of the sample was measured using a UV-VIS spectrophotometer at a wavelength of 282 nm. The amounts of the released HP from each interval were determined. The release percentage can be calculated using the formula:

Release (%)=M_1/M_t ×100 (1)

where M_1 represents the mass of the substance being released (HP), and M_t represents the mass of HP being loaded.

Blood Collection and Processing

Ten individuals in good health provided new blood specimens collected and stored in HP-coated tubes following the guidelines established by the National Institute of Drug Administration. These procedures have been carried out following ethical standards. The research subjects have been provided with information regarding the significance of the study before the commencement of data or specimen collection. The researchers obtained written permission and approval from the people involved in the study.

Coagulation test

The coagulation test is a laboratory procedure used to assess the ability of certain substances or organisms to cause the breakdown of red blood cells. The coagulation test has been conducted on the synthesized HP, GNP, and GNP-HPCH samples using a previously established methodology with certain adaptations. In this experiment, 150 µL of fresh blood was mixed with 750 µL of Phosphate-Buffered Saline (PBS). Additionally, 150 µL of either HP, GNP, or GNP-HPCH at various concentrations (25, 75, 150, and 240 µg/mL) have been introduced. The Negative Control Group (NCG) consisted of PBS, which resulted in 0% coagulation, while the Positive Control Group (PCG) involved DI water, leading to 100% coagulation. Three replicate specimens have been utilized and underwent culture at 38 °C for 1.5 hours. Ultimately, the mixtures were subjected to spinning (750 revolutions per minute, 7 minutes), and the absorbance was measured. The coagulation value has been obtained using the following technique:

% coagulation=OC specimen-OC NCG/OC(PCG) -OC (NCG) (2)

The percentage of coagulation is inversely proportional to the OC(PCG) of the sample. Subsequently, the samples were subjected to optical microscopy for further examination.

The assessment of cytotoxicity towards MDA-MB-231 cell line

The MDA-MB-231 cells were seeded at a concentration of 1×105 cells mL−1 in 250 µL volume using 96-well flat-bottom culture plates manufactured by Falcon, USA. After two days of exponential growth, the cells were incubated with HP, GNPs, and Hsp-GNPs at varying amounts of 0, 20, 40, 60,

80, and 100 µg/mL for one day. Subsequently, a solution comprising MTT stain and PBS (50 µL) was administered to the wells, followed by incubation of the cells for 20 minutes at 38 °C. Following removing the stain, a subsequent washing procedure was conducted using tap water. Subsequently, an application of isopropanol (150 µL) was employed to facilitate the dissolution of the stain. The cells were subsequently incubated for 15 minutes to remove any bubbles present. Following this, the absorbance was measured at a wavelength of 485 nm using a microplate reader (ELx 800, Bio-Tek Instruments Inc., USA).

The inhibition rate, expressed as a percentage, can be calculated using the formula:

Inhibition rate (%)=[X-Y/X)]×100 (2)

In this formula, X represents the OC of the CG, while Y represents the OC of the sample. To obtain further validation regarding the inhibition of MDA-MB-231 cell growth through induction by HP, GNPs, and GNP-HPCH, in vitro studies have been carried out. In this study, cell seeding was performed by placing 250 µL of a cell suspension with a concentration of 1 × 105 cells per mL onto a sterilized coverslip. The covering was placed within a culture plate with a flat-bottom design, specifically a 24-well plate. After two days of exponential growth, the cells were incubated for one day with the compounds' half-maximal inhibitory concentration (IC50) being tested. Subsequently, the cells were subjected to staining using a combination of crystal violet and PBS in a volume of 55 µL, followed by incubation at 38 °C for 20 minutes. Following removing the stain and subsequent cleaning with water, the coverings have been air-dried and subsequently subjected to photography.

RESULTS AND DISCUSSION

The Surface plasmon resonance (SPR) peaks of the GNP-HPCH have been evaluated through UV-Vis Spectroscopy utilizing a Shimadzu UV-1601 spectrophotometer within the wavelength range of 300 to 900 nm. The high-resolution TEM has been conducted using the FEI TECNAI G2 model T-30 instrument, operating at an accelerating voltage of 250 kilovolts, to acquire the images. The preparation of samples for TEM imaging involved the deposition of a droplet of gold solution onto a copper grid coated with carbon, followed by air drying at ambient temperature.

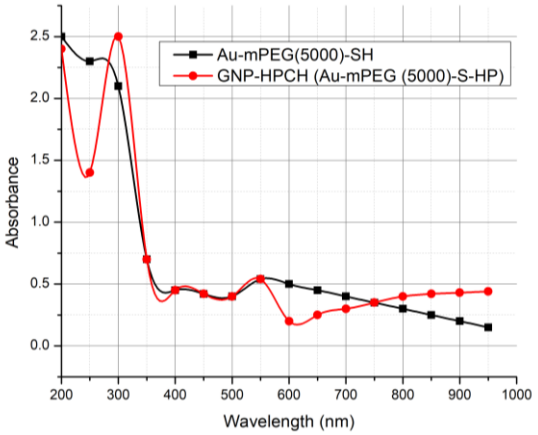

Fig.2. UV-Vis spectra of Au-mPEG(5000)-SH and the proposed GNP-HPCH (Au-mPEG (5000)-S-HP).

Fig. 2 shows the UV-Vis spectra of Au-mPEG(5000)-SH and the proposed GNP-HPCH (Au-mPEG (5000)-S-HP). The spectra display distinct absorption peaks at various wavelengths, signifying discrepancies in their optical characteristics. The Au-mPEG(5000)-SH compound exhibits a progressive decline in absorbance across the wavelength range of 200 nm to 950 nm, indicating a reduction in its optical density with increasing wavelength. On the other hand, it can be observed that GNP-HPCH exhibits a more prominent and distinctive absorption peak at approximately 250 nm, which is significantly greater than the corresponding value observed for Au-mPEG(5000)-SH. A characteristic peak in the data indicates the successful synthesis of the GNP-HPCH, potentially resulting from the interaction between the GNPs and the HPCH coating. The optical phenomena observed in the UV-Vis spectra provide insights into these nanoparticles' distinct characteristics and surface alterations, which may have significant ramifications for their utilization in diverse domains such as pharmaceutical transportation, diagnostic techniques, and nanomedical applications.

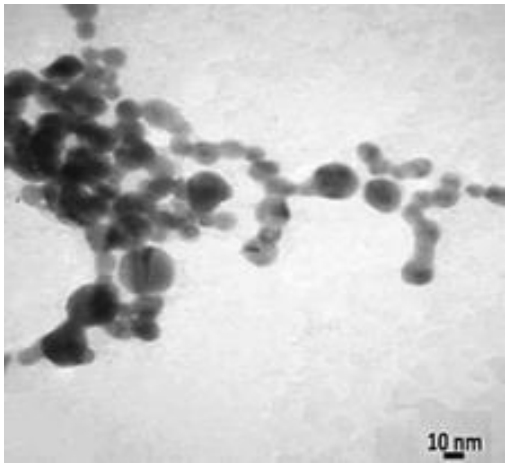

Fig.3. TEM image of the synthesized GNP-HPCH (Au-mPEG (5000)-S-HP).

Fig. 3 depicts the TEM image of the synthesized GNP-HPCH (Au-mPEG (5000)-S-HP). The spherical shape, crystalline nature, apparent structural distribution, smooth exterior, and diameter range of 15 to 55 nm of the GNP-HPCH are evident in the TEM image depicted in Fig. 3. The findings of this study demonstrate that the HP molecules exhibit a uniform distribution across the surface of the GNPs.

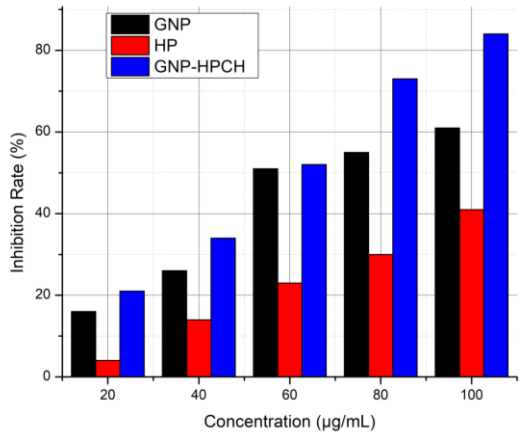

Fig.4. Inhibition rate (%) of breast cancer MDA-MB-231 for varying concentrations of GNP, HP, and GNP-HPCH.

Fig. 4 depicts the inhibition rate (%) of breast cancer MDA-MB-231 for varying concentrations of GNP, HP, and GNP-HPCH. As the concentration of these components increases, a discernible dose-dependent relationship is observed concerning the inhibition rates. The compound GNP-HPCH consistently demonstrates the highest inhibition rates across all concentration levels, surpassing the inhibitory effects of individual GNP and HP compounds. Significantly, when GNP-HPCH is present at 100 µg/mL, it demonstrates a noteworthy inhibition rate of 84%, indicating its heightened potential as an anti-cancer agent. The results of this study emphasize the advantageous outcomes achieved by the amalgamation of gold nanoparticles and a hydrophilic polymer coating. This highlights the potential of GNP-HPCH as a potent anti-cancer agent, thereby carrying substantial implications for the treatment of breast cancer.

CONCLUSION

This paper presents a direct and efficient method for synthesizing biocompatible GNP-HPCH. The utilization of these nanoparticles exhibits potential for application in DDS. The polymer-enriched GNP (Au-mPEG(5000)-SH) was synthesized by combining HAuCl4 with the polymer. GNP-HPCH synthesis has been confirmed through various characterization techniques, such as UV-VIS spectroscopy and TEM. The cytotoxic effects of GNP-HPCH on a female breast cancer cell line were investigated using MTT assays. The compound GNP-HPCH, when present at a concentration of 100 µg/mL, exhibits a significant inhibition rate of 84% against the breast cancer cell line MDA-MB-231. This finding suggests that GNP-HPCH possesses promising characteristics as a potential anti-cancer therapeutic agent. The results indicated a significant decrease in cellular division and growth inhibition in the treated cells compared to the control breast epithelial cell line.

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